
Jeffrey I. Weitz, Jack Hirsh and Meyer M. Samama

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New Antithrombotic Drugs*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)*

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

This chapter focuses on new antithrombotic drugs that are in phase II or III clinical testing. Development of these new agents was prompted by limitations of existing antiplatelet, anticoagulant, or fibrinolytic drugs. Addressing these unmet needs, this chapter (1) outlines the rationale for development of new antithrombotic agents, (2) describes the new antiplatelet, anticoagulant, and fibrinolytic drugs, and (3) provides clinical perspectives on the opportunities and challenges faced by these novel agents.

Key words: anticoagulants; antiplatelet drugs; antithrombotic drug; fibrinolytic agents

Abbreviations: ACS = acute coronary syndrome; CYP = cytochrome P450; DVT = deep vein thrombosis; factor VIIai = active site-blocked factor VIIa; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NAPc2 = nematode anticoagulant peptide c2; PAI-1 = type 1 plasminogen activator inhibitor; PAR = protease activated receptor; PCI = percutaneous coronary intervention; PE = pulmonary embolism; FF4 = platelet factor 4; TAFI = thrombin activatable fibrinolysis inhibitor; TIMI = Thrombolysis in Myocardial Infarction; tPA = tissue-type plasminogen activator; TRAP = thrombin receptor agonist peptide; u-PA = urokinase-type plasminogen activator; VTE = venous thromboembolism

Arterial and venous thrombosis are major causes of morbidity and mortality. Whereas arterial thrombosis is the most common cause of myocardial infarction (MI), ischemic stroke and limb gangrene, deep vein thrombosis (DVT) leads to pulmonary embolism (PE), which can be fatal, and to the post-phlebitic syndrome. Arterial thrombi, which form under high shear conditions, consist of platelet aggregates held together by small amounts of fibrin. Because of the predominance of platelets, strategies to inhibit arterial thrombogenesis focus mainly on drugs that block platelet function, but include anticoagulants for prevention of cardioembolic events in patients with atrial fibrillation or mechanical heart valves. Fibrinolytic drugs are used for rapid restoration of antegrade blood flow in patients with acute myocardial infarction who do not undergo a primary percutaneous coronary intervention (PCI) and for treatment of acute ischemic stroke.

Venous thrombi, which form under low shear, are composed mainly of fibrin and trapped red cells, and contain relatively few platelets. With the predominance of fibrin in venous thrombi, anticoagulants are the agents of choice for the prevention and treatment of venous thromboembolism (VTE). Systemic fibrinolytic therapy is used for treatment of massive PE and for management of selected patients with submassive PE, whereas catheter-directed fibrinolytic therapy is used in some patients with extensive iliofemoral DVT.

Limitations of existing antithrombotic drugs have prompted a search for novel agents. Focusing on new drugs for the prevention and treatment of arterial and venous thrombosis, this chapter outlines the rationale for development of new antithrombotic drugs, describes the new antithrombotic drugs, focusing primarily on those in Phase II or III clinical testing.
testing, and provides perspective on the unmet needs in antithrombotic therapy.

2.0 RATIONALE FOR DEVELOPMENT OF NEW ANTITHROMBOTIC DRUGS

Better understanding of the molecular mechanisms underlying thrombogenesis, advances in recombinant DNA technology, isolation and characterization of antithrombotic proteins from hematophagous 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 antithrombotic drugs.

The established efficacy of aspirin and the thienopyridines validates platelet cyclooxygenase-1 and ADP receptors as targets for antithrombotic drugs. By irreversibly acetylating cyclooxygenase-1, aspirin inhibits arachidonate-induced platelet aggregation and reduces thromboxane A2 synthesis by > 98%. Although cheap and effective, breakthrough cardiovascular events occur despite aspirin therapy. Some patients are resistant to usual doses of aspirin as manifested by incomplete inhibition of platelet aggregation and/or ongoing thromboxane A2 production. Such patients may be more prone to recurrent cardiovascular events.

Thromboxane A2 receptor antagonists were developed, at least in part, to overcome the limitations of aspirin. Thromboxane A2 induces platelet aggregation by binding to the thromboxane A2 receptor on platelets. The thromboxane A2 receptor also binds prostanoids, such as prostaglandin F2α, which can promote platelet aggregation by causing vasoconstriction.

