Emerging Anticoagulant Drugs
Shannon M. Bates, Jeffrey I. Weitz

Abstract—The limitations of traditional anticoagulants, heparin and warfarin, have prompted the development of new anticoagulant drugs for prevention and treatment of both venous and arterial thromboembolism. After a brief review of thrombogenesis and its regulation, this study focuses on new anticoagulant agents in more advanced stages of clinical testing. (Arterioscler Thromb Vasc Biol. 2003;23:1491-1500.)

Key Words: anticoagulant ▪ antithrombotic ▪ venous thromboembolism ▪ arterial thromboembolism ▪ direct thrombin inhibitor

Hemostasis, the physiological response to vascular injury, results in the formation of a hemostatic plug that prevents blood loss. Under normal conditions, factors that promote blood coagulation are balanced by those that inhibit it. Pathologic thrombosis occurs when procoagulant stimuli overwhelm natural anticoagulant and fibrinolytic systems.1

Venous thrombi, which form under low shear conditions, are predominantly composed of fibrin and red cells. Thrombi may develop anywhere within the venous system but most commonly arise in the deep veins of the leg2 through an interplay among 3 factors that include vessel wall damage, venous stasis, and hypercoagulability.2 Direct damage to the veins helps explain the propensity to deep vein thrombosis (DVT) after major orthopedic surgery. Thrombi often originate in the calf, either in the muscular sinuses or valve cusps of deep veins. Immobility delays emptying of muscular veins and retards clearance of activated clotting factors. With stasis, endothelial cells lining the avascular valve cusps are activated by hypoxemia, a process exacerbated by inflammatory cytokines generated postoperatively or in medical illness. Leukocytes tethered to activated endothelial cells express tissue factor, whereas platelets become activated and aggregate. Congenital or acquired disorders associated with hypercoagulability promote coagulation at these sites, thereby increasing the risk of thrombosis. Signs and symptoms develop when there is obstruction to venous outflow and inflammation of the vessel wall and perivascular tissue. Symptoms of pulmonary embolism arise when segments of thrombus detach and embolize to the pulmonary circulation.

Arterial thrombi form under high shear conditions and are composed primarily of platelet aggregates held together by fibrin strands. Obstruction of antegrade arterial flow leads to ischemia, which manifests as unstable angina or myocardial infarction in the case of coronary arteries or stroke if cerebral vessels are involved.3 Most arterial thrombi are superimposed on disrupted atherosclerotic plaques.4,5 After damage to the endothelial lining of veins or arteries, platelets adhere to newly exposed subendothelial matrix components, particularly collagen and von Willebrand factor, via constitutively expressed receptors. Adherent platelets become activated and recruit additional platelets by synthesizing thromboxane A2 and releasing adenosine diphosphate (ADP).6 Platelet activation induces conformational changes in glycoprotein (GP) IIb/IIIa, one of the most abundant receptors on the platelet surface. By binding fibrinogen or under high shear conditions, von Willebrand factor, conformationally activated GPIIb/IIIa cross-links adjacent platelets,6 resulting in platelet aggregation.

Damage to the vascular wall and the resultant exposure of tissue factor (TF)-expressing cells to blood6 initiates coagulation in both the arteries and veins. In the presence of calcium, TF binds activated factor VII (factor VIIa), which is found in small amounts in plasma, thereby forming factor VIIa/TF complex. This complex, also known as extrinsic tenase, activates factors IX and X, although factor X activation is more efficient.6 Factor Xa then converts small amounts of prothrombin to thrombin. This thrombin activates factors V and VIII, key cofactors in coagulation, and activates platelets, a process that induces expression of anionic phospholipid on their surface. These thrombin-mediated events are critical for propagation of coagulation.

Propagation is effected when factor IXa binds to factor VIIIa on the surface of activated platelets to form intrinsic tenase, a complex that efficiently activates factor X. Factor Xa binds to factor Va on the activated platelet surface to form the prothrombinase complex that converts prothrombin to thrombin.6 In the final step of coagulation, thrombin converts fibrinogen to fibrin and activates factor XIII, which stabilizes the platelet/fibrin thrombus by cross-linking the fibrin network. In addition, thrombin triggers thrombus growth via several mechanisms. It amplifies its own generation by feedback activation of factors V and VIII, it activates factor...
XI on the platelet surface, thereby augmenting factor IXa generation, and it also serves as a potent platelet agonist.6

Normally, the vessel wall inhibits thrombosis. Endothelial cells express thombomodulin, a thrombin receptor, on their surface.7 Once bound to thombomodulin, the substrate specificity of thrombin is altered such that its procoagulant activities are abolished. Instead, thrombin’s ability to activate protein C is enhanced approximately 1000-fold.8,9 Activated protein C, along with its cofactor, protein S, acts as an inhibitor of coagulation by inactivating factors Va and VIIIa,10 thereby attenuating thrombin generation. Although the density of thombomodulin is greater on small vessels than it is on larger ones, large vessels also express more endothelial protein C receptor than smaller vessels. By binding protein C, endothelial protein C receptor localizes it in the vicinity of the thrombin/thombomodulin complex.11

The endothelial surface also contains heparan sulfate, a heparin-like substance that catalyzes the antithrombin-mediated inhibition of thrombin, factor Xa, and other clotting enzymes.12 Heparan sulfate and other glycosaminoglycans on the endothelial cell surface contribute to the binding of tissue factor pathway inhibitor (TFPI), a bivalent Kunitz-type inhibitor that blocks the initiation of coagulation by inhibiting TF-bound factor VIIa in a factor Xa-dependent fashion.13

Endothelial cells also produce prostacyclin, nitric oxide, and ectoADPase, substances that inhibit platelet aggregation.14 In addition, endothelial cells play a critical role in fibrinolysis. They synthesize and release tissue plasminogen activator and urokinase plasminogen activator and express annexin II on their surface.15 By serving as a coreceptor for tissue plasminogen activator and plasminogen, annexin II promotes plasmin generation on the endothelial cell surface.16

**Targets for New Anticoagulants**

New anticoagulant drugs target specific steps in coagulation (Figure). Initiation of coagulation can be inhibited by agents that target the factor VIIa/TF complex, whereas propagation of coagulation can be blocked by drugs that target factors IXa or Xa or by inactivation of factors Va or VIIIa. Thrombin inhibitors prevent fibrin formation, block thrombin-mediated feedback activation of factors V, VIII, and XI, and attenuate thrombin-induced platelet aggregation.

**Inhibitors of Initiation of Coagulation**

Because the factor VIIa/TF complex initiates thrombosis,6 drugs that target this complex are potent inhibitors of coagulation. Agents in the most advanced stage of development are recombinant TFPI, nematode anticoagulant peptide (NAPc2), and active-site blocked factor VIIa (FVIIai).

**TFPI**

Based on studies in animals demonstrating that TFPI attenuates the coagulopathy and improves survival in sepsis models,17–19 a recombinant form of TFPI has been evaluated for this indication in humans. With promising phase II data,20 TFPI was compared with placebo in a large phase III clinical trial in patients with severe sepsis. Although the results have yet to be published, the sponsor reported that prespecified end points were not achieved and additional development has been halted.

**NAPc2**

An anticoagulant protein isolated from the nematode, *Ancylostoma caninum*, NAPc2 binds to a noncatalytic site on both factor X and factor Xa and inhibits factor VIIa within the factor VIIa/TF complex.21 Functionally, therefore, NAPc2 behaves much like TFPI. Because NAPc2 binds to factor X as well as factor Xa, it has a half-life of almost 50 hours after subcutaneous injection. In a phase II study, NAPc2 showed promise in preventing venous thromboembolism after elective knee replacement surgery.22 A series of studies are underway to evaluate the utility of NAPc2 in patients with unstable angina or non–ST-elevation myocardial infarction (MI). In these trials, NAPc2 is added to routine therapy that includes aspirin, clopidogrel, heparin, or low-molecular-weight heparin (LMWH) and, in some cases, a GPIIb/IIIa antagonist. The hemorrhagic consequences of adjunctive NAPc2 in these settings remain to be established, and the long half-life of NAPc2 may be problematic if patients require urgent percutaneous coronary interventions or aortocoronary bypass surgery.

**FVIIai**

By competing with factor VIIa for tissue factor binding, FVIIai, an inactivated form of factor VIIa, serves as a competitive inhibitor of TF-dependent factor IX or X activation. In studies in vitro and in animals, FVIIai infusion prevented thrombus formation on artificial surfaces or injured vasculature.23–28 Compared with heparin in a phase II study of patients undergoing percutaneous coronary intervention,29 there was no significant difference in the primary end point,
a composite of death, MI, need for urgent revascularization, abrupt vessel closure, or bailout use of GP IIb/IIIa antagonists or heparin at day 7 or hospital discharge. Furthermore, rates of major bleeding were similar in patients receiving factor VIIai or heparin. Consequently, factor VIIai has not been developed further.

**Inhibitors of Propagation of Coagulation**

Propagation of coagulation can be inhibited by drugs that block factors IXa or Xa or by agents that inactivate their respective cofactors, factor VIIIa or factor Va.

**Factor IXa Inhibitors**

Factor IXa is essential for amplification of coagulation. Strategies to block factor IXa activity are in the early stages of development. Active site-blocked factor IXa (factor IXai) competes with factor IXa for incorporation into the intrinsic tenase complex that assembles on the surface of activated platelets. Factor IXai inhibits clot formation in vitro and has been shown to block coronary artery thrombosis in a canine model. Monoclonal antibodies against factor IXa/IXai have been described. One, a chimeric humanized derivative of an antibody that inhibits factor XI–mediated activation of factor IX and blocks factor IXa activity, has demonstrated antithrombotic activity in rat arterial thrombosis models. Factor IXa inhibitors have yet to reach phase II clinical testing.

**Factor Xa Inhibitors**

Both indirect and direct factor Xa inhibitors have been investigated (Table 1). Synthetic pentasaccharide (fondaparinux), an analog of the pentasaccharide sequence of heparin that mediates its interaction with antithrombin, is a new indirect factor Xa inhibitor that blocks factor Xa in an antithrombin-dependent fashion. Direct factor Xa inhibitors, agents that bind directly to factor Xa and block its activity, include recombinant analogs of natural inhibitors as well as synthetic drugs that target the active site of factor Xa. The ability of the direct factor Xa inhibitors to access and inhibit platelet-bound factor Xa, in addition to free factor Xa, is a potential advantage of these agents over indirect inhibitors.

**Indirect Factor Xa Inhibitors**

Fondaparinux and idraparinux are parenteral synthetic pentasaccharide analogs with high affinity for antithrombin. Neither agent interacts with plasma proteins other than antithrombin; as a result, these drugs produce a predictable dose response. Small studies have shown no cross-reactivity of fondaparinux with sera from patients with heparin-induced thrombocytopenia. Because they are too short to bridge antithrombin to thrombin, fondaparinux and idraparinux enhance the rate of factor Xa inactivation by antithrombin, thereby blocking thrombin generation, but have no effect on the rate of thrombin inhibition. Both agents have almost complete bioavailability after subcutaneous injection. Fondaparinux is not metabolized and clearance is almost exclusively by the kidney. Fondaparinux exhibits a dose-independent elimination half-life of approximately 15 hours and can be administered subcutaneously once daily.

Idraparinux, a more sulfated derivative of fondaparinux, binds antithrombin with such high affinity that it assumes a plasma half-life of 130 hours, similar to that of antithrombin. Consequently, idraparinux can be given subcutaneously on a once-weekly basis. Neither fondaparinux nor idraparinux interacts with protamine sulfate, the antidote for heparin. If uncontrolled bleeding occurs, a procoagulant such as recombinant factor VIIa may be beneficial. However, recombinant factor VIIa is not available in all hospitals, and the drug is expensive and can induce thrombotic complications. Fondaparinux, an analog of the naturally occurring pentasaccharide, is degraded and inactivated by heparinases, so these agents offer promise as potential antidotes. In contrast, idraparinux is not susceptible to heparinase digestion. Because of its long half-life, the absence of an antidote is a potential limitation of idraparinux.

The antithrombotic efficacy of fondaparinux was demonstrated in 4 phase III trials comparing this agent with enoxaparin for thromboprophylaxis after surgery for hip fracture or for elective hip or knee arthroplasty. In these trials, fondaparinux started 6 hours after surgery reduced the risk of venous thromboembolism by approximately 55% compared with enoxaparin. Although major bleeding occurred more frequently in fondaparinux-treated patients, the incidence of bleeding in a critical organ or bleeding leading to death or reoperation was similar to that in patients receiving enoxaparin. These results may reflect the administration regimens rather than intrinsic differences in the efficacy of fondaparinux relative to enoxaparin. Thus, the reduced risk of venous thromboembolism with fondaparinux may be attributable to the fact that it was started 6 hours after surgery, whereas initiation of enoxaparin was delayed until 12 to 24 hours after surgery. The earlier start with fondaparinux also could explain the increase in major bleeding observed with this agent. In support of this concept, post-hoc analysis reveals similar rates of major bleeding with fondaparinux and enoxaparin in those patients whose fondaparinux was started 6 to 8 hours after surgery.

In a recent phase III trial (PENTHIFRA-Plus), prolonging the duration of prophylaxis with fondaparinux from 1 to 4 weeks after hip fracture surgery reduced the primary end

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**TABLE 1. Properties of Factor Xa Inhibitors**

<table>
<thead>
<tr>
<th>Property</th>
<th>DX-9065a</th>
<th>DPC 906</th>
<th>Fondaparinux</th>
<th>Idraparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitory mechanism</td>
<td>Direct</td>
<td>Direct</td>
<td>Indirect</td>
<td>Indirect</td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal</td>
<td>Extra-renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IV</td>
<td>Oral</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Approved indications</td>
<td>None</td>
<td>None</td>
<td>Orthopedic thromboprophylaxis</td>
<td>None</td>
</tr>
</tbody>
</table>

IV indicates intravenous; SC, subcutaneous.
Inhibitors of Factors VIIIa and Va

Direct Factor Xa Inhibitors

Natural direct inhibitors of factor Xa include tick anticoagulant peptide (TAP) and antistasin. TAP and antistasin were originally isolated from the soft tick and the Mexican leech, respectively. Both are available in recombinant forms. TAP is a 60-amino-acid polypeptide that forms a stoichiometric complex with factor Xa. TAP seems to bind to factor Xa in a 2-step fashion in which an initial low affinity interaction involving a site distinct from the catalytic site of the enzyme is followed by a high-affinity interaction with the active site, resulting in the formation of a stable enzyme inhibitor complex. Antistasin, a 119-amino-acid polypeptide, also is a tight-binding, slowly reversible inhibitor of factor Xa. TAP and antistasin have been shown to reduce arterial thrombosis and restenosis in animal models. Because they are antigenic, neither has been tested in humans.

DX-9065a and DPC 906 are synthetic nonpeptidic, low-molecular-weight, reversible inhibitors of factor Xa. DX-9065 binds reversibly to the active site of factor Xa. In a phase I study in patients with stable coronary artery disease, intravenous DX-9065a appeared safe and did not cause excess bleeding. Ongoing phase II studies are comparing DX-9065a with heparin in patients undergoing percutaneous coronary interventions.

DPC 906, an aminobenzisoxazole that binds factor Xa with high affinity, has good oral bioavailability. The antithrombotic potential of this agent was investigated in a phase II trial of thromboprophylaxis in knee arthroplasty patients. The trial was stopped prematurely, but the results have yet to be published.

Soluble Thrombomodulin

Soluble thrombomodulin is a recombinant analog of the extracellular domain of thrombomodulin. Like membrane-bound thrombomodulin, soluble thrombomodulin binds thrombin and converts it from a procoagulant enzyme into a potentiator of activated protein C. Recombinant soluble thrombomodulin has been shown to be an effective antithrombotic agent in a variety of animal models. In an open-label, dose-escalation study, soluble thrombomodulin attenuated coagulation abnormalities in patients with disseminated intravascular coagulation. A phase II trial examining the utility of subcutaneous soluble thrombomodulin for thromboprophylaxis after elective hip arthroplasty has been completed, and the results will soon be available.

Thrombin Inhibitors

The procoagulant effects of thrombin can be blocked either by inactivating the enzyme itself or by preventing its generation. Direct thrombin inhibitors bind directly to thrombin and block its interaction with substrates, thus preventing fibrin formation, thrombin-mediated activation of factors V, VIII, XI, or XIII, and thrombin-induced platelet aggregation. As a class, these agents have potential biologic and pharmaco kinetic advantages over heparin. Unlike unfractionated heparin and LMWH, direct thrombin inhibitors inactivate
fibrin-bound thrombin\textsuperscript{70} in addition to fluid-phase thrombin. Consequently, direct thrombin inhibitors may attenuate thrombus accretion more effectively. In addition, direct thrombin inhibitors produce a more predictable anticoagulant effect than heparin because they do not bind to plasma proteins and are not neutralized by platelet factor 4 and high-molecular-weight multimers of von Willebrand factor generated at sites of vascular injury.\textsuperscript{71,72} Three parenteral direct thrombin inhibitors (hirudin, bivalirudin, and argatroban) have been licensed in North America for limited indications. Ximelagatran, a prodrug of melagtran, is the first orally available direct thrombin inhibitor. The characteristics of these agents are highlighted in Table 2.

**Hirudin**

A 65-amino-acid polypeptide originally isolated from the saliva of the medicinal leech, hirudin binds to thrombin’s active site by its globular amino-terminal domain and to thrombin’s substrate-recognition site (exosite 1) via its carboxy-terminal domain.\textsuperscript{73,74} Hirudin binds tightly to the enzyme, forming a slowly reversible complex.\textsuperscript{75} The almost irreversible nature of this complex may be considered a relative weakness, because there is no available antidote should bleeding occur. Hirudin is not absorbed via the gastrointestinal tract and must be administered intravenously.\textsuperscript{72} Because hirudin is predominantly cleared by the kidneys, it should not be used in patients with renal insufficiency.\textsuperscript{72,76–78} It has a plasma half-life of approximately 60 minutes after intravenous administration and approximately 120 minutes after subcutaneous injection.\textsuperscript{72} Hirudin’s narrow therapeutic window makes anticoagulant monitoring necessary, particularly when the drug is given in conjunction with thrombolytic agents.\textsuperscript{79–83} Generally, treatment is monitored with the activated partial thromboplastin time (aPTT), which should be determined before treatment, 4 hours after the start of intravenous hirudin therapy, 4 hours after every dosage change, and then at least once daily.\textsuperscript{78} Unfortunately, there are problems when the aPTT is used to monitor hirudin therapy, including variability in responsiveness between patients\textsuperscript{82} and the lack of a linear correlation with plasma hirudin levels. At higher doses, use of the ecarin clotting time may be more appropriate, because its correlation with plasma hirudin levels is more linear.\textsuperscript{83,84}

Hirudin is licensed for treatment of arterial or venous thrombosis complicating heparin-induced thrombocytopenia and as an alternative to heparin for cardiopulmonary bypass surgery in these patients. Hirudin has been extensively evaluated in acute coronary syndromes and for venous thromboprophylaxis.\textsuperscript{85,86} Hirudin appears at least as effective as heparin when used as an adjunct to thrombolytic therapy in patients with acute MI.\textsuperscript{87–91} When the results of the OASIS-1 and OASIS-2 trials are combined, hirudin 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) in patients with unstable angina or non–ST-elevation MI.\textsuperscript{92–94} However, it is unlikely that hirudin will ever be approved for acute coronary syndromes because of its narrow therapeutic window and concerns about the risk of bleeding.\textsuperscript{79–81,86,94} Although hirudin was more effective than heparin\textsuperscript{95} or LMWH\textsuperscript{96} when used for thromboprophylaxis after hip arthroplasty, clinical development of hirudin for venous thromboprophylaxis has not been pursued.

**Bivalirudin**

Like hirudin, bivalirudin also acts as a bivalent inhibitor of thrombin.\textsuperscript{97} This synthetic 20-amino-acid polypeptide is comprised of an active site-directed moiety, D-Phe-Pro-Arg-Pro, linked via a tetraglycine spacer to a dodecapeptide analogue of the carboxy-terminal of hirudin\textsuperscript{97} that interacts with exosite 1 on thrombin.\textsuperscript{98} Unlike hirudin, bivalirudin produces only transient inhibition of the active site of thrombin, because, once bound, thrombin cleaves the Pro-Arg bond within the amino-terminal of bivalirudin.\textsuperscript{99,100} Without its amino-terminal segment, the carboxy-terminal portion of bivalirudin bound to thrombin’s substrate recognition site is a much weaker thrombin inhibitor.\textsuperscript{99} Consequently, substrates can compete with cleaved bivalirudin for access to exosite 1. Bivalirudin’s plasma half-life after intravenous infusion is 25 minutes.\textsuperscript{101} This shorter half-life may confer bivalirudin with a better safety profile than hirudin. Only a fraction of bivalirudin is renally excreted, suggesting that proteolysis at sites other than the liver and kidneys contributes to its clearance.\textsuperscript{101}

Bivalirudin was approved as an alternative to heparin in patients undergoing percutaneous coronary angioplasty based on the results of a phase III study that compared bivalirudin with heparin in 4098 patients with unstable angina undergoing percutaneous angioplasty.\textsuperscript{102} In the Bivalirudin Angioplasty Study, major bleeding occurred less frequently in those randomized to bivalirudin than in those receiving heparin (3.8% and 9.8%, respectively, \(P<0.001\)), although there was no difference in the rate of intracranial hemorrhage between the 2 patient groups. The primary end point (a composite of

<table>
<thead>
<tr>
<th>TABLE 2. Properties of Direct Thrombin Inhibitors</th>
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<tr>
<td>Property</td>
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<tr>
<td>Site(s) of interaction with thrombin</td>
</tr>
<tr>
<td>Predominant mechanism of clearance</td>
</tr>
<tr>
<td>Route of administration</td>
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<tr>
<td>Half-life, min</td>
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<td>Approved indications</td>
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IV indicates intravenous; HIT, heparin-induced thrombocytopenia.
in-hospital death, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin) occurred in a similar proportion of patients in the 2 treatment groups. However, in a prospectively specified subgroup analysis involving 704 patients with postinfarction angina, bivalirudin was superior to heparin (incidence of the primary outcome of 9.1% and 14.2%, respectively; \( P = 0.04 \)). In a recent reanalysis of the study results using data from the entire intention-to-treat cohort and a more contemporary definition of MI, bivalirudin was more effective than heparin at reducing the risk of death, MI, and revascularization at 7 days (6.2% and 7.9%, respectively; \( P = 0.04 \)). As in the original report, the reanalysis demonstrated lower rates of major bleeding with bivalirudin than with heparin (3.5% and 9.3%, respectively; \( P < 0.001 \)). Recent meta-analyses\(^{86,105}\) have confirmed that bivalirudin seems to be an effective alternative to heparin in patients undergoing coronary angioplasty.

More contemporary studies have evaluated the utility of bivalirudin in patients undergoing coronary stenting.\(^{106,107}\) REPLACE-2 was a large phase III clinical trial in which 6010 patients undergoing percutaneous coronary interventions were randomized to either bivalirudin plus provisional GPIIb/IIIa antagonist (abciximab or eptifibatide) or heparin plus a GPIIb/IIIa antagonist.\(^{107}\) Although the primary end point (a composite of death, MI, urgent revascularization, or major bleeding at 30 days) occurred in similar numbers of patients in each group, a GPIIb/IIIa antagonist was required in only 7% of patients randomized to bivalirudin. Rates of major bleeding were significantly lower in patients given bivalirudin than in those treated with heparin. Therefore, based on available data, including recent meta-analyses,\(^{86,105}\) bivalirudin seems to be at least as effective as heparin in patients undergoing percutaneous coronary interventions. In this setting, bivalirudin produces less bleeding and seems to obviate the need for adjunctive GPIIb/IIIa antagonists in most patients.\(^{107}\)

**Argatroban**

Argatroban is a univalent competitive inhibitor of thrombin that binds noncovalently to the active site of thrombin to form a reversible complex.\(^{108,109}\) This agent has a plasma half-life of 45 to 60 minutes and prolongs the aPTT in a dose-dependent manner. Argatroban is extensively metabolized in the liver; its plasma levels are not influenced by renal function.\(^{108,110}\) Therefore, argatroban must be used with caution in patients with hepatic dysfunction.\(^{111}\) This drug is an effective alternative to heparin in patients with heparin-induced thrombocytopenia and is approved for this indication. Argatroban has been evaluated in phase II trials involving patients with acute coronary syndromes and as an alternative to heparin in those undergoing coronary angioplasty.\(^{112,113}\) However, these studies are small and none has demonstrated a definitive advantage of argatroban over heparin.

**Ximelagatran**

An uncharged lipophilic drug with little intrinsic activity against thrombin, ximelagatran is a prodrug of melagatran, an active site-directed thrombin inhibitor. Ximelagatran is well absorbed from the gastrointestinal tract and undergoes rapid biotransformation to melagatran via 2 intermediate metabolites, H3385/57 and H415/04.\(^{114,115}\) Ximelagatran has a plasma half-life of 3 to 4 hours and is administered twice daily. The drug produces a predictable anticoagulant response after oral administration, and no coagulation monitoring seems to be necessary. Because melagatran, the active agent, is eliminated via the kidneys, however, dose adjustments may be needed in the elderly\(^{116}\) and in patients with renal insufficiency. One of the side effects of ximelagatran is elevation of liver transaminases, which occurs in approximately 6% of patients.\(^{117}\) Typically, changes in liver enzymes are asymptomatic and reversible, even if the medication is continued. Similar changes in liver transaminases have been noted in patients receiving heparin\(^{118}\) or LMWH.\(^{117}\)

In phase II studies, ximelagatran, in combination with subcutaneous melagatran or as monotherapy, was shown to be safe and to have antithrombotic efficacy when used as prophylaxis against venous thromboembolism after elective hip or knee arthroplasty.\(^{117,118}\) Results of phase III studies suggest that the combination of subcutaneous melagatran started preoperatively followed by oral ximelagatran postoperatively is more effective than enoxaparin for thromboprophylaxis after hip or knee arthroplasty but may cause more bleeding.\(^{120}\) Although postoperative subcutaneous melagatran followed by oral ximelagatran\(^{121}\) or melagatran alone\(^{122}\) seems less effective than enoxaparin in patients undergoing joint arthroplasty, available data suggest that postoperative ximelagatran is likely to be at least as effective as warfarin for thromboprophylaxis after knee arthroplasty.\(^{123,124}\)

A recently completed trial compared ximelagatran with placebo in 1233 patients who had completed a 6-month course of anticoagulant therapy for venous thromboembolism. Ximelagatran treatment significantly reduced the risk of recurrent thrombosis without increasing the risk of major bleeding.\(^{125}\) Based on phase II data suggesting that ximelagatran also is effective for acute treatment of venous thromboembolism,\(^{126}\) a large phase III trial comparing ximelagatran monotherapy with LMWH followed by warfarin has been completed. The data will soon be available.

Designed to be administered in fixed doses without coagulation monitoring, ximelagatran has the potential to replace warfarin in patients with atrial fibrillation. Because of multiple food and drug interventions, the anticoagulant response to warfarin is unpredictable and frequent monitoring is necessary to ensure that a therapeutic response is achieved. Even with optimal warfarin monitoring in patients with atrial fibrillation, therapeutic anticoagulation is obtained only half of the time. Because of these limitations, it is estimated that at least half of the patients with nonvalvular atrial fibrillation who are eligible for warfarin therapy do not receive such treatment.

Promising data from phase II studies comparing ximelagatran with warfarin in patients with nonvalvular atrial fibrillation\(^{127,128}\) prompted 2 phase III trials.\(^{129}\) In a randomized, open-label, parallel-group study of approximately 3400 such patients (SPORTIF III), fixed-dose twice-daily ximelagatran was at least as effective at warfarin targeted to an international normalized ratio of 2.0 to 3.0 in preventing stroke and systemic thromboembolism. Although the combined inci-
idence of major and minor bleeding was significantly lower in those receiving ximelagatran than in those receiving warfarin, there was no statistically significant difference between the 2 groups with respect to major bleeding or intracranial hemorrhage. The results of a double-blinded, randomized trial comparing ximelagatran with warfarin (SPORTIF V) will soon be available. Ximelagatran is undergoing phase II evaluation for long-term therapy in patients with acute coronary syndromes.

Conclusions

Although several promising new anticoagulants have been evaluated, the role of many of these agents remains to be delineated. The challenge is to determine which of the agents presently under development will provide the greatest efficacy with the greatest degree of safety at a reasonable cost.

To gain acceptance for prophylaxis and treatment of venous thromboembolism, new anticoagulants must have a benefit-to-risk ratio that is at least as good as LMWH and warfarin at a comparable cost. Fondaparinux has been evaluated for these indications and is presently licensed for the prevention of venous thromboembolism in high-risk orthopedic patients. However, acceptance of fondaparinux for this indication has been slower than expected because of the perception that it causes more bleeding than LMWH in this setting. Although recently completed studies suggest that fondaparinux is at least as safe and effective as heparin or LWMH for initial treatment of venous thromboembolism, acceptance for this indication also may be slow because of the cost differential between fondaparinux and LMWH. As an orally available agent that does not require routine coagulation monitoring, ximelagatran may prove suitable for extended use in both the prophylaxis and treatment of venous thromboembolism.

Of the new anticoagulants, only bivalirudin has shown consistent benefit in patients undergoing percutaneous coronary interventions and is approved for this indication. Prevention of thromboembolism in patients with atrial fibrillation and prosthetic valves and prevention and treatment of thrombosis in pregnancy are other areas where there is a need for new anticoagulant drugs. Ximelagatran has the potential to replace warfarin in patients with nonvalvular atrial fibrillation. Its utility in other areas remains to be established.

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