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and Thrombolytic Therapy**

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New Anticoagulant Drugs

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

Jeffrey I. Weitz, MD, FCCP; Jack Hirsh, MD, FCCP; and Meyer M. Samama, MD

This article about new anticoagulant drugs is part of the seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. The limitations of existing oral and parenteral anticoagulant agents have prompted a search for novel agents. Focusing on new anticoagulant drugs for the prevention and treatment of arterial and venous thrombosis, this article (1) reviews arterial and venous thrombogenesis, (2) discusses the regulation of coagulation, (3) describes the pathways for testing new anticoagulant agents, (4) describes new anticoagulant strategies focusing primarily on agents in phase II or III clinical testing, and (5) provides clinical perspective as to which of these new strategies is most likely to succeed.

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Key words: anticoagulants; antithrombotic drugs; profibrinolytic agents

Abbreviations: APTT = activated partial thromboplastin time; CI = confidence interval; DVT = deep-vein thrombosis; EPCR = endothelial protein C receptor; factor IXa = activated factor IX; factor VIIa = activated factor VII; factor VIIai = active site-blocked factor VIIa; factor Xa = activated factor X; factor XIIIa = activated factor XIII; FSAP = factor VII-activating protease; GP = glycoprotein; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; HIT = Hirudin for Improvement of Thrombolysis; INR = international normalized ratio; MI = myocardial infarction; NAPc2 = nematode anticoagulant peptide c2; OASIS = Organization to Assess Strategies for Ischemic Syndromes; OR = odds ratio; PAI-1 = type 1 plasminogen activator inhibitor; PE = pulmonary embolism; PF4 = platelet factor 4; SPORTIF = Stroke Prevention Using Oral Thrombin Inhibition in Atrial Fibrillation; TAFI = thrombin activatable fibrinolysis inhibitor; TAFIa = activated thrombin activatable fibrinolysis inhibitor; TFPI = tissue factory pathway inhibitor; THRIVE = thrombin inhibitor in venous thromboembolism; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue-type plasminogen activator; uPA = urokinase-type plasminogen activator

$\mathbf{A}$rterial and venous thrombosis are major causes of morbidity and mortality. Whereas arterial thrombosis is the most common cause of myocardial infarction (MI), stroke, and limb gangrene, venous thrombosis leads to pulmonary embolism (PE), which can be fatal, and to postphlebitic syndrome. Because arterial thrombi consist of platelet aggregates that are held together by small amounts of fibrin, strategies to inhibit arterial thrombogenesis focus mainly on drugs that block platelet function but often include anticoagulant agents to prevent fibrin deposition. In contrast, because venous thrombi are composed mainly of fibrin, anticoagulants are the drugs of choice for their prevention and treatment. Anticoagulants also are used for the prevention of cardioembolic events in patients with atrial fibrillation or mechanical heart valves.

The limitations of existing oral and parenteral anticoagulants have prompted a search for novel agents. Focusing on new anticoagulant drugs for the prevention and treatment of arterial and venous thrombosis, this article (1) reviews arterial and venous thrombogenesis, (2) discusses the regulation of coagulation, (3) describes the pathways for testing new anticoagulants, (4) describes new anticoagulant strategies focusing primarily on agents that are in phase II or III clinical testing, and (5) provides a clinical perspective as to which of these new strategies is most likely to succeed.

1.0 Thrombogenesis

Arterial thrombosis usually is initiated by the spontaneous or mechanical rupture of atherosclerotic plaque, a process that exposes thrombogenic material in the lipid-rich core of the plaque to the blood.[1] Typically, thrombi that form at sites of plaque disruption extend both into the plaque and into the vessel lumen (Fig 1). If the intraluminal thrombus is nonocclusive, and if blood flow remains rapid, the thrombus may embolize downstream, or it may organize and become incorporated into the vessel wall. With more extensive intraluminal thrombosis, however, blood flow diminishes and shear increases. Higher shear promotes further platelet and fibrin deposition, which may result in the formation of an occlusive thrombus that obstructs blood flow to organs, such as the heart or brain, or to the extremities. Alternatively, vascular obstruction may reflect explosive thrombosis at sites of severe plaque disruption.

Whereas arterial thrombi are predominantly composed of platelet aggregates, venous thrombi consist mainly of fibrin and RBCs.[2] Venous thrombosis occurs when procoagulant stimuli overwhelm natural protective mechanisms. Procoagulant stimuli include the excessive activation of coagulation, particularly when protective pathways are compromised by thrombophilic abnormalities, vessel wall damage, or stasis. Patients with a congenital deficiency of antithrombin, protein C, or protein S are prone to thrombosis because naturally occurring anticoagulant pathways are compromised. The factor V Leiden mutation also predisposes patients to thrombosis because, once activated, factor V Leiden is resistant to degradation by activated protein C. Consequently, individuals with this mutation have increased thrombin generation. Increased thrombin generation also may underline the propensity to thrombosis in patients with the prothrombin gene mutation, a defect that results in increased levels of prothrombin, or in patients with elevations of other clotting factors, including factors VIII, IX, or X.

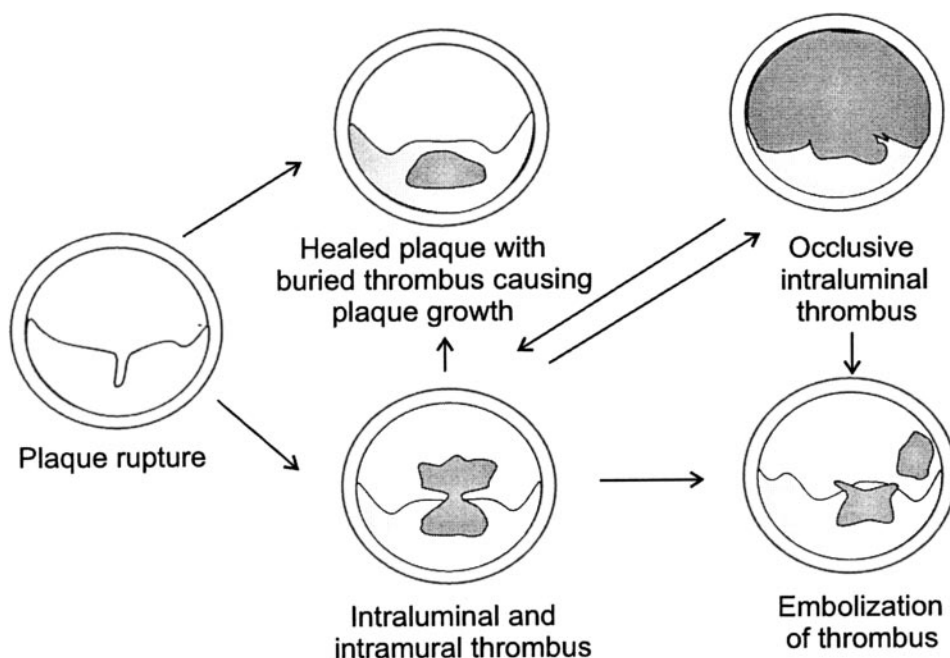Venous thrombi develop under low-flow conditions and

FIGURE 1. Arterial thrombogenesis. Spontaneous or mechanical plaque rupture exposes thrombogenic material in the lipid-rich plaque core. Platelets adhere to the exposed collagen and von Willebrand factor, where they become activated and aggregate. The platelet thrombus is stabilized by fibrin once coagulation is triggered by exposed tissue factor. Platelet-rich thrombus extends into the vessel wall and into the lumen. The plaque may heal, burying the thrombus into the vessel wall and causing the plaque to grow, or the thrombus may embolize distally. Alternatively, the thrombus may extend to occlude the lumen.

usually originate in the muscular veins of the calf or in the valve cusp pockets of the deep calf veins.[3,4] Because the venous valve cusps are avascular, they depend on the circulating blood for their oxygen and nutrient supply. With venous stasis, there is local hypoxemia, which can induce tissue factor expression in the valve cusps. Coagulation in the veins also can be initiated by vascular trauma. Damage to the vessel wall is a particularly important predisposing factor to venous thrombosis after major hip or knee surgery.[5] Indwelling central venous catheters also can injure the vein wall, causing deep-vein thrombosis (DVT) in the upper extremities.

Inflammatory cytokines generated after trauma, surgery, or medical illness can contribute to the procoagulant state that occurs with these conditions. Endothelial cells are activated by inflammatory cytokines and express adhesion molecules that tether leukocytes onto their surface. Bound monocytes elaborate tissue factor and express receptors for factor X and fibrinogen, that promote coagulation on their surfaces.[6,7] Tethered neutrophils damage the endothelium by generating oxygen free radicals and releasing hydrolytic enzymes, thereby enhancing local clot formation.[8,9] Finally, tissue factor-containing leukocyte and platelet-derived microparticles also accumulate at sites of vascular damage where they augment coagulation.[10] It is through these mechanisms that inflammation is intimately linked with coagulation.

The initiation of coagulation in arteries or veins is triggered by tissue factor (Fig 2), a cellular receptor for

activated factor VII (factor VIIa).[11] Although a small fraction of circulating factor VII is activated, factor VIIa has little or no enzymatic activity until it is bound to tissue factor. Most nonvascular cells express tissue factor in a constitutive fashion, whereas *de novo* tissue factor synthesis can be induced in monocytes.[12,13] Injury to the arterial or venous wall exposes nonvascular, tissue factor-expressing cells to blood.[11] Lipid-laden macrophages in the core of atherosclerotic plaques are particularly rich in tissue factor,[1] thereby explaining the propensity for thrombus formation at sites of plaque disruption.

Once bound to tissue factor, factor VIIa activates factor IX and factor X, leading to the generation of activated factor IX (factor IXa) and activated factor X (factor Xa), respectively. Factor X activation is more efficient than factor IX activation. Factor Xa converts small amounts of prothrombin to thrombin.[14] This low concentration of thrombin is sufficient to activate platelets, and to activate factors V and VIII, which are key cofactors in coagulation. These thrombin-mediated steps are essential for the propagation of coagulation.

The propagation of coagulation is effected by factors IXa and Xa. In the presence of calcium, factor IXa binds to factor VIIIa on the surface of activated platelets to form intrinsic tenase, the complex that activates factor X. Factor Xa then binds to factor Va on the activated platelet surface, a process that also is calcium-dependent, to form the prothrombinase complex. This complex activates prothrombin, and the resultant thrombin then dissociates
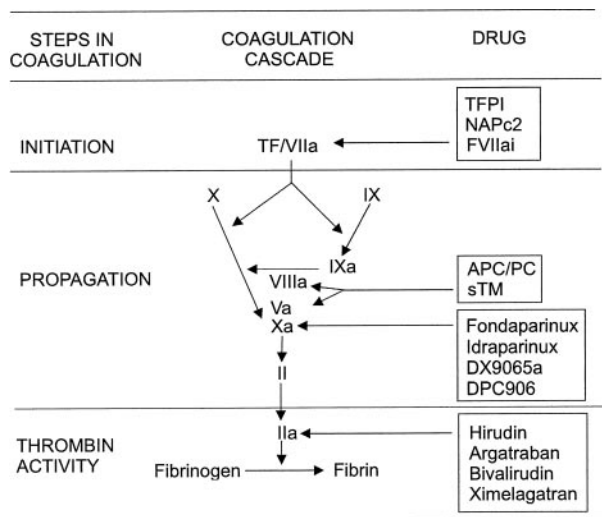
FIGURE 2. Steps in blood coagulation. The initiation of coagulation is triggered by the tissue factor/factor VIIa complex (TF/VIIa), which activates factor IX (IX) and factor X (X). Activated factor IX (IXa) propagates coagulation by activating factor X in a reaction that utilizes activated factor VIII (VIIIa) as a cofactor. Activated factor X (Xa), with activated factor V (Va) as a cofactor, converts prothrombin (II) to thrombin (IIa). Thrombin then converts fibrinogen to fibrin. TFPI, NAPc2, and factor VIIai (FVIIai) target TF/VIIa. Activated protein C (APC) blocks the propagation of coagulation by inactivating factors Va and VIIIa. Protein C (PC) and soluble thrombomodulin (sTM) also target this step. PC does so once it is activated to APC by the thrombin/thrombomodulin complex, whereas sTM accomplishes this task by binding thrombin and converting it into a potent activator of PC. Fondaparinux, idraparinux, DX9065a, and DPC 906 target factor Xa, whereas hirudin, argatroban, bivalirudin, and ximelagatran inactivate thrombin.
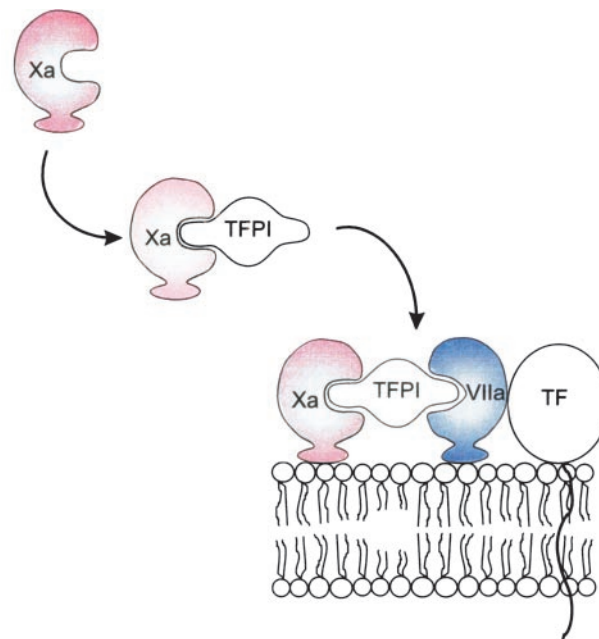

FIGURE 3. Mechanism of action of TFPI. TFPI inactivates factor VIIa in an activated factor X-dependent fashion. TFPI first complexes and inactivates factor Xa. The activated factor X/TFPI complex then inhibits factor VIIa within the factor VIIa/tissue factor (TF) complex. See the legend of Figure 2 for abbreviations not used in the text.

from the platelet surface and converts fibrinogen to fibrin monomer.[11,14] Fibrin monomers polymerize to form the fibrin mesh that is stabilized and crosslinked by activated factor XIII (factor XIIIa), a thrombin-activated transglutaminase. Thrombin amplifies its own generation by the feedback activation of factor V and factor VIII, as described above, and by activating platelet-bound factor XI, thereby leading to further factor Xa generation.[15]

2.0 Regulation of Coagulation

Coagulation is regulated at several levels. Key inhibitors include tissue factor pathway inhibitor (TFPI), antithrombin, and the protein C pathway. In addition, the fibrinolytic system serves to degrade fibrin once it has served its role in hemostasis and wound healing. Because many new anticoagulant strategies are aimed at enhancing endogenous anticoagulant or fibrinolytic mechanisms, it is relevant to briefly review these pathways.

TFPI

The inhibition of the factor VIIa/tissue factor complex is effected by TFPI.[16] A bivalent, Kunitz-type inhibitor, TFPI acts in a two-step manner (Fig 3). In the first step, TFPI complexes and inactivates factor Xa to form a TFPI/factor

Xa complex. The TFPI within this complex then inactivates tissue factor-bound factor VIIa as the second step. Because the formation of the TFPI/factor Xa complex is a prerequisite for the efficient inactivation of factor VIIa, the system ensures that some factor Xa generation occurs before factor VIIa-mediated initiation of the coagulation system is shut down.

The propagation of coagulation occurs because TFPI concentrations are low. In addition, factor XI, which is efficiently activated by thrombin when bound to the activated platelet surface,[15,17] generates factor IXa. A key component of the intrinsic tenase complex, factor IXa triggers the formation of sufficient amounts of factor Xa to propagate coagulation.

Most circulating TFPI is bound to lipoproteins. TFPI also is found in platelet α-granules and on the endothelial cell surface.[16] TFPI bound to the endothelium is released with therapeutic doses of heparin or low-molecular-weight heparin, suggesting that TFPI binds to endogenous glycosaminoglycans on the endothelial wall surface.[16] It is uncertain, however, whether released TFPI contributes to the antithrombotic properties of these agents.

Antithrombin

Antithrombin inhibits thrombin, factor Xa, and other activated clotting factors, but these reactions are slow in the absence of heparin. With heparin, the rate of inhibition is accelerated about 1,000-fold.[18] Heparin binds to antithrombin via its high-affinity pentasaccharide sequence and, by altering the conformation of the reactive

center loop of antithrombin, renders the protease trap more accessible to target enzymes. Although heparin is not normally found in the blood, the vascular endothelium is rich in heparan sulfate, a glycosaminoglycan that also contains the antithrombin-binding pentasaccharide sequence. Most of the heparan sulfate is located on the abluminal surface of the endothelium and is exposed only when the vessel lining is damaged.[19] Nevertheless, the small amounts of proteoglycan located on the luminal surface may help to render intact endothelium nonthrombogenic.

Protein C pathway

In addition to inactivation by antithrombin, thrombin also is inhibited by binding to thrombomodulin, a thrombin receptor found on the endothelium (Fig 4). Once bound to thrombomodulin, thrombin undergoes a conformational change at its active site that converts it from a procoagulant enzyme into a potent activator of protein C, a vitamin K-dependent protein. Activated protein C serves as an anticoagulant by proteolytically degrading and inactivating factors Va and VIIIa, thereby attenuating thrombin generation.[20] This reaction occurs on negatively charged phospholipid surfaces where protein S, another vitamin K-dependent protein, serves as a cofactor.[10]

The density of thrombomodulin on capillaries is greater than that on large vessels. To compensate for this, large vessels express endothelial protein C receptor (EPCR), a transmembrane receptor that binds protein C and activated protein C with similar affinities.[21] By localizing protein C in the vicinity of the thrombin/thrombomodulin complex, EPCR promotes protein C activation on the surface of large vessels.[21]

Fibrinolytic system

Designed to remove intravascular fibrin, thereby restoring blood flow, fibrinolysis is initiated by plasminogen activators that convert plasminogen to plasmin (Fig 5). A trypsin-like protease, plasmin degrades fibrin into soluble fibrin degradation products. The following two immunologically distinct plasminogen activators are found in blood: tissue-type plasminogen activator (tPA); and urokinase-type plasminogen activator (uPA). Both plasminogen activators are synthesized and released from endothelial cells.[22]

Intravascular plasminogen activation is initiated by tPA. Plasminogen activation is targeted to fibrin because plasminogen and tPA bind to fibrin, and the enzymatic activity of tPA is enhanced by fibrin.[22] Endothelial cells also support plasminogen activation by expressing annexin II on their surface. A coreceptor for tPA and plasminogen, annexin II promotes plasmin generation on the endothelial cell surface.[23]

A protease that links fibrinolysis with coagulation has been identified. Known as *factor VII-activating protease* (FSAP), this protease not only activates factor VII, as its name implies, but also converts single-chain uPA (prourokinase) into the active two-chain form.[24] Genetic analyses have identified common polymorphisms in FSAP, one of which is designated Marburg 1.[25] FSAP from subjects with the Marburg 1 polymorphism exhibits reduced capacity to activate prourokinase,[25] and an epidemiologic study[26] has suggested that there may be an association between this polymorphism and the risk of carotid stenosis secondary to atherosclerosis. Although it is tempting to attribute this association to defective uPA-mediated fibrinolysis in subjects with the Marburg 1 polymorphism, it is as yet unclear whether these individuals also have reduced activation of factor VII. If so, the Marburg 1 polymorphism should offer protection from the thrombotic complication of atherosclerosis. Consequently, additional studies are needed to clarify the role of FSAP in atherosclerosis and thrombosis.

The fibrinolytic system is regulated at two levels. Plasminogen activator inhibitors, the most important of which is endothelial cell-derived type 1 plasminogen activator inhibitor (PAI-1), block tPA, whereas α_2-antiplasmin in-
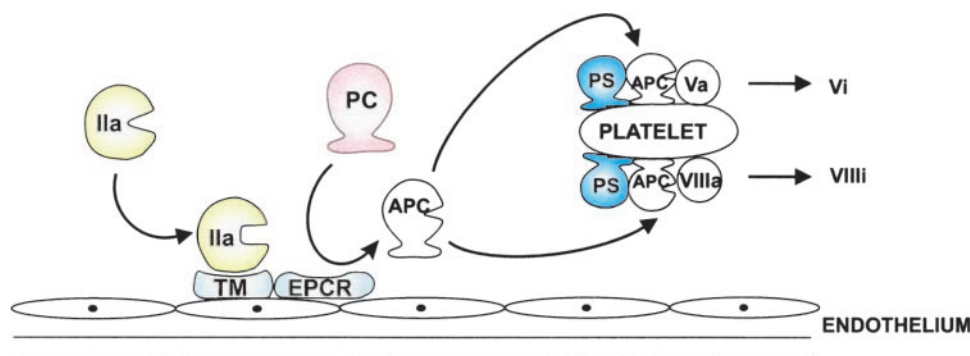
FIGURE 4. Protein C anticoagulant pathway. Thrombin binds to thrombomodulin (TM), an endothelial cell thrombin receptor. Once bound, thrombin undergoes a conformational change at its active site that coverts it from a procoagulant to a potent activator of protein C. The activation of protein C occurs on the endothelial cell surface where the zymogen binds to EPCR. Activated protein C, together with its cofactor protein S (PS), acts as an anticoagulant by proteolytically degrading and inactivating activated factor V or activated factor VIII on the platelet surface. Vi = inactivated factor V; VIIIi = inactivated factor VIII. See the legend of Figure 2 for abbreviations not used in the text.

FIGURE 5. Anticoagulant and antifibrinolytic activities of the thrombin/thrombomodulin complex. Once bound to thrombomodulin, thrombin attenuates coagulation by activating protein C. Activated protein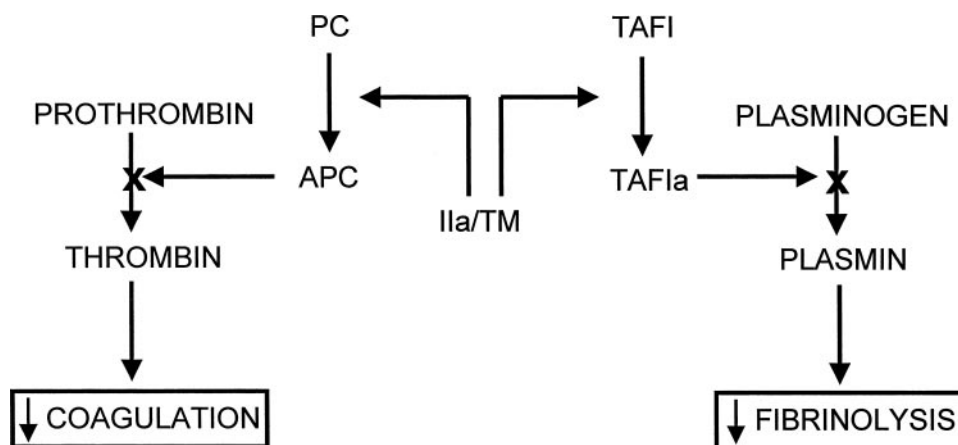 C then down-regulates thrombin generation by inactivating activated factor V and activated factor VIII. Fibrinolysis is attenuated because the thrombin bound to thrombomodulin also activates TAFI. Once activated, TAFIa down-regulates fibrinolysis by removing carboxy-terminal lysine residues from degraded fibrin, thereby removing the binding sites for plasminogen and plasmin. With reduced plasmin binding, fibrinolysis is retarded. See the legends of Figures 2 and 4 for abbreviations not used in the text.

hibits plasmin.[22] Although α_2-antiplasmin rapidly complexes and inactivates free plasmin, fibrin-bound plasmin is relatively protected from inactivation so that fibrinolysis can occur despite physiologic levels of this inhibitor.[22]

A procarboxypeptidase B that serves as a link between coagulation and fibrinolysis has been identified in plasma (Fig 5).[27] Activated by the thrombin/thrombomodulin complex, this enzyme, known as *thrombin activatable fibrinolysis inhibitor* (TAFI), attenuates fibrinolysis by cleaving carboxyl-terminal lysine residues from fibrin.[27] The removal of these lysine residues decreases plasminogen and plasmin binding to fibrin, thereby retarding the lytic process.

3.0 Pathways for Development of New Anticoagulants

A better understanding of the molecular mechanisms underlying blood coagulation, recombinant DNA technology, isolation and characterization of anticoagulant proteins from blood-sucking organisms, and improvements in structure-based drug design have accelerated the pace of drug discovery. With these advances, we now have an array of new anticoagulants that target specific clotting enzymes or steps in coagulation. As new drug targets are identified and potent inhibitors are developed, the validity of these targets requires testing in well-designed clinical trials (Table 1). For initial evaluation, many of the new anticoagulants have been tested as thromboprophylaxis in high-risk orthopedic patients. This approach has been chosen because the rates of venographically documented DVT remain high in this patient population despite currently accepted thromboprophylaxis regimens, and regulatory agencies are willing to accept this end point as a surrogate for clinically important venous thromboembolism. Consequently, antithrombotic efficacy can be estab-

lished in relatively small numbers of patients. In contrast, demonstrating efficacy in acute coronary syndromes requires a much larger sample size. As a result, studies for arterial indications are often delayed until the utility of the drug has been established in the prevention and treatment of venous thromboembolism.

Recombinant forms of TFPI and activated protein C, which are naturally occurring anticoagulants, have been evaluated in patients with severe sepsis.[28,29] This condition was selected because microvascular thrombosis is a hallmark of sepsis, highlighting linkages between coagulation and inflammation. Microvascular thrombosis causes end-organ ischemia, thereby amplifying the inflammatory response.[30] Because the uncontrolled activation of coagulation in patients with severe sepsis overwhelms natural anticoagulant pathways, it is logical to evaluate the efficacy of replacement therapy in this setting.

3.1 Inhibitors of initiation of coagulation

Drugs that target the factor VIIa/tissue factor complex inhibit the initiation of coagulation. Agents in this category that have reached phase II clinical testing include recombinant TFPI, recombinant nematode anticoagulant peptide (NAPc2), and active site-blocked factor VIIa (factor VIIai).

3.1.1 TFPI

A recombinant form of TFPI (tifacogin; Chiron Corporation; Emeryville, CA) has been evaluated in patients with sepsis. In a phase II trial,[28] 210 such patients were randomized to receive one of two doses of tifacogin by continuous infusion (25 or 50 μg/kg/h) or placebo for 4 days. Compared with placebo, tifacogin produced a 20% relative reduction in all-cause mortality at 28 days. Major bleeding occurred in 9% of patients treated with tifacogin,

Table 1—*Status of New Anticoagulant Drugs**

Target	Drug	Route	Status	Indication
VII/TF	TFPI	IV	Phase III	Sepsis
	NAPc2	Subcutaneous	Phase II	Thromboprophylaxis in patients undergoing elective knee arthroplasty; adjunctive therapy in patients with unstable angina or non-ST-MI
Va/VIIIa	APC	IV	Approved	Sepsis
	PC	IV	Phase II	Meningococcemia
	sTM	Subcutaneous	Phase II	Thromboprophylaxis in patients undergoing elective hip arthroplasty
Xa	Fondaparinux	Subcutaneous	Approved	Thromboprophylaxis for major orthopedic surgery
			Phase III	Treatment of venous thrombosis; thromboprophylaxis in general medical and surgical patients
	Idraparinux	Subcutaneous	Phase II	Alternative to warfarin for secondary prophylaxis in patients with venous thromboembolism
	DX-9065a	IV	Phase II	Coronary artery disease
	DPC 906	Oral	Phase II	Thromboprophylaxis in patients undergoing elective knee arthroplasty
IIa	Hirudin	IV	Approved	Heparin-induced thrombocytopenia
	Bivalirudin	IV	Approved	Alternative to heparin in patients undergoing percutaneous coronary interventions
	Argatroban	IV	Approved	Heparin-induced thrombocytopenia or persons at risk or with HIT undergoing PCI
	Ximelagatran	Oral	Phase III	Thromboprophylaxis in patients undergoing elective hip or knee arthroplasty; initial treatment of venous thrombosis; prevention of recurrent venous thromboembolism
			Phase III	Alternative to warfarin in patients with atrial fibrillation
				Myocardial Infarction
				Extended prevention of recurrent venous thromboembolism
			Phase II	Acute coronary syndromes

*APC = activated protein C; sTM = soluble thrombomodulin; PC = protein C; TF = tissue factor; VII = factor VII; Va = activated factor V; VIIIa = activated factor VIII; IIa = thrombin.

and in 6% of those treated with placebo, a difference that was not significant. Building on these results, a phase III trial[31] compared tifacogin with placebo in 1,754 patients with severe sepsis. The primary end point, all-cause mortality rate at 28 days, was similar in both groups (tifacogin group, 34.2%; placebo group, 33.9%), and the rate of bleeding was significantly higher with tifacogin than with placebo (6.5% and 4.8%, respectively). With these results, further development of tifacogin for sepsis has been halted.

3.1.2 NAPc2

An 85-amino acid polypeptide that was originally isolated from the canine hookworm, *Ancylostoma caninum*,[32] NAPc2 can be expressed in yeast. NAPc2 binds to a noncatalytic site on factor X or factor Xa.[33] Once bound to factor Xa, the NAPc2/factor Xa complex inhibits factor VIIa bound to tissue factor. Because it binds to factor X with high affinity, NAPc2 has a half-life of approximately 50 h after subcutaneous injection.

Initial clinical trials with NAPc2 focused on venous thromboprophylaxis. In a phase II dose-finding study,[34] 293 patients undergoing elective knee arthroplasty were given subcutaneous NAPc2 on the day of surgery and every second day thereafter to a maximum of four doses. The best results were observed with an NAPc2 dose of 3.0 μg/kg administered 1 h after surgery. With this dose, the overall rate of venographically detected DVT in the operated leg was 12%, while the rate of proximal DVT was 1%. Major bleeding occurred in 2% of these patients. When compared with historical control subjects,[5] the efficacy and safety of NAPc2 are similar to those with low-molecular-weight heparin. However, prospective randomized trials are needed to confirm these findings.

Current studies with NAPc2 are focusing on arterial thrombosis. In a series of phase II clinical trials, NAPc2 is being evaluated in patients with unstable angina or non-ST-elevation MI and in those undergoing percutaneous coronary interventions. For each of these indications, NAPc2 is being compared with placebo as an adjunct to antiplatelet therapy (with aspirin, clopidogrel, and, in some cases, a glycoprotein (GP) IIb/IIIa antagonist and an antithrombin [either heparin or low-molecular-weight heparin]).

3.1.3 Factor VIIai

By competing with factor VIIa for tissue factor binding, factor VIIai attenuates the initiation of coagulation by the

factor VIIa/tissue factor complex. Based on promising results in animal models of thrombosis,[35,36] treatment with factor VIIai, in doses ranging from 50 to 400 μg/kg with or without adjunctive heparin, was compared with treatment with heparin alone in 491 patients undergoing elective percutaneous coronary interventions.[37] Compared with heparin therapy alone, factor VIIai therapy, with or without adjunctive heparin, produced no significant reduction in the primary end point, a composite of death, MI, the need for urgent revascularization, abrupt vessel closure, or bailout use of GPIIb/IIIa antagonists or heparin at day 7 or at hospital discharge. The rates of major bleeding were similar with therapy with factor VIIai and heparin. Because of these disappointing results, factor VIIai has not been developed further.

3.2 Inhibitors of propagation of coagulation

Drugs that block factor IXa, factor Xa or their respective cofactors, factor VIIIa and factor Va, inhibit the propagation of coagulation. Factor IXa inhibitors have yet to reach phase II clinical testing and will not be discussed. New factor Xa inhibitors include agents that block factor Xa indirectly or directly. Indirect inhibitors act by catalyzing factor Xa inhibition by antithrombin. In contrast, direct factor Xa inhibitors bind directly to the active site of factor Xa, thereby blocking its interaction with its substrates. Unlike the heparin/antithrombin complex, direct factor Xa inhibitors not only inhibit free factor Xa, but also inactivate factor Xa bound to platelets within the prothrombinase complex.[38,39] This property may endow these agents with an advantage over indirect factor Xa inhibitors.

Fondaparinux and idraparinux are two new parenteral indirect factor Xa inhibitors. A parenteral and an orally active direct factor Xa inhibitor, DX9065a and DPC 906, respectively, are currently undergoing phase II clinical testing. The inhibition of factors Va and VIIIa is effected by activated protein C. From a therapeutic standpoint, this can be achieved by directly administering recombinant activated protein C or its precursor, protein C. Recombinant soluble thrombomodulin, another means of generating activated protein C, also is under evaluation.

3.2.1 Fondaparinux

A synthetic analog of the antithrombin-binding pentasaccharide sequence found in heparin and low-molecular-weight heparin, fondaparinux binds antithrombin and enhances its reactivity with factor Xa.[40] Because it is too short to bridge antithrombin to thrombin, fondaparinux has no activity against thrombin.

In plasma, fondaparinux binds to antithrombin, and there is no detectable binding to other plasma proteins. With excellent bioavailability after subcutaneous injection and a plasma half-life of about 17 h, fondaparinux can be administered subcutaneously once daily. The drug is excreted unchanged in the urine. Consequently, dose adjustments are necessary in patients with renal insufficiency, and fondaparinux should not be used in those with renal failure.

Fondaparinux does not bind to platelets or platelet

factor 4 (PF4). Because it does not induce the formation of heparin/PF4 complexes that serve as the antigenic target for the antibodies that cause heparin-induced thrombocytopenia, heparin-induced thrombocytopenia is unlikely to occur with fondaparinux. However, fondaparinux also fails to interact with protamine sulfate, the antidote for heparin. If uncontrolled bleeding occurs with fondaparinux, a procoagulant such as recombinant factor VIIa might be effective.[41] However, recombinant factor VIIa is not available in all hospitals, and the drug is expensive and can cause thrombotic complications.

Fondaparinux has been evaluated for the prevention and treatment of venous thromboembolism, and for the treatment of arterial thrombosis. The results of the venous thrombosis prevention trials are described elsewhere in this supplement and will not be described in detail. Instead, the focus will be on the evaluation of fondaparinux for the treatment of venous or arterial thrombosis.

Venous thromboprophylaxis. Fondaparinux has been evaluated for thromboprophylaxis in patients undergoing major orthopedic surgery, and in general medical and surgical patients. Based on four large phase III trials comparing fondaparinux with enoxaparin for thromboprophylaxis in patients undergoing surgery for hip fracture or elective hip or knee arthroplasty, fondaparinux has been licensed for this indication.[42–45] In these trials, fondaparinux was found to reduce the risk of venous thromboembolism by approximately 55% compared with enoxaparin. Major bleeding occurred more frequently in the fondaparinux-treated group (p = 0.008), but the incidence of bleeding leading to death or reoperation, or occurring in a critical organ was not significantly different between the two groups. It is possible that the increase in major bleeding with fondaparinux relative to enoxaparin reflects the fact that fondaparinux therapy was started 6 h after surgery, whereas enoxaparin therapy was initiated 12 to 24 h after surgery, with or without a dose 12 h prior to surgery. It also is unclear whether the asymmetry in the timing of the initiation of prophylaxis accounts for the superior efficacy of fondaparinux relative to enoxaparin.

A recent phase III trial (Pentasaccharide in Hip-Fracture Surgery Plus)[46] evaluated the efficacy of extended fondaparinux thromboprophylaxis in 656 patients undergoing surgery for hip fracture. All patients received 2.5 mg fondaparinux subcutaneously once daily for 7 days. Patients then were randomized to receive fondaparinux on a continuing basis or to receive placebo for an additional 3 weeks. Based on the results of routine venography performed at 1 month, fondaparinux treatment decreased the rate of venous thrombosis from 35 to 1.4%, a highly significant reduction (p < 0.001). More importantly, the rate of symptomatic venous thromboembolic events also was reduced from 2.7 to 0.3% with extended fondaparinux treatment (p = 0.021). This trial adds to a mounting body of evidence indicating that patients remain at risk for several weeks after major orthopedic surgery and that extended anticoagulant prophylaxis can reduce this risk.[47–50]

Fondaparinux also has been evaluated for thromboprophylaxis in general medical and general surgical patients.

In a blinded, placebo-controlled, phase III trial,[51] 849 medical patients who were ≥ 65 years of age were randomly assigned to receive subcutaneous fondaparinux (2.5 mg once daily) or placebo for 6 to 14 days. The primary end point, a composite of venographically diagnosed DVT, symptomatic DVT, and nonfatal and fatal PE at day 15 occurred in 5.6% of patients randomized to receive fondaparinux, and in 10.5% of those randomized to receive placebo (p = 0.03). Major bleeding while receiving therapy was infrequent and occurred in 0.2% of patients in both groups.

In a blinded, phase III trial,[52] 2,297 patients undergoing abdominal surgery were randomly assigned to receive subcutaneous fondaparinux (2.5 mg once daily) or dalteparin (2,500 U preoperatively and 2,500 U postoperatively the evening of surgery, and 5,000 U qd thereafter) for 5 to 9 days. Fondaparinux treatment was started 6 h after surgery. The primary end point, a composite of venographically documented DVT, symptomatic DVT, and nonfatal and fatal PE at postoperative day 30, occurred in 4.6% of those patients randomized to receive fondaparinux, and in 6.1% of those randomized to receive dalteparin (p = 0.14). Symptomatic venous thromboembolism occurred in 0.4% of those given fondaparinux and in 0.3% of those given dalteparin, whereas major bleeding occurred in 3.4% and 2.4%, respectively. The differences were not statistically significant. In the subgroup of patients with cancer, fondaparinux therapy reduced the incidence of the composite end point from 7.7 to 4.6% (p = 0.02).

Treatment of venous thromboembolism. Fondaparinux also has been evaluated for the initial treatment of established venous thromboembolism in two phase III clinical trials. In the MATISSE DVT trial,[53] 2,205 patients with DVT were randomized, in a blinded fashion, to receive either fondaparinux (weight adjusted < 50 kg 5.0 mg subcutaneously qd; 50 to 100 kg 7.5 mg subcutaneously qd, and > 100 kg 10 mg subcutaneously qd) or enoxaparin (1 mg/kg subcutaneously twice daily) for 5 days followed by a minimum 3-month course of treatment with an oral vitamin K antagonist. At 3 months, the rates of recurrent symptomatic venous thromboembolism with fondaparinux or enoxaparin were 3.9% and 4.1%, respectively, whereas major bleeding rates were 1.1% and 1.2%, respectively. None of these differences were statistically significant.

In the open-label MATISSE PE trial,[54] 2,213 patients with PE were randomized to receive either fondaparinux (weight adjusted < 50 kg 5.0 mg subcutaneously qd; 50 to 100 kg 7.5 mg subcutaneously qd, and > 100 kg 10 mg subcutaneously qd) or unfractionated heparin (by continuous infusion) for 5 days followed by a minimum 3-month course of therapy with an oral vitamin K antagonist. At 3 months, the rates of recurrent symptomatic venous thromboembolism occurring after therapy with fondaparinux or unfractionated heparin were 3.8% and 5.0%, respectively, whereas major bleeding rates were 1.3% and 1.1%, respectively. Based on these two trials, fondaparinux appears to be at least as effective and safe as low-molecular-weight heparin or unfractionated heparin for the initial treatment of venous thromboembolism.

Treatment of acute coronary syndromes. On the arterial side, fondaparinux has been evaluated for the treatment of acute coronary syndromes. The Synthetic Pentasaccharide as an Adjunct to Fibrinolysis in ST-Elevation Acute Myocardial Infarction trial[55] was an open-label, phase II trial that randomized 326 patients with evolving ST-elevation MI to receive either fondaparinux, in various doses, or unfractionated heparin as adjuncts to therapy with alteplase and aspirin. Using patency of the infarct-related artery as the primary end point, grade 3 Thrombolysis in Myocardial Infarction (TIMI) flow at 90 min ranged from 60 to 68% and was similar in all treatment groups. Bleeding rates also were similar after therapy with fondaparinux and heparin.

The phase II Pentasaccharide in Unstable Angina trial[56] randomized 1,134 patients with unstable angina or non-ST-elevation myocardial infarction to subcutaneous fondaparinux (in once-daily doses ranging from 2.5 to 12 mg) or enoxaparin (1 mg/kg twice daily). Overall, the primary outcome, a composite of death, MI, or recurrent angina at day 9, occurred in 37% of those receiving any dose of fondaparinux and in 40.2% of patients treated with enoxaparin. There was no evidence of a dose response with fondaparinux therapy. In fact, the lowest dose appeared to produce the best results. Bleeding was similar in all treatment groups.

Summary. Based on these phase II results, phase III trials with fondaparinux are planned in patients with ST-elevation MI and non-ST-elevation MI. However, the lack of a dose response with fondaparinux therapy in the phase II trials makes it difficult to identify the optimal dose. Consequently, additional dose-finding studies may be necessary before undertaking a large-scale phase III clinical trial program.

3.1.2 Idraparinux

A more highly sulfated derivative of fondaparinux, idraparinux binds antithrombin with such high affinity that its plasma half-life of 130 h is similar to that of antithrombin.[57] Because of its long half-life, idraparinux can be given subcutaneously on a once-weekly basis. In a phase II trial,[58] idraparinux therapy was compared with warfarin therapy in 659 patients with proximal DVT. After 5 to 7 days of initial treatment with enoxaparin, patients were randomized to receive once-weekly subcutaneous doses of idraparinux (2.5, 5.0, 7.5, or 10 mg) or warfarin for 12 weeks. The primary end point, changes in compression ultrasound and perfusion lung scan findings, was similar in all idraparinux groups and did not differ from that in the warfarin group. There was a clear dose response for major bleeding in patients who had received idraparinux with an unacceptably high frequency in those receiving the 10-mg dose. Two patients, both of whom received 5 mg idraparinux once weekly, experienced a fatal bleeding incident. Patients who received the lowest dose of idraparinux had less bleeding than those randomized to receive warfarin (p = 0.029). Based on these results, a once-weekly 2.5-mg dose of idraparinux will be used in phase III clinical trials.

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3.1.3 DX-9065a

A nonpeptidic arginine derivative, DX-9065a binds reversibly to the active site of factor Xa. Administered as a continuous IV infusion, a small phase II trial[59] compared four different doses of DX-9065a with placebo in 73 stable patients with coronary artery disease to assess safety. There were no major bleeding incidents among patients receiving DX-9065a. Additional phase II studies are comparing DX-9065a therapy with heparin therapy in patients undergoing percutaneous coronary interventions.

3.1.4 DPC 906

An orally active agent, DPC 906 must be administered twice daily. In a phase II dose-finding study, DPC 906 was compared with enoxaparin in patients undergoing knee arthroplasty. This study was stopped prematurely, but the results have yet to be published.

3.1.5 Activated protein C

Recombinant activated protein C, drotrecogin alfa (activated), was compared with placebo in 1,690 patients with severe sepsis.[29] When given as an infusion of 24 μg/kg/h over > 96 h, activated protein C produced a 19% reduction in mortality at 28 days (reduction, 30.8 to 24.7%; p = 0.005). The rate of major bleeding was higher with activated protein C therapy than with placebo (3.5% and 2%, respectively; p = 0.06). Based on these results and economic analyses supporting the benefits of recombinant activated protein C,[60] this agent has been licensed in North America for the treatment of patients with severe sepsis.

3.1.6 Protein C

Although promising results with protein C concentrates have been reported in patients with meningococcemia,[61,62] additional studies are needed. For theoretical reasons, activated protein C may be a better choice than protein C in patients with severe sepsis because inflammatory cytokines down-regulate thrombomodulin expression on the endothelial surface. This phenomenon may explain the results of immunohistochemical analyses of skin biopsy specimens from patients with meningococcemia, which revealed reduced thrombomodulin staining.[63]

3.1.7 Soluble thrombomodulin

A recombinant analog of the extracellular domain of thrombomodulin, soluble thrombomodulin binds thrombin and induces a conformation change in the active site of the enzyme that converts it into a potent activator of protein C. In an open-label, dose-escalation study,[64] soluble thrombomodulin attenuated coagulation abnormalities in patients with disseminated intravascular coagulation. Soluble thrombomodulin has recently been evaluated in a phase II dose-ranging study[65] in patients undergoing elective hip arthroplasty. Patients were given thrombomodulin subcutaneously (dose, 0.3 or 0.45 mg/kg) 2 to 4 h after surgery. Those patients receiving the lower dose of thrombomodulin received a second injection 5 days later. The primary end point, a composite of venographically detected DVT and symptomatic venous thromboembolism, occurred in 4.3% of the 94 patients who received the lower dose of soluble thrombomodulin and in none of the 99 patients receiving the higher dose. Major bleeding occurred in 1.6% and 5.7%, respectively, of patients receiving the low dose or high dose of soluble thrombomodulin. Phase III clinical trials are necessary to compare soluble thrombomodulin with other forms of thromboprophylaxis, such as low-molecular-weight heparin or fondaparinux.

3.2 Inhibitors of fibrin formation

Thrombin, the enzyme that converts fibrinogen to fibrin, can be inhibited indirectly or directly. Indirect thrombin inhibitors act by catalyzing antithrombin and/or heparin cofactor II. In contrast, direct inhibitors bind directly to thrombin and block its interaction with substrates. All of the new agents that block fibrin formation are direct thrombin inhibitors.

Direct thrombin inhibitors have properties that give them potential mechanistic advantages over indirect thrombin inhibitors, such as heparin.[66,67] First, because direct thrombin inhibitors do not bind to plasma proteins, they produce a more predictable anticoagulant response. Second, unlike heparin, direct thrombin inhibitors do not bind to PF4. Consequently, the anticoagulant activity of direct thrombin inhibitors is unaffected by the large quantities of PF4 released in the vicinity of platelet-rich thrombi. Finally, direct thrombin inhibitors inactivate fibrin-bound thrombin, as well as fluid-phase thrombin.[66,67]

Three parenteral direct thrombin inhibitors (ie, hirudin, argatroban, and bivalirudin) have been licensed in North America for limited indications. Hirudin and argatroban are approved for the treatment of patients with heparin-induced thrombocytopenia, whereas bivalirudin is licensed as an alternative to heparin in patients undergoing percutaneous coronary interventions. Ximelagatran, a prodrug of melagatran, is the first orally available direct thrombin inhibitor.

3.2.2 Hirudin

A 65-amino acid polypeptide originally isolated from the salivary glands of the medicinal leech *Hirudo medicinalis*,[68,69] hirudin is now available in recombinant form. Hirudin inhibits thrombin in a bivalent fashion. Its globular amino-terminal domain interacts with the active site of thrombin, whereas its anionic carboxy-terminal tail binds to exosite 1 on thrombin, the substrate recognition site.[68] The hirudin/thrombin complex is essentially irreversible, which is a potential drawback because there is no specific antidote.

The plasma half-life of hirudin is 60 min after IV injection, and 120 min after subcutaneous injection.[70] Hirudin is cleared via the kidneys and should not be used in patients with renal insufficiency.[70] The anticoagulant effect of hirudin can be monitored using the activated partial thromboplastin time (APTT).

Recombinant hirudin (lepirudin) is licensed for the treatment of arterial or venous thrombosis complicating heparin-induced thrombocytopenia, and as an alternative for heparin for cardiopulmonary bypass surgery in these patients. Hirudin has been evaluated in acute coronary syndromes and, to a lesser extent, for the prevention and treatment of venous thrombosis. The results for each of these indications will be discussed separately.

Unstable angina. The largest phase II study to compare hirudin with heparin, the Organization to Assess Strategies for Ischemic Syndromes (OASIS)-1 pilot trial,[71] randomized 909 patients with unstable angina or non-ST-elevation MI to receive a 72-h infusion of hirudin, in either a low dose or medium dose, or to heparin. Doses of hirudin and heparin were adjusted to maintain the APTT between 60 and 100 s. Compared with heparin, hirudin produced a promising reduction in the primary outcome, a composite of cardiovascular death, MI, or refractory angina at 7 days (odds ratio [OR] 0.57; 95% confidence interval [CI], 0.32 to 1.02) and a significant reduction in the secondary outcome, a composite of death, MI, or refractory or severe angina requiring revascularization at 7 days (OR, 0.49; 95% CI, 0.27 to 0.86). Major bleeding occurred in about 1% of patients in both treatment groups and was not significantly higher in those who received hirudin (OR, 0.86; 95% CI, 0.23 to 3.19). Minor bleeding, however, was more frequent in patients given a medium or low dose of hirudin than it was in those treated with heparin (21.3%, 16.2%, and 10.5%, respectively), and the differences were statistically significant (medium-dose or low-dose hirudin, p = 0.033; heparin, p = 0.001).

The results of the OASIS-1 trial prompted the OASIS-2 trial,[72] a phase III trial that randomized 10,141 patients with unstable angina or non-ST-elevation MI to receive a 72-h infusion of medium-dose hirudin or heparin. During treatment, hirudin produced a significant reduction in the composite end point of death or MI compared with heparin (2.0% and 2.6%, respectively; OR, 0.76, 95% CI, 0.59–0.99). Although the primary outcomes, a composite of death or MI at 7 days (3.6% and 4.2%, respectively; OR, 0.84; 95% CI, 0.69 to 1.02) and 35 days (6.8% and 7.7%, respectively; OR, 0.87; 95% CI, 0.75 to 1.01) were not significantly different between the two groups, the absolute risk reduction in death or MI produced by hirudin during the 72-h treatment period was maintained at 7 and 35 days. Major bleeding occurred more frequently with hirudin therapy than with heparin therapy (1.2% and 0.7%, respectively; OR, 1.73; 95% CI, 1.13 to 2.63), but the rates of life-threatening bleeding were similar (0.4% in both groups).

When the results of the OASIS-1 and OASIS-2 trials are combined, hirudin therapy produces a significant reduction in the composite outcome of death or MI at 35 days compared with heparin (6.7% and 7.7%, respectively; OR, 0.86; 95% CI, 0.74 to 0.99). Thus, the early treatment benefits of hirudin that were observed in both trials were maintained, at least for 1 month. Despite these results, however, hirudin has not been licensed for the treatment of acute coronary syndromes, reflecting the fact that, compared with heparin, hirudin failed to show a significant

reduction in the primary end point in the OASIS-2 trial and produced an increase in major bleeding.

Adjunct to thrombolytic therapy. Hirudin was compared with heparin as adjuncts to thrombolytic therapy in three trials. The TIMI-9A trial[73] and the Hirudin for Improvement of Thrombolysis (HIT)-III trial[74] only enrolled patients with acute MI, whereas the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-IIA trial[75] also included patients with unstable angina and those with MI who were ineligible for thrombolytic therapy. The doses of hirudin given in the TIMI-9A study[73] and the GUSTO-IIA study[74] were higher than that used in the OASIS-2 trial,[72] and the TIMI-9A trial[73] and GUSTO-IIA trial[74] also used higher doses of heparin than that used in the GUSTO-I study.[76] Although, the HIT-III trial[74] utilized a lower dose hirudin regimen, one that was identical to that used in the OASIS-2 study,[72] the heparin doses administered in the HIT-III study[74] also were higher than that used in the GUSTO-I study.[76]

All three initial phase III trials were stopped prematurely because of unacceptably high rates of major hemorrhage. The rate of major bleeding was higher with hirudin therapy than with heparin therapy in the TIMI-9A trial,[73] and there was a trend for more intracranial bleeding with hirudin in the GUSTO-IIA trial[74] and the HIT-III trial.[75,76] Consequently, the GUSTO-IIA trial[75] and the TIMI-9A trial[73] were restarted as the GUSTO-IIB trial[77,78] and the TIMI-9B trial[79] using doses of hirudin that were lower than that used in the OASIS-2 trial.[72] The hirudin dose was adjusted to achieve a target APTT of 55 to 85 s in the TIMI-9B trial,[79] and 60 to 85 s in the GUSTO-IIB trial.[77,78] In addition, the dose of heparin also was reduced to more closely match that used in the GUSTO-I trial.[76] With lower doses of anticoagulants, both trials completed their planned enrollment.

In the GUSTO-IIB trial,[77] hirudin therapy produced a modest reduction in the primary outcome, a composite of death or MI at 30 days, compared with heparin therapy (OR, 0.89; 95% CI, 0.79 to 1.00). During the initial 24 h of treatment, hirudin therapy produced a significant reduction in death or MI compared with heparin therapy (1.3% and 2.1%, respectively; OR, 0.61, 95% CI, 0.46 to 0.81). A retrospective subgroup analysis[78] has suggested that when used as an adjunct to streptokinase therapy hirudin produced a greater reduction in death or MI at 30 days than did heparin therapy (9.1% and 14.9%, respectively; OR, 0.57; 95% CI; 0.38 to 0.87). In contrast, hirudin therapy was not superior to heparin therapy in patients receiving tPA.

Hirudin therapy was no better than heparin therapy in the TIMI-9B trial.[79] Thus, the primary outcome, a composite of death, MI, cardiac failure, or cardiogenic shock at 30 days, was similar in the hirudin and heparin groups (OR, 1.09; 95% CI, 0.88 to 1.36), as was the composite of death or MI at 30 days (OR, 1.02; 95% CI, 0.80 to 1.31). There was a trend for a reduction in nonfatal MI with hirudin therapy during hospitalization (OR, 0.65; 95% CI, 0.42 to 1.01) and at 30 days (OR, 0.81; 95% CI, 0.56 to 1.18). The rates of major bleeding and intracranial bleed-

ing were similar with hirudin and heparin therapy in both the TIMI-9B trial[75] and the GUSTO-IIB trial.[77]

Taken together, the TIMI-9B trial[75] and the GUSTO-IIB trial[77] suggest that hirudin therapy is at least as effective as heparin therapy when used as an adjunct to thrombolytic therapy. When the results of these trials are pooled with those of the OASIS-2 study,[72] hirudin therapy produced a 10% reduction in the risk of death or MI at 30 to 35 days compared with heparin therapy. However, the lack of a clear benefit of hirudin over heparin at 30 days in the GUSTO-IIB trial[77] and TIMI-9B trial[75] limits the strength of this conclusion in patients with acute MI. Given the lack of a clear benefit of hirudin over heparin as adjuncts to thrombolytic therapy, hirudin has not been licensed for this indication.

Coronary angioplasty. Hirudin therapy was compared with heparin therapy for the prevention of restenosis after percutaneous coronary angioplasty in the Hirudin in a European Trial Versus Heparin in the Prevention of Restinosis After PTCA (HELVETICA) study.[80] A total of 1,141 patients who were scheduled for coronary angioplasty were randomized to receive either hirudin, administered as a bolus dose plus infusion for 24 h followed by a subcutaneous hirudin injection or placebo for an additional 72 h, or heparin, administered as a bolus dose plus infusion for 24 h followed by subcutaneous placebo injections for 72 h. An additional bolus of placebo (in the hirudin group) or heparin (in those randomized to receive heparin) could be given if the procedure lasted longer than 1 h, but no subsequent dose adjustments were allowed. The primary outcome was event-free survival at 30 weeks, which was defined as the absence of death, MI, coronary artery bypass grafting, or bailout angioplasty with or without coronary stenting at the previous angioplasty site.

At 7 months, event-free survival was similar in those receiving heparin, IV hirudin, or IV hirudin followed by subcutaneous hirudin (67.3%, 63.5%, and 68.0%, respectively). Likewise, on repeat angiography at 6 months, there was no significant differences in the mean luminal diameter of the dilated vessel among the three groups. Compared with heparin therapy, however, hirudin therapy produced a significant reduction in the primary composite outcome at 96 h (OR, 0.61; 95% CI, 0.41 to 0.90) that was preserved at 30 days. The time-to-event curves converged thereafter, possibly reflecting the development of restenosis in both groups. No excess bleeding was seen with hirudin.

Venous thromboprophylaxis. Hirudin has been compared with unfractionated heparin and low-molecular-weight heparin for thromboprophylaxis in patients undergoing elective hip arthroplasty. In a randomized blinded multicenter phase III trial, Eriksson and colleagues[81] compared therapy with subcutaneous unfractionated heparin (5,000 U three times daily) with that using subcutaneous hirudin (15 mg twice daily) in 445 patients undergoing total hip replacement. Hirudin therapy was started preoperatively and was continued for 8 to 11 days. The incidence of venographically detected proximal and total DVT was significantly lower in the hirudin group than in the heparin group. Four patients in the heparin group and none in the hirudin group experienced a PE.

In the largest phase III thromboprophylaxis study performed with hirudin to date, Eriksson and colleagues[82] randomized 2,069 patients undergoing elective hip arthroplasty to receive subcutaneous hirudin therapy (15 mg twice daily starting 30 min prior to surgery) or subcutaneous enoxaparin therapy (40 mg once daily starting 12 h prior to surgery). Treatment was administered for 8 to 12 days, and DVT was verified by bilateral venography, which was performed at the end of the treatment period or earlier if symptomatic venous thromboembolism was suspected. The rate of venographically detected proximal DVT was significantly lower in patients treated with hirudin than in those treated with enoxaparin (4.5% and 7.5%, respectively; p = 0.01), as was the overall rate of DVT (18.4% and 25.5%, respectively; p = 0.001) based on data from 1,587 analyzed patients. The rates of major bleeding were similar in the two treatment groups.

Based on these two studies, hirudin therapy appears to be more effective than therapy with heparin or low-molecular-weight heparin for thromboprophylaxis after hip arthroplasty. Despite these data, however, hirudin has not been approved for this indication.

Treatment of venous thromboembolism. In a phase II trial, Schiele et al[83] randomized patients with DVT to receive one of three doses of subcutaneous hirudin (ie, 0.75, 1.25, or 2.0 mg/kg twice daily) or unfractionated heparin administered by continuous IV infusion. All patients underwent venography and ventilation/perfusion lung scanning on days 1 and 5 so that changes in these tests could be evaluated. When the results with the two higher hirudin doses were combined, thrombus extension occurred more frequently in patients treated with unfractionated heparin than in those treated with hirudin (10% and 3%, respectively). In addition, new perfusion abnormalities seen on lung scans were more frequent in the heparin group (26%) than the hirudin groups (< 10% in each group). Major bleeding was seen only in those patients receiving the highest dose of hirudin and in those receiving heparin, occurring in 3% of patients in both groups. Despite these promising early results, no further work in this area has been performed.

Summary. Hirudin is at least as effective as heparin in treating patients with unstable angina, non-ST-elevation MI, and ST-elevation MI, and is more effective than low-molecular-weight heparin and unfractionated heparin for the prevention of venous thrombosis in patients undergoing elective hip arthroplasty. Because of its narrow therapeutic window and the associated bleeding risk, however, it is unlikely that hirudin will ever be approved for the treatment of acute coronary syndromes. Although hirudin appears promising for the prevention and treatment of venous thrombosis, the clinical development of the drug for these indications has not been pursued.

3.2.2 Bivalirudin

A 20-amino acid synthetic polypeptide, bivalirudin is an analog of hirudin.[84] The amino-terminal D-Phe-Pro-Arg-Pro sequence, which binds to the active site of thrombin,

is connected via four Gly residues to a carboxy-terminal dodecapeptide that interacts with exosite 1 on thrombin.[85] Like hirudin, bivalirudin forms a 1:1 stoichiometric complex with thrombin. However, once bound, thrombin cleaves the Pro-Arg bond within the amino terminal of bivalirudin, thereby allowing the recovery of thrombin activity.[86] This phenomenon may render bivalirudin safer than hirudin. Bivalirudin has a plasma half-life of 25 min after IV injection,[87] and only a fraction is excreted via the kidneys.[88] Bivalirudin has been evaluated in patients undergoing percutaneous coronary interventions and as an adjunct to streptokinase therapy in patients with acute MI.

Coronary angioplasty. Bivalirudin is licensed as an alternative therapy to heparin in patients undergoing percutaneous coronary angioplasty. It was approved for this indication based on the results of a phase III study[89] that compared bivalirudin with heparin in 4,098 patients undergoing coronary angioplasty for unstable or postinfarction angina. The primary end point, a composite of in-hospital death, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin, occurred in a similar percentage of patients in the two treatment groups (bivalirudin group, 11.4%; heparin group, 12.2%). However, in the prospectively stratified, high-risk subgroup of 704 patients with postinfarction angina, bivalirudin therapy significantly reduced the incidence of the primary outcome compared with heparin therapy (9.1% and 14.2%, respectively; p = 0.04). Overall, the rate of major bleeding was significantly lower with bivalirudin therapy than with heparin therapy (3.8% and 9.8%, respectively; p < 0.001).

In 2001, the results of this trial[90] were reanalyzed according to intention-to-treat principles and using a more contemporary definition of MI. The reanalysis demonstrated that, compared with heparin therapy, bivalirudin therapy significantly reduced the combined end point of death, MI, or repeat revascularization at 7 days from 7.9 to 6.2% (p = 0.04), a difference that persisted at 90 days. As in the original report, the rate of major bleeding was significantly lower with bivalirudin therapy than with heparin therapy (3.5% and 9.3%, respectively; p < 0.001).

More contemporary studies have evaluated the utility of bivalirudin in patients undergoing coronary stenting. The Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial[91] was a pilot study performed in 268 patients undergoing percutaneous coronary intervention. In three sequential phases, patients received (1) bivalirudin (1.0 mg/kg bolus followed by an infusion of 2.5 mg/kg/h) plus abciximab, (2) bivalirudin (0.5 mg/kg bolus followed by an infusion of 1.75 mg/kg/h) plus provisional abciximab, (3) bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h) plus provisional abciximab, or (4) the control regimen. For each phase, the control regimen consisted of low-dose, weight-adjusted heparin plus abciximab. The rates of the primary end point, a composite of death, MI, repeat revascularization, and major bleeding at 7 days, ranged from 0 to 6% in the bivalirudin groups compared with 10.6% in the heparin-plus-abciximab group, which was a significant difference (p = 0.02). Provisional abciximab therapy was required in

24% of the bivalirudin-treated patients. The rates of major bleeding were lower in patients who received bivalirudin plus abciximab than in those who received heparin plus abciximab (4.7% and 6.3%, respectively), but this difference was not statistically significant.

Building on these promising results, the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial,[92] a large phase III clinical trial, randomized 6,010 patients undergoing percutaneous coronary interventions to receive bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h) plus a provisional GPIIb/IIIa antagonist (ie, abciximab and eptifibatide) or heparin plus a GPIIb/IIIa antagonist (eg, abciximab or eptifibatide). The primary end point, a composite of death, MI urgent revascularization, or major bleeding at 30 days, occurred in 9.2% of the patients treated with bivalirudin and in 10% of those treated with heparin (p = 0.32). A GPIIb/IIIa antagonist was required in only 7% of patients randomized to receive bivalirudin. The rates of major bleeding were significantly lower in patients treated with bivalirudin than in those treated with heparin (2.4% and 4.1%, respectively; p < 0.001).

Adjunct to thrombolysis. Bivalirudin has been compared with heparin as an adjunct to thrombolytic therapy. The Hirulog and Early Reperfusion or Occlusion-2 trial[93] randomized 17,073 patients with acute ST-elevation MI to receive an IV bolus followed by a 48-h infusion of either bivalirudin (8,516 patients) or heparin (8,557 patients) in conjunction with streptokinase. The doses of bivalirudin were not adjusted, whereas the doses of heparin were adjusted based on the results of coagulation testing. The primary end point was 30-day mortality, and the secondary end points included reinfarction within 96 h and bleeding. Mortality at 30 days was similar in patients who were randomized to receive bivalirudin or heparin (10.8% and 10.9%, respectively; p = 0.85). Significantly fewer reinfarctions occurred with bivalirudin therapy compared with heparin therapy (OR, 0.70; 95% CI, 0.56 to 0.87; p = 0.001). Severe bleeding occurred in 0.7% and 0.5%, respectively, of patients randomized to receive bivalirudin or heparin (p = 0.07), whereas intracerebral bleeding occurred in 0.6% and 0.4%, respectively, of those treated with bivalirudin or heparin (p = 0.09). The incidence of moderate and mild bleeding was significantly higher in the bivalirudin group than in the heparin group (OR, 1.32; 95% CI, 1.34 to 1.62; p < 0.0001). A post hoc analysis suggested that the increased bleeding with bivalirudin therapy relative to that with heparin therapy could be accounted for by bivalirudin-induced excessive anticoagulation, as reflected by the APTT.

Summary. With its predictable anticoagulant response and short half-life, bivalirudin is a convenient drug to use in treating patients who are undergoing percutaneous coronary interventions. In this setting, bivalirudin appears to be at least as effective as heparin and produces less bleeding. For patients with a low-to-moderate risk of bleeding who are undergoing percutaneous coronary interventions without receiving an adjunctive GPIIb/IIIa antagonist, bivalirudin may be a better choice than heparin.

Based on the results of the Hirulog and Early Reper-

fusion or Occlusion-2 study,[93] bivalirudin can be used in place of heparin as an adjunct to streptokinase for the treatment of patients with acute ST-elevation MI. In this setting, bivalirudin may reduce the risk of reinfarction compared with heparin. However, bivalirudin therapy requires monitoring, and a dose adjustment may be necessary to reduce the risk of bleeding.

3.2.3 Argatroban

A competitive inhibitor of thrombin, argatroban binds noncovalently to the active site of thrombin to form a reversible complex.[94–96] The plasma half-life of argatroban is 45 min. It is metabolized in the liver[94] and must be used with caution in patients with hepatic dysfunction.[96] Argatroban is licensed for the treatment of heparin-induced thrombocytopenia. Although phase II trials have evaluated argatroban for the treatment of unstable angina,[97] as an adjunct to thrombolysis[98] and as an alternative therapy to heparin in patients undergoing coronary angioplasty,[99] the studies are small, and none has shown definitive advantages of argatroban over heparin.

3.2.4 Ximelagatran

A prodrug of the active site-directed thrombin inhibitor, melagatran, ximelagatran is absorbed from the small intestine.[100] Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran via two intermediate metabolites, labeled H338/57 and H415/04, respectively. Ximelagatran has a plasma half-life of 3 to 4 h and is administered orally twice daily. To date, no foods or drugs have been documented to influence its absorption. Because ximelagatran produces such a predictable anticoagulant response, coagulation monitoring is unnecessary. Melagatran, the active agent, is eliminated via the kidneys. Consequently, dose adjustments may be needed in the elderly and in patients with renal insufficiency.[100]

Ximelagatran is being evaluated for thromboprophylaxis in high-risk orthopedic patients, for the treatment of venous thromboembolism, for the prevention of cardioembolic events in patients with nonvalvular atrial fibrillation, and for the prevention of recurrent ischemia in patients who have recently experienced MIs. Studies for each of these indications will be briefly described.

Venous thromboprophylaxis. For thromboprophylaxis, ximelagatran, in combination with subcutaneous melagatran or as monotherapy, has been compared with low-molecular-weight heparin or warfarin. In the Melagatran for Thrombin Inhibition in Orthopaedic Surgery II study,[101] subcutaneous melagatran (administered preoperatively and twice daily for 1 to 3 days postoperatively) followed by oral ximelagatran therapy (in various doses) was compared with subcutaneous dalteparin therapy (5,000 U once daily started the evening before surgery) in patients undergoing elective hip or knee arthroplasty. A highly significant dose response for both effectiveness and safety was seen with the ximelagatran/melagatran combination.

Because of a trend for excess bleeding at the operative site, an attempt was made to omit the preoperative melagatran dose in the subsequent phase III trial. Consequently, the Melagatran for Thrombin Inhibition in Orthopaedic Surgery III trial[102] randomized 2,788 patients undergoing hip or knee arthroplasty to receive either subcutaneous melagatran (3 mg) postoperatively followed by oral ximelagatran (24 mg twice daily) or subcutaneous enoxaparin (40 mg once daily) starting 12 h before surgery. Although the rates of venographically detected proximal DVT and symptomatic PE were similar in patients treated with melagatran/ximelagatran or enoxaparin (5.7% and 6.2%, respectively), the rates of total venous thromboembolism were slightly higher in the melagatran/ximelagatran group (31% and 27.3%, respectively). The rates of bleeding did not differ between the two groups. Based on these unfavorable results, a subsequent phase III trial again started melagatran treatment preoperatively.

The EXPRESS study,[103] which was completed in 2002, randomized 2,764 patients undergoing hip or knee arthroplasty to receive melagatran/ximelagatran or enoxaparin. Subcutaneous melagatran (2 mg) was administered immediately prior to surgery with a subsequent 3-mg subcutaneous dose administered on the evening after surgery. This was followed by the oral administration of ximelagatran (24 mg twice daily). In the enoxaparin group, subcutaneous enoxaparin (40 mg) was given once daily starting the evening before surgery. The primary end point, a composite of venographically detected proximal DVT and symptomatic PE, occurred in 2.3% and 6.3%, respectively, of patients treated with melagatran/ximelagatran and enoxaparin (p < 0.001). Symptomatic venous thrombosis was rare, occurring in 8 patients in the melagatran/ximelagatran group and 12 in the enoxaparin group. Although bleeding was more common with ximelagatran/melagatran therapy than with enoxaparin therapy (3.3% and 1.2%, respectively), there was no difference in the rates of fatal bleeding, critical organ bleeding, or bleeding requiring reoperation. Thus, melagatran therapy that is started immediately prior to surgery followed by postoperative ximelagatran therapy reduces the incidence of proximal DVT and PE by 63% compared with enoxaparin therapy.

In North America, thromboprophylaxis is started postoperatively in orthopedic patients because many patients have spinal anesthesia. To evaluate the utility of ximelagatran therapy in this setting, the Platinum-Hip trial[104] randomized patients but analysis was based on 1,557 patients with adequate venography undergoing total hip arthroplasty to receive oral ximelagatran (24 mg twice daily) or enoxaparin (30 mg twice daily) for 7 to 12 days. Therapy with both drugs was started on the morning after surgery. The overall rates of venographically detected DVT in the operated leg and symptomatic PE by day 12 were 7.9% and 4.6%, respectively, in patients treated with ximelagatran and enoxaparin (p < 0.05), whereas the rates of proximal DVT were 3.6% and 1.2%, respectively (p < 0.05). The rates of major bleeding were similar in the two treatment groups (0.8% and 0.9%, respectively). Thus, when started postoperatively, a 24-mg twice-daily dose of ximelagatran is less effective than enoxaparin in patients who are undergoing total hip arthroplasty.

The same dose of ximelagatran also has been compared

with warfarin for thromboprophylaxis in patients undergoing elective knee arthroplasty. The Platinum-Knee trial[104] randomized 680 such patients to receive postoperative ximelagatran (24 mg twice daily) or warfarin (in doses sufficient to produce an international normalized ratio (INR) of 2.0 to 3.0). The rates of total DVT with ximelagatran and warfarin were 19.2% and 25.7%, respectively (p = 0.07), whereas the rates of proximal DVT or symptomatic PE were 3.3% and 5.0%, respectively (p > 0.2). There was no significant difference in the rate of major bleeding in the ximelagatran and warfarin groups (1.7% and 0.9%, respectively).

To determine whether the 24-mg twice-daily dose of ximelagatran is optimal for postoperative thromboprophylaxis, the first phase of the Exanta Used to Lessen Thrombosis trial[105] randomized 2,301 patients undergoing elective knee arthroplasty to receive one of two doses of unmonitored ximelagatran (ie, 24 or 36 mg twice daily) or to receive warfarin (in doses sufficient to produce an INR of 2.0 to 3.0). Ximelagatran therapy was started the morning after surgery, whereas the first dose of warfarin was given on the evening of the day of surgery. The primary end point, a composite of total venous thromboembolism and all-cause mortality, was significantly lower with the 36-mg dose of ximelagatran than with warfarin (20.3% and 27.6%, respectively; p = 0.003). Likewise, the point estimate for proximal venous thrombosis and all-cause mortality also was lower (2.7% and 4.1%, respectively), although this difference did not reach statistical significance. Major bleeding occurred in 4.8% and 5.3%, respectively, of patients treated with low-dose or high-dose ximelagatran and in 4.5% of those treated with warfarin, differences that were not statistically significant. Based on these data, the second phase of the Exanta Used to Lessen Thrombosis trial will randomize an additional 2,300 patients to receive ximelagatran (36 mg twice daily) or warfarin.

The data available to date suggest that (1) the combination therapy of subcutaneous melagatran started prior to surgery followed by oral ximelagatran postoperatively is more effective than enoxaparin therapy for thromboprophylaxis after hip or knee arthroplasty, but may cause more bleeding, and (2) postoperative ximelagatran therapy, at a dose of 36 mg twice daily, is likely to be at least as effective as warfarin therapy for thromboprophylaxis after knee arthroplasty. Unlike warfarin, however, ximelagatran does not require coagulation monitoring. Consequently, ximelagatran may be particularly useful for extended out-of-hospital prophylaxis in high-risk patients, a concept that will require testing in future studies.

Treatment of venous thrombosis. Thrombin Inhibition in Venous Thromboembolism (THRIVE) I, a phase II dose-ranging study,[106] randomized 350 patients with venous thrombosis to receive monotherapy with ximelagatran (in doses ranging from 24 to 60 mg twice daily) or subcutaneous dalteparin followed by warfarin for 2 weeks. Based on follow-up venograms, the rate of thrombus regression plus changes in clinical symptoms were similar in both groups. There was a trend for more thrombus

progression with ximelagatran than with dalteparin (8% and 3%, respectively), but this difference was not statistically significant. The rates of bleeding were similar in both treatment groups. Building on this information, a phase III placebo-controlled, blinded trial[107] comparing oral ximelagatran monotherapy (36 mg twice daily) for 6 months with enoxaparin therapy (1 mg/kg subcutaneously twice daily) followed by warfarin therapy (in doses sufficient to produce an INR of 2 to 3) for 6 months has recently been completed. A total of 2,489 patients with venous thromboembolism were entered into the trial, with 1,249 randomized to receive ximelagatran and 1,249 randomized to receive enoxaparin followed by warfarin. The primary end point, objectively documented recurrent venous thromboembolism, occurred in 2.1% and 2.0%, respectively, of those randomized to receive ximelagatran or enoxaparin/warfarin, a difference that was not statistically significant. Major bleeding occurred in 1.3% and 2.2% of those patients randomized to receive ximelagatran or enoxaparin/warfarin, respectively, a difference that was not statistically significant. The all-cause mortality rates were 2.3% and 3.4%, respectively, in the ximelagatran and enoxaparin/warfarin groups.

This study suggests that therapy with oral ximelagatran is as effective and safe as conventional anticoagulation therapy with low-molecular-weight heparin followed by warfarin for the initial treatment of patients with venous thromboembolism. Unlike low-molecular-weight heparin, ximelagatran can be given orally, and, in contrast to warfarin, ximelagatran does not require anticoagulation monitoring. Consequently, ximelagatran is more convenient to administer than conventional treatment.

Ximelagatran also has been evaluated for the prevention of recurrent thrombosis in patients with venous thromboembolism. The THRIVE III trial[108] randomized 1,233 patients who had completed a 6-month course of anticoagulant therapy for the treatment of venous thromboembolism to receive ximelagatran (24 mg twice daily) or placebo for an additional 18 months. Recurrent venous thromboembolism, the primary end point, occurred in 12 patients who had been randomized to receive ximelagatran and 71 who had been randomized to receive placebo (hazard ratio, 0.16; p < 0.001). Major bleeding occurred in six patients who had been treated with ximelagatran and five patients who had been treated with placebo, and there were no incidents of fatal or intracranial bleeding.

Atrial fibrillation. Ximelagatran has been compared with warfarin in the treatment of patients with nonvalvular atrial fibrillation. In the Stroke Prevention Using Oral Thrombin Inhibition in Atrial Fibrillation (SPORTIF) II trial,[109] 257 patients were randomized to receive one of three doses of ximelagatran (20, 40, or 60 mg twice daily) or warfarin (in doses sufficient to produce an INR of 2.0 to 3.0). Ximelagatran was administered without coagulation monitoring. At 12 weeks, fewer patients in the ximelagatran group had experienced transient ischemic attacks (0.5% and 3%, respectively), and one patient in the ximelagatran group had an ischemic stroke compared with none in the warfarin group. There were no major incidents of bleeding in any patients in the ximelagatran groups, but

one major incident of non-intracranial bleeding was observed in a patient receiving warfarin. The ongoing SPORTIF IV trial[110] is an open-label continuation of this trial comparing therapy with a fixed dose of unmonitored ximelagatran (36 mg twice daily) with warfarin therapy.

The promising results of the SPORTIF II trial[109] prompted two phase III trials comparing ximelagatran with warfarin.[111] The SPORTIF III trial,[112] which used an open-label design, was conducted in Europe, whereas the blinded SPORTIF V trial[111] was conducted in North America. Both trials enrolled patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. The SPORTIF III trial[112] randomized 3,407 such patients to receive ximelagatran (36 mg twice daily) or warfarin (in doses sufficient to produce an INR of 2 to 3) for 12 to 26 months. In the intention-to-treat analysis, there were 40 strokes (ischemic or hemorrhagic) or systemic embolic events in patients who were randomized to receive ximelagatran (event rate, 1.6% per year) and 56 strokes in those randomized to receive warfarin (event rate, 2.3% per year), a difference that was not significant. For those who continued to receive treatment, there were 29 ischemic strokes or systemic embolic events in patients randomized to receive ximelagatran and 52 strokes in those randomized to receive warfarin (p = 0.018). The annualized rate of major bleeding was similar with ximelagatran and warfarin therapy (1.3% and 1.8%, respectively), whereas the annualized rate of major plus minor bleeding was significantly lower with ximelagatran therapy than with warfarin therapy (25.5% and 29.5%, respectively; p = 0.007). The all-cause mortality rate was 3.2% per year in both treatment groups.

The SPORTIF V trial[111] enrolled 3,922 patients. In the intention-to-treat analysis, there were 51 strokes or systemic embolic events in patients who had been randomized to receive ximelagatran (event rate, 1.6% per year) and 37 strokes in those randomized to receive warfarin (event rate, 1.2% per year), a difference that was not significant (p = 0.13). The rates of major bleeding incidents were similar in patients randomized to receive ximelagatran or warfarin (2.4% and 3.1%, respectively; p = 0.16), and intracranial hemorrhage occurred in 0.06% of participants in both treatment groups.

When the results of the SPORTIF III trial[112] and the SPORTIF V trial[111] are combined, the absolute difference in the rate of stroke and systemic embolic events is 0.03% lower in those treated with ximelagatran, a difference that is not significant (p = 0.94). The rates of major bleeding incidents with ximelagatran and warfarin therapy are 1.9% and 2.5% per year, respectively (p = 0.54). Thus, these studies indicate that unmonitored ximelagatran therapy is as effective and safe as dose-adjusted warfarin therapy. It is important to note that warfarin control was excellent in the SPORTIF III trial[112] and the SPORTIF V trial.[111] Using an expanded therapeutic INR range of 1.8 to 3.2, 81% and 83%, respectively, of INR values were within the therapeutic range in the SPORTIF III trial[112] and the SPORTIF V trial.[111] In contrast, reports have suggested that < 50% of INR values are in the therapeutic range when warfarin therapy is managed in the community setting. Thus, the SPORTIF trials compared ximelagatran therapy with optimally controlled warfarin therapy.

MI. In the phase II Efficacy and Safety of the Oral Thrombin Inhibitor Ximelagatran in Combination with Aspirin, in Patients with Recent Myocardial Damage (ESTEEM) trial,[113] ximelagatran therapy was compared with placebo in patients who had experienced ST-elevation or non-ST-elevation MI within the past 14 days. A total of 1,883 such patients were randomized to receive oral ximelagatran (in doses of 24, 36, 48, or 60 mg twice daily) or placebo for 6 months. All patients were given aspirin (160 mg daily) and optimal medical management that included therapy with statins and angiotensin-converting enzyme inhibitors. Compared with placebo, all four ximelagatran doses significantly reduced the frequency of the primary end point, a composite of all-cause mortality, MI, and severe recurrent ischemia, by about 4% with no evidence of a dose response. When treatment with placebo was compared with the four combined ximelagatran dose groups, ximelagatran produced a statistically significant 24% reduction in the composite end point (from 16.3% to 12.7%; hazard ratio, 0.76; 95% CI, 0.59 to 0.98; p = 0.036). Mortality was low and similar between the groups. *Post hoc* analysis, using the composite end point of all-cause mortality, MI, and stroke, demonstrated a reduction from 11.1 to 7.4% with ximelagatran therapy compared with placebo (hazard ratio, 0.66; 95% CI, 0.48 to 0.90). Major bleeding occurred in 1% of patients treated with placebo and in 2% of those treated with ximelagatran, a difference that was not statistically different. Minor bleeding occurred in 13% and 22%, respectively, of those treated with placebo and ximelagatran. Building on this information, a phase III trial using the 24-mg twice-daily dose of ximelagatran is under consideration.

The most important side effect of ximelagatran is the elevation of liver enzymes. Overall, approximately 4 to 10% of patients who receive long-term treatment with ximelagatran develop an increase in alanine aminotransferase levels. Typically, this problem occurs after 6 weeks to 4 months of treatment. The increase in alanine aminotransferase levels is usually asymptomatic and reversible, even if treatment with the medication is continued. For comparison purposes, the elevation of transaminase levels occurs in about 4 to 8% of patients treated with heparin[114] or low-molecular-weight heparin, and 1% of those treated with warfarin. Although the increase in transaminase levels with ximelagatran therapy appears to be benign, more information is needed. It is likely, however, that liver function test results will need to be monitored when initiating ximelagatran therapy, as is done when starting patients on therapy with statins. If abnormalities are detected, the drug can be stopped, or the patient can be closely monitored with continuing therapy to ensure that the liver function test results return to normal.

3.3 Modulation of endogenous fibrinolytic activity

Although traditional antithrombotic strategies have been aimed at inhibiting platelet function or blocking coagulation, a better understanding of physiologic fibrino-

lysis has identified potential methods to enhance endogenous fibrinolytic activity. These include inhibitors of PAI-1, activated TAFI (TAFIa), or factor XIIIa. Although these drugs are in the early stages of development, the preclinical data are interesting and worthy of presentation because they describe novel approaches to attenuating thrombosis.

3.3.1 PAI-1 inhibitors

PAI-1 is the major physiologic inhibitor of tPA and uPA. Consequently, the inhibition of PAI-1 results in increased endogenous fibrinolytic activity. PAI-1 activity can be reduced by (1) decreasing PAI-1 gene expression or (2) by reducing the activity of PAI-1. Lipid-lowering drugs, such as niacin and fibrates,[115,116] decrease PAI-1 synthesis *in vitro*. These agents are not specific for PAI-1, however, and also affect the synthesis of other proteins.

Peptides have been identified that block PAI-1 activity either by preventing the insertion of the reactive center loop into the body of the inhibitor after cleavage by the target protease[117] or by converting PAI-1 into its latent conformation.[118] However, the effectiveness of these agents has yet to be tested *in vivo*. More promising are small-molecule PAI-1 inhibitors, some of which exhibit antithrombotic activity *in vivo*.[119]

3.3.2 TAFIa inhibitors

Studies *in vitro* indicate that TAFIa attenuates fibrinolysis by cleaving carboxy-terminal lysine residues from fibrin.[120] the removal of these lysine residues decreases plasminogen or plasmin binding to fibrin, thereby retarding the lytic process. Given this mechanism of action, the inhibitors of TAFIa should enhance fibrinolytic activity, a concept supported by studies[121,122] in dogs and rabbits demonstrating that a potato-derived TAFIa inhibitor increases plasminogen activator-induced thrombolysis. These observations have prompted the development of small-molecule TAFIa inhibitors. A potential limitation of some such agents is the paradoxical enhancement of TAFIa activity at low doses.[123,124] Presumably, this reflects allosteric modulation at the active site of the enzyme. If this phenomenon is common to all TAFIa inhibitors, the optimal dosing of these agents will be problematic.

3.3.3 Factor XIIIa inhibitors

A thrombin-activated transglutaminase, factor XIIIa crosslinks the α-chain and γ-chain of fibrinogen to form α-polymers and γ-dimers, respectively. Crosslinking stabilizes the fibrin polymer and renders it more refractory to degradation by plasmin.[125] The inhibition of factor XIIIa, therefore, has the potential to increase the susceptibility of the thrombus to lysis.[126]

Tridegin, a peptide isolated from the giant Amazon leech, *Haementeria ghilianti*, is a specific inhibitor of factor XIIIa and enhances fibrinolysis *in vitro* when added before clotting of fibrinogen.[127,128] Destabilase, a leech enzyme that hydrolyzes crosslinks, also provides a promising approach to reversing the consequences of factor XIIIa-mediated fibrin crosslinking.[129,130] Neither of these agents has yet to be tested in humans.

4.0. Conclusions and Future Directions

The development of new anticoagulant agents is challenging. Adequately powered phase II clinical trials are needed to identify the optimal anticoagulant dose, and large and expensive phase III programs are necessary to compare the benefit-to-risk profiles of new agents with those of conventional treatment regimens. Even if new anticoagulant agents prove to be superior to the currently available agents, their advantages have to be substantial to offset the additional cost. The challenges for the development of new anticoagulant agents are different for the prevention and treatment of venous thrombosis than they are for those of arterial thrombosis. Consequently, each will be considered separately.

4.1 Venous thrombosis

Low-molecular-weight heparin and warfarin are well-established as safe and effective agents for thromboprophylaxis in high-risk patients and for the treatment of venous thromboembolism. Consequently, to gain wide acceptance, new anticoagulant agents must have a benefit/risk ratio that is at least as good as these agents and must have a comparable cost. Fondaparinux has been extensively evaluated for these indications and is already licensed for use in venous thromboprophylaxis in high-risk orthopedic patients. Although the rates of venographically detected DVT were lower with fondaparinux therapy than with enoxaparin therapy,[42–45] orthopedic surgeons have been slow to embrace fondaparinux because of the perception that it causes more bleeding. This observation highlights the fact that postoperative bleeding is of greater concern to surgeons than venographically detected DVT, likely because many of these thrombi are small and not clinically relevant.

Fondaparinux also is effective for thromboprophylaxis in general medical and surgical patients. It has yet to be compared with heparin or low-molecular-weight heparin in general medical patients. In the general surgery setting, fondaparinux is at least as effective and safe as low-molecular-weight heparin and may be more effective than low-molecular-weight heparin in patients undergoing cancer surgery.

The recently completed MATISSE trials[53] suggest that fondaparinux is as effective and safe as unfractionated heparin or low-molecular-weight heparin for the initial treatment of patients with venous thromboembolism. The extent to which fondaparinux will replace low-molecular-weight heparin for these indications will depend on cost. If fondaparinux is more expensive than low-molecular-weight heparin, it will be difficult to rationalize a change in practice.

A potential limitation of fondaparinux is its lack of reversibility with protamine sulfate.[131] With a half-life of about 17 h, this could be problematic in a patient with life-threatening bleeding. Although recombinant factor VIIa may be useful in this setting,[41] factor VIIa is not

widely available except in centers that care for hemophiliacs. Furthermore, factor VIIa is expensive and can promote thrombosis.

Heparinase will degrade fondaparinux into inactive disaccharides.[122] At present, however, there is no commercially available heparinase.[132] A neutralizing agent may be particularly important for idraparinux because of its long half-life. Idraparinux, which is more heavily sulfated than the naturally occurring pentasaccharide, is not degraded by heparinase. Although procoagulants, such as factor VIIa, may be useful in treating major bleeding in patients treated with idraparinux, repeated doses of factor VIIa may be necessary if there is ongoing bleeding.

An emerging theme in the prevention and treatment of venous thromboembolism is the need for extended thromboprophylaxis. There is mounting evidence that patients undergoing major orthopedic surgery, particularly hip surgery, remain at risk for clinically important venous thromboembolism for at least 4 weeks after the procedure.[47–50] This risk can be reduced with extended treatment with low-molecular-weight heparin, fondaparinux, or warfarin. However, with progressive reductions in the length of hospitalization for these patients, thromboprophylactic regimens would be streamlined with an oral anticoagulant that does not require monitoring. Additional studies are needed to determine whether ximelagatran will be useful for this indication. Given the success of fondaparinux, a parenteral factor Xa inhibitor for extended thromboprophylaxis,[46] it is possible that orally active direct factor Xa inhibitors also may be effective in this setting.

Long-term anticoagulation therapy is of benefit in patients with unprovoked venous thromboembolism. There is increasing evidence that the risk of recurrent venous thromboembolism in these subjects is about 7 to 10% per annum if anticoagulant therapy is stopped after 3, 6, 12, or 27 months.[133–137] Although long-term warfarin therapy markedly reduces the risk of recurrence, its benefit is offset, at least in part, by the risk of major bleeding, which is estimated to be about 1 to 3% per annum. Furthermore, because of multiple food and drug interactions, the anticoagulant response to warfarin is unpredictable so that frequent monitoring is necessary to ensure that a therapeutic response has been obtained. In contrast, ximelagatran therapy does not appear to require coagulation monitoring and, at least with the dose used in the THRIVE III trial,[108] ximelagatran appears to be safe. Despite these promising results, the role of ximelagatran in extended thromboprophylaxis has yet to be established.

The ximelagatran treatment study[107] has suggested that ximelagatran monotherapy is as effective and safe as the current treatment regimens for venous thromboembolism. If these results are confirmed in other studies, ximelagatran has the potential to streamline care by obviating the need for initial treatment with a parenteral anticoagulant and the coagulation monitoring that is required when warfarin is administered. Still to be determined is the effectiveness of ximelagatran in high-risk patients, such as those with advanced cancer or with antiphospholipid antibody syndrome.

4.2 Arterial thrombosis

Like venous thromboembolism, issues in arterial thromboembolism focus on prevention and treatment. The prevention of cerebral and systemic embolism in patients with atrial fibrillation is an area in which there is considerable room for improvement. Although warfarin is more effective than aspirin in reducing the risk of embolization in this setting, its use is problematic.[138] Frequent monitoring is necessary to ensure that a therapeutic anticoagulant response is obtained. Even with monitoring in specialized clinics, the level of anticoagulation is outside the therapeutic range almost half of the time. Furthermore, the risk of major bleeding with long-term treatment increases in the elderly, the population that is most at risk for atrial fibrillation. Because of these problems, it is estimated that warfarin is not given to almost half of the eligible atrial fibrillation patients.[138] Based on the results of the SPORTIF III trial[112] and the SPORTIF V trial,[111] unmonitored ximelagatran therapy appears to be at least as effective and safe as dose-adjusted warfarin therapy. Thus, ximelagatran therapy is a promising alternative to warfarin therapy for stroke prevention in this population. With no need for coagulation monitoring, ximelagatran is more convenient than warfarin, a feature that may increase anticoagulant use in high-risk patients with atrial fibrillation.

Parenteral anticoagulants continue to have a role in the treatment of acute coronary syndromes. The results of the REPLACE-2 trial[93] suggest that bivalirudin obviates the need for GPIIb/IIIa antagonists in the majority of patients with low-to-moderate risk who are undergoing percutaneous coronary interventions, thereby reducing the risk of bleeding.

Fondaparinux and DX9065a have yet to find a place in the treatment of acute coronary syndromes, but further studies are planned. Likewise, NAPc2 is undergoing evaluation for these indications. Although most of the attention has focused on the use of parenteral anticoagulants for short-term treatment, rapidly acting, orally active agents also may have a role in long-term therapy. There is mounting evidence that, despite initial treatment, patients with acute coronary syndromes remain at risk for recurrent ischemic attacks for months after the index event. Some studies have indicated[139] that long-term treatment with the combination of aspirin and clopidogrel is more effective at reducing the risk of recurrent ischemia than aspirin alone. Likewise, long-term warfarin therapy also appears to be effective.[140] We do not yet know whether therapy with aspirin plus clopidogrel is as effective as warfarin therapy, or whether treatment with all three agents can be safely administered on a long-term basis. However, recent results with warfarin raise the possibility that ximelagatran therapy may be useful for this indication, either alone or in combination with antiplatelet agents.

Another unanswered question is the utility of ximelagatran in patients with mechanical heart valves. With no need for anticoagulation monitoring, ximelagatran has the potential to streamline the care of these patients, particularly those living in remote areas who cannot access a coagulation laboratory. The anticoagulation management

of women with mechanical heart valves during pregnancy also remains a major challenge. If the use of ximelagatran is safe in this setting, treatment would be simplified.

Summary

With a large number of new anticoagulant agents in advanced stages of development, our armamentarium of treatment options is likely to soon be expanded. Particularly promising are new oral anticoagulant agents because they have the potential to streamline the long-term prevention and treatment of patients with venous and arterial thrombosis.

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