Thromboxane A2 receptor antagonists block platelet aggregation in response to both thromboxane A2 and prostanoids. In contrast, aspirin has no effect on prostanoid synthesis and incompletely inhibits thromboxane A2 synthesis in some patients. Therefore, thromboxane A2 receptor antagonists have the potential to be more effective than aspirin.

The thienopyridines irreversibly inhibit P2Y12, a major ADP receptor on the platelet surface. Currently available thienopyridines include ticlopidine and clopidogrel. Clopidogrel has largely replaced ticlopidine because the risk of hematological toxicity is lower and the drug can be given once daily. When given in usual doses, these drugs incompletely inhibit ADP-induced platelet aggregation producing a maximum of 70% inhibition. The extent of inhibition varies between patients and some are resistant to clopidogrel.

The thienopyridines have a delayed onset of action because they require metabolic activation. This is problematic in patients undergoing percutaneous coronary interventions (PCI) where rapid platelet inhibition is required. Administration of loading doses of clopidogrel accelerates its antiplatelet effects, but maximum inhibition remains delayed for several hours. Not only do the thienopyridines have a slow onset of action, but their offset of action also is delayed for at least 5 days because the active metabolites of these drugs irreversibly inhibit their target receptor. This causes problems for patients who require urgent surgery because clopidogrel increases the risk of bleeding.

The limitations of existing antiplatelet drugs provide opportunities for new agents. Attempts to replace aspirin with other inhibitors of the thromboxane A2-mediated pathway of platelet aggregation have not yet been successful. Instead, attention has focused on novel ADP receptor antagonists and on drugs that target protease activated receptor (PAR)-1, the major thrombin receptor on platelets. New P2Y12 antagonists have been developed to replace clopidogrel. Drugs that produce more predictable inhibition of ADP-induced platelet aggregation may overcome clopidogrel resistance, whereas those with a rapid onset and offset of action may have advantages in the PCI setting. Whether a rapid onset and offset of action is an advantage for long-term administration is uncertain. Although new P2Y12 antagonists have the potential to be more efficacious than clopidogrel because they produce more profound inhibition of ADP-induced aggregation, there may be issues with safety. Thus, enhancing the extent of platelet inhibition by adding clopidogrel to aspirin increases the risk of major bleeding and more potent ADP receptor antagonists may further increase this risk. Finally, clinical development of PAR-1 antagonists has started and preliminary results are encouraging. Clinical trials with these agents will help define the role of PAR-1 in atherothrombosis.

Currently available anticoagulants include both parenteral and oral agents. Rapidly acting parenteral anticoagulants are usually used for initial treatment of arterial or venous thromboembolism, whereas oral agents are employed for long-term therapy. For initial treatment, low-molecular-weight heparin (LMWH) has replaced heparin for most indications because LMWH is more convenient to administer and meta-analyses of clinical trials comparing it with heparin indicate that LMWH is at least as effective and safe. More recently, fondaparinux, a synthetic pentasaccharide, has been licensed for VTE prevention in high-risk orthopedic surgery patients and in some countries, in general surgical or medical patients. Fondaparinux also is licensed as an alternative to heparin or LMWH for initial treatment of VTE.
Fondaparinux appears to be more effective than LMWH for VTE prophylaxis in high-risk orthopedic patients. It is as effective and safe as LMWH for prophylaxis in general surgical patients and as effective and safe as heparin or LMWH for initial VTE treatment. Fondaparinux also is a promising drug for patients with non-ST-segment elevation acute coronary syndromes (ACS). In this setting, fondaparinux is as effective as LMWH at preventing recurrent ischemia but is associated with a 50% reduction in the risk of major bleeding. Furthermore, fondaparinux, which requires only once-daily injection, is more convenient to administer than LMWH and is less expensive. However, there are at least two limitations of fondaparinux in the non-ST-segment elevation ACS setting. First, there is a risk of catheter thrombosis in fondaparinux-treated patients unless adjunctive heparin is given. Second, fondaparinux is cleared via the kidneys. Therefore, the drug accumulates in patients with renal insufficiency, which can be problematic in the elderly where renal impairment is common.

Building on the results with fondaparinux, second and third generation synthetic pentasaccharides include variants with longer half-lives and a pentasaccharide-containing hexadecasaccharide. The long-acting pentasaccharides can be given subcutaneously on a once-weekly basis, and the anticoagulant effects of the biotinylated variant can be rapidly reversed with IV avidin. With the focus on extended treatment, long-acting pentasaccharides are being compared with warfarin. The efficacy and safety of these new agents are uncertain. Safety is particularly concerning in the elderly where renal impairment may cause drug accumulation. It also is unclear whether compliance with once-weekly injections will be an issue.

Like heparin, the pentasaccharide-containing hexadecasaccharide accelerates the inhibition of both factor Xa and thrombin by antithrombin. In contrast to heparin, the hexadecasaccharide exhibits better bioavailability after subcutaneous injection, is excreted via the kidneys and is unlikely to cause heparin-induced thrombocytopenia. Whether this agent has efficacy or safety advantages over LMWH or fondaparinux is uncertain.

Some of the new parenteral anticoagulants are direct inhibitors that target thrombin or factor Xa. Aimed at niche indications, these drugs are being investigated for treatment of heparin-induced thrombocytopenia or as alternatives to heparin in patients undergoing PCI. Other new parenteral drugs target factor VIIa or IXa or promote protein C activation. Because most of these targets have yet to be validated, the ultimate indications for these agents are uncertain.

For long-term anticoagulation, oral agents are preferred over parenteral drugs. The vitamin K antagonists, such as warfarin, have been the only oral anticoagulants available for the past 65 years. This situation could change with the development of small molecule, orally active, direct inhibitors of thrombin or factor Xa. Although withdrawn from the market because of potential hepatotoxicity, the results with ximelagatran validate thrombin as a target for new oral anticoagulants. Ongoing clinical trials with other orally active direct thrombin inhibitors will determine whether hepatic toxicity is unique to ximelagatran or whether it represents a class effect. The data with fondaparinux and emerging results with oral factor Xa inhibitors suggest that factor Xa also is a good target for anticoagulants. It is unclear whether upstream inhibition at the level of factor Xa is safer or more effective than downstream inhibition of thrombin. Ultimately, head-to-head trials comparing the two classes of anticoagulants will be needed to address this issue.

3.0 New Antiplatelet Agents

New antiplatelet agents in advanced stages of development target the thromboxane A2, ADP or thrombin receptors on platelets (Fig 1). Most of the new ADP receptor antagonists target P2Y12, whereas the thrombin receptor antagonists target PAR-1.

3.1 Thromboxane A2 Receptor Antagonists

A selective inhibitor of the thromboxane A2 receptor on platelets, S18886 is orally active. Peak drug levels are obtained within 1 to 2 h of drug administration and the drug has a half-life of 6 to 10 h. S18886 inhibits thromboxane A2-induced platelet aggregation in a dose-dependent fashion with maximum inhibition obtained with drug levels > 10 ng/mL; a concentration that can be achieved with S18886 doses of 10 to 30 mg.

Single-dose administration of 10 mg of S18886 to 12 patients with coronary artery disease who were receiving aspirin (100 mg/d) improved forearm blood flow after acetylcholine infusion compared with the results in 8 aspirin-treated patients who received placebo. S18886 is now being investigated for secondary prevention of stroke in a large phase II trial.

3.2 ADP Receptor Antagonists

New ADP receptor antagonists include prasugrel, a thienopyridine, as well as cangrelor and AZD6140, direct competitive inhibitors of P2Y12 that are administered parenterally and orally, respectively.
3.2.1 Prasugrel

Like ticlopidine and clopidogrel, prasugrel is a prodrug that requires hepatic conversion to express its antiplatelet activity. Prasugrel is rapidly absorbed from the GI tract with little intersubject variability. Once absorbed, the drug is hydrolyzed by esterases to an inactive metabolite that is then further metabolized by the hepatic cytochrome P450 (CYP) enzyme system (primarily via CYP3A and CYP2B6) to an active form, which is designated R-138727. Hepatic conversion to R-138727, the active metabolite, involves a single-step oxidation. In contrast, once absorbed, esterases convert clopidogrel into an inactive metabolite making less available for activation. Therefore, the activation of prasugrel is more efficient than that of clopidogrel.

Like prasugrel, clopidogrel is activated by the CYP system through multiple oxidative steps. However, common genetic polymorphisms in CYP enzymes affect the metabolism of clopidogrel and prasugrel differently. For example, the genetic polymorphisms in CYP3A4 that are reported to limit clopidogrel activation and to cause clopidogrel resistance in some patients are unlikely to influence the activity of prasugrel. Likewise, common polymorphisms in CYP2C9 and CYP2C19 that affect the pharmacological response to clopidogrel have no effect on the activity of prasugrel.

Like ticlopidine and clopidogrel, prasugrel irreversibly inhibits the P2Y_{12} receptor. R-138727, the active metabolite of prasugrel, is a sulfhydryl compound that binds covalently to P2Y_{12} in a fashion similar to the active metabolite of clopidogrel. Studies in animals and humans suggest that prasugrel attenuates ADP-induced platelet aggregation more effectively than clopidogrel. Although the onset of platelet inhibition is more rapid with prasugrel than it is with clopidogrel, both drugs have a delayed onset of action because they irreversibly inhibit their target receptor.

In the Joint Utilization of Medications to Block Platelets Optimally Thrombolysis in Myocardial Infarction (JUMBO TIMI)-26 phase 2 trial, patients undergoing elective or urgent PCI were randomized to receive one of three dosage regimens of prasugrel (40, 60 or 60 mg as a loading dose followed by 7.5, 10, or 15 mg, respectively, as a once-daily maintenance dose) or clopidogrel (300 mg as a loading dose followed by a maintenance dose of 75 mg qd). The study was designed to compare the safety profile of prasugrel with that of clopidogrel. Bleeding (major plus minor) occurred in 1.7% of patients given prasugrel and in 1.2% of those treated with clopidogrel. Rates of bleeding were similar among the three prasugrel dosage regimens. Treatment with prasugrel was associated with a nonsignificant decrease in the combined end point of death, MI, stroke, recurrent myocardial ischemia requiring hospitalization and clinical target vessel thrombosis through 30 days (7.2% and 9.4%, respectively; relative risk 0.77 with 95% confidence intervals of 0.5 to 1.2).

A large phase III trial known as TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition) TIMI-38 compared prasugrel (60 mg loading dose followed by a maintenance dose of 10 mg once daily) with clopidogrel (300 mg loading dose followed by a maintenance dose of 75 mg once daily) in 13,608 moderate to high risk ACS patients scheduled to undergo PCI. Treatment was given for 6 to 15 months and the primary efficacy outcome was a composite of cardiovascular death, nonfatal MI or nonfatal stroke, while the key safety end point was major bleeding.
The primary efficacy end point occurred in 9.9% of patients receiving prasugrel and in 12.1% of those given clopidogrel (hazard ratio 0.81; 95% CI, 0.73 to 0.90; p < 0.001). Rates of MI also were lower with prasugrel than with clopidogrel (7.4% and 9.7%, respectively; p < 0.001), as were the rates of urgent target vessel revascularization and stent thrombosis (2.5% and 3.7%; p < 0.001 and 1.1% and 2.4%; p < 0.001, respectively).

Major bleeding occurred more frequently with prasugrel than with clopidogrel (2.4% and 1.8%, respectively; hazard ratio, 1.32; 95% CI, 1.03 to 1.68; p = 0.03). Rates of life-threatening bleeding and fatal bleeding also were higher with prasugrel than with clopidogrel (1.4% and 0.9%, respectively; p = 0.01 and 0.4% and 0.1%, respectively; p = 0.002). Post hoc analysis suggested that the elderly (75 years or older), those with a body weight < 60 kilograms and patients with a history of stroke or transient ischemic attack prior to enrolment were at particularly high risk for bleeding; risk factors that have previously been associated with a higher bleeding risk with other antithrombotic agents. Thus, although more efficacious than clopidogrel, prasugrel, at least in the doses used in this trial, is associated with a higher risk of major bleeding, including fatal bleeding. Further studies are needed to determine whether dose adjustment or careful patient selection will improve the benefit-to-risk profile of prasugrel. Nonetheless, this trial supports the concept that more intensive ADP receptor blockade results in improved efficacy, but also increases the risk of bleeding.

3.2.2 Cangrelor

An ATP analog, cangrelor is a direct competitive inhibitor of P2Y12. In contrast to clopidogrel or prasugrel, cangrelor does not require hepatic conversion to an active metabolite. Therefore, cangrelor produces almost immediate and dose-proportional inhibition of ADP-induced platelet aggregation after IV administration. The drug has a half-life of about 3 to 5 min and, with cessation of therapy, there is recovery of platelet function within 60 min.

Cangrelor has been evaluated in a two-part phase II trial in patients undergoing PCI. In part 1, 200 patients were randomized to an 18 to 24 h infusion of cangrelor (in doses of 1, 2 or 4 μg/kilogram/min) or placebo in addition to aspirin plus heparin. In part 2, an additional 199 patients were randomized to cangrelor (4 μg/kg/min) or abciximab prior to PCI. In the first part of the study, the primary end point, major and minor bleeding up to 7 days, occurred in 13% of patients given cangrelor and in 8% of those given placebo, a difference that was not statistically significant. In part 2, bleeding occurred in 7% and 10% of those randomized to cangrelor and abciximab, respectively. The 30-day composite of adverse cardiac events (death, MI, and unplanned repeat coronary intervention) was not significantly different in patients given cangrelor or abciximab (7.6% and 5.3%, respectively). Based on these results, cangrelor is currently undergoing phase III evaluation in PCI patients.

3.2.3 AZD6140

An orally active agent, AZD6140 acts as a direct competitive inhibitor of P2Y12. Like cangrelor, AZD6140 does not require hepatic conversion to an active metabolite. Therefore, AZD6140 produces rapid reversible inhibition of ADP-induced platelet aggregation. Because of its rapid onset of action, there is no need for a loading dose. However, the drug likely requires bid administration to ensure that the receptor remains blocked.

When compared with clopidogrel in 200 aspirin-treated patients with atherosclerosis, AZD6140, in doses of 100 or 200 mg twice–daily, or 400 mg qd, produced more rapid and more potent inhibition of ADP-induced platelet aggregation. The Dose Confirmation Study Assessing Antiplatelet Effects of AZD6140 Vs. Clopidogrel in nonST-elevation MI (DISPERSE 2) study compared AZD6140 plus aspirin with clopidogrel plus aspirin in 990 patients with nonST-segment elevation acute coronary syndromes (ACS). Patients were randomized to receive AZD6140 (90 or 180 mg bid) or clopidogrel (75 mg qd). Half of the patients randomized to AZD6140 were given a loading dose of 270 mg, while the other half only received the maintenance dose. The primary end point, a combination of major and minor bleeding, occurred in 10.2% of patients given either dose of AZD6140 and in 9.2% of those treated with clopidogrel.

Side effects of AZD6140 include dyspnea, which is usually mild, and bradycardia. AZD6140 is an ATP analog that is metabolized to adenosine. In some patients with reactive airways, adenosine can trigger dyspnea. Adenosine also could be responsible for the bradycardia. Other potential explanations for the dyspnea include fluid retention or subclinical thrombotic thrombocytopenia purpura. Increased levels of uric acid have been reported in some AZD6140-treated patients. The clinical significance of these side effects will become clearer in the ongoing phase III trials of AZD6140.

3.3 PAR-1 Antagonists

PAR-1 belongs to a family of G-protein-coupled receptors that are activated by proteolytic cleavage.
Human platelets express PAR-1 and PAR-4, both of which can be activated by thrombin to induce platelet secretion and aggregation. Although activation of either receptor can cause platelet aggregation independently of the other, PAR-1 and PAR-4 act synergistically to effect platelet activation. However, the affinity of PAR-1 for thrombin is 40-fold higher than that of PAR-4. Consequently, PAR-1 is activated by relatively low concentrations of thrombin, whereas PAR-4 activation requires higher thrombin concentrations. Therefore, PAR-1 is considered to be the major thrombin receptor on human platelets.

PAR-1 also is found on endothelial cells, smooth muscle cells, fibroblasts, and cardiac myocytes. Thrombin-mediated activation of PAR-1 on these cells may contribute to the proliferative and proinflammatory effects of thrombin. Therefore, it is possible that PAR-1 antagonism will not only attenuate arterial thrombosis, but may also modulate other thrombin-mediated processes, including restenosis. At least two orally active PAR-1 antagonists are undergoing phase II clinical evaluation. These are SCH-530348 and E5555.

3.3.1 SCH-530348

A synthetic analog of himbacine, an alkaloid isolated from the bark of Australian magnolia trees that is used in several natural products, SCH-530348 is a potent and specific inhibitor of PAR-1. The drug has excellent oral bioavailability and produces dose-dependent inhibition of thrombin- or thrombin receptor agonist peptide (TRAP)-induced platelet aggregation. It does not affect platelet aggregation in response to other agonists. SCH-530348 has a long half-life and inhibits TRAP-induced platelet aggregation for up to 4 weeks. In phase I studies, SCH-530348 does not appear to increase the bleeding time when administered to healthy volunteers. A phase II trial in 1031 patients scheduled for coronary angiography and possible PCI randomized patients to SCH-530348 (at loading doses of 10, 20 or 40 mg) or placebo (www.schering-plough.com). A total of 573 patients actually underwent PCI. All received aspirin, clopidogrel and an anticoagulant (either heparin or bivalirudin). Those randomized to SCH-530348 received maintenance therapy at doses of 0.5, 1.0 or 2.5 mg once daily for 2 months. The primary outcome, a combination of TIMI major and minor bleeding occurred in 3.3% of the 151 patients randomized to placebo and in 2.8% of the 422 patients given SCH-530348. Major bleeding occurred in 1.3% and 0.7%, respectively. Although underpowered for efficacy and safety, the results with SCH 530348 are promising. Thus, there was no increase in bleeding and the combination of death, major adverse coronary events and stroke occurred in 8.6% of patients randomized to placebo and in 6.2% of those given SCH-530348, whereas death and major adverse cardiovascular events, the primary efficacy end point, occurred in 8.6% and 5.9%, respectively. Building on these phase II results, SCH-530348 is now undergoing phase III evaluation in a wide range of ACS patients.

3.3.2 E5555

A reversible PAR-1 antagonist, E5555 binds PAR-1 with high affinity and blocks thrombin and TRAP-induced platelet aggregation. The drug exhibits good oral bioavailability and is rapidly absorbed. Maximal platelet inhibition is achieved within 5 h of dosing. The antiplatelet effects of E5555 persist for about one week (www.eisai.com). Like SCH-530348, E5555 does not appear to prolong the bleeding time when administered to healthy volunteers. Phase II trials evaluating E5555 in patients with ACS are underway.

4.0 New Anticoagulants

Anticoagulants can inhibit the initiation or propagation of coagulation, or by targeting thrombin, they can attenuate fibrin formation. Drugs that target the tissue factor/factor VIIa complex block the initiation of coagulation, while those that inhibit factor IXa or factor Xa, or their cofactors, factor VIIa and factor Va, block the propagation of coagulation. Finally, anticoagulants that target thrombin attenuate fibrin generation. New anticoagulants can be further subclassified as direct or indirect inhibitors (Fig 2). Direct inhibitors bind directly to the target enzyme and block substrate interactions. In contrast, indirect inhibitors exert their anticoagulant effects by binding to naturally occurring plasma cofactors, such as antithrombin or heparin cofactor II, thereby accelerating their interaction with clotting enzymes.

4.1 Inhibitors of Initiation of Coagulation

Drugs that target the factor VIIa/tissue factor complex inhibit the initiation of coagulation. Only parenteral agents in this category have reached phase II or III clinical testing (Table 1). These include tifacogin, recombinant tissue factory pathway inhibitor, recombinant nematode anticoagulant peptide (NAPc2) and active site inhibited factor VIIa (factor VIIai).

4.1.1 Tifacogin

A recombinant form of tissue factory pathway inhibitor expressed in Saccharomyces cerevisae, tifa-
cogin has been evaluated in patients with sepsis. The drug has a half-life of minutes, which necessitates IV infusion, and is cleared by the liver. In a phase II trial, 210 sepsis patients were randomized to receive one of two doses of tifacogin (25 or 50 μg/kg/h) by continuous infusion or placebo for 4 days. Compared with placebo, tifacogin produced a 20% relative reduction in 28-day mortality. Major bleeding occurred in 9% of patients treated with tifacogin and in 6% of those given placebo, a difference that was not statistically significant. Building on these results, a phase III trial compared tifacogin with placebo in 1754 severe sepsis patients. The primary end point, 28-day mortality, was similar with tifacogin and placebo (34.2% and 33.9%, respectively), while the rate of bleeding was significantly higher with tifacogin (6.5% and 4.8%, respectively). An ongoing phase III clinical trial is comparing two doses of tifacogin with placebo in patients with severe community acquired pneumonia (www.clinicaltrials.gov).

4.1.2 NAPc2

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

Initial clinical trials with NAPc2 focused on venous thromboprophylaxis. In a phase II dose-finding study, 293 patients undergoing elective knee arthroplasty were given subcutaneous NAPc2 on the day of surgery, and every second day thereafter to a maximum of 4 doses. Best results were observed with a NAPc2 dose of 3.0 μg/kg administered one hour after surgery. With this dose, the 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 patients. Compared with historical controls, NAPc2 appears to

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**Table 1—Inhibitors of the Factor VIIa—Tissue Factor Complex**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tifacogin</td>
<td>IV</td>
<td>Inhibits factor VIIa in a factor Xa-dependent fashion</td>
<td>Phase III</td>
</tr>
<tr>
<td>NAPc2</td>
<td>Subcutaneous</td>
<td>Inhibits factor VIIa in a factor X or Xa-dependent fashion</td>
<td>Phase II</td>
</tr>
<tr>
<td>Factor VIIa</td>
<td>IV</td>
<td>Competes with factor VIIa for tissue factor</td>
<td>Halted</td>
</tr>
</tbody>
</table>

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*Figure 2. Classification of new anticoagulants. Indirect anticoagulants act in an antithrombin (AT)- or heparin cofactor II (HCII)-dependent fashion or exert their effect via the protein C pathway. Direct anticoagulants do not require a plasma cofactor. Instead, these agents directly target a specific coagulation enzyme.*
have efficacy and safety similar to those of LMWH. 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 has been evaluated in patients with unstable angina or non–ST-elevation myocardial infarction and in those undergoing percutaneous coronary interventions (PCI). Addition of NAPc2 to usual antithrombotic therapy in 203 patients with ACS reduced levels of prothrombin fragment 1.2 in a dose-dependent fashion without increasing the risk of bleeding.50 In a second trial, adjunctive NAPc2 (in doses ranging from 3.5 to 10 μg/kg), suppressed levels of prothrombin fragment 1.2 in patients undergoing elective PCI.51 An ongoing trial is evaluating NAPc2 as a substitute for heparin in PCI patients.

4.1.3 Factor VIIai

Recombinant factor VIIa that has its active site irreversibly blocked competes with factor VIIa for tissue factor binding, thereby attenuating the initiation of coagulation by the factor VIIa/tissue factor complex. Based on promising results in animal models of thrombosis,52,53 factor VIIai, given in doses ranging from 50 to 400 μg/kg with or without adjunctive heparin, was compared with heparin alone in 491 patients undergoing elective PCI.54 Factor VIIai, with or without adjunctive heparin, produced no significant reduction in the primary end point, a composite of death, MI, need for urgent revascularization, abrupt vessel closure, or bailout use of Glycoprotein IIb/IIIa antagonists or heparin at day 7 or at hospital discharge. Rates of major bleeding were similar with factor VIIai and heparin. Because of these disappointing results, factor VIIai has not been developed further for treatment of arterial thrombosis.

4.2 Inhibitors of Propagation of Coagulation

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

4.2.1. Factor IXa Inhibitors

Both parenteral and oral factor IXa inhibitors are under development (Table 2). The parenteral factor IXa inhibitor is an RNA aptamer (designated RB006) that binds factor IXa with high affinity.55 In phase I studies,56 this aptamer produced rapid anticoagulation as evidenced by a dose-dependent prolongation of the activated partial thromboplastin time. A unique aspect of RB006 is its potential for rapid neutralization by a complementary oligonucleotide (designated RB007). This drug-antidote pair is being developed for use in cardiopulmonary bypass surgery, or other indications where rapid anticoagulant reversal may be beneficial.57 An orally active direct factor IXa inhibitor also has been developed. Designated TTP889, this agent completed a phase IIa clinical trial that was negative.58

4.2.2 Factor Xa Inhibitors

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, which has limited capacity to inhibit factor Xa incorporated into the thrombinase complex,59,60 direct factor Xa inhibitors inhibit both free and platelet-bound factor Xa.61,62 This property may endow these agents with an advantage over indirect factor Xa inhibitors.

4.2.2.1 Indirect Factor Xa Inhibitors: The prototype of the new indirect factor Xa inhibitors is fondaparinux, a first generation synthetic analog of the antithrombin-binding pentasaccharide found in heparin or LMWH.63 Based on the results of well designed randomized clinical trials, fondaparinux is already licensed for prevention of VTE in patients undergoing high-risk orthopedic surgery17,18 and, in some countries, for VTE prevention in general surgical19 or medical patients.64 Fondaparinux also is approved as a substitute for heparin or LMWH for initial treatment of VTE.20,21 Fondaparinux has been evaluated in patients with non–ST-segment elevation and with ST-segment elevation MI.22,65 Additional studies are needed to better understand the safety of fondaparinux when adjunctive heparin is given to those patients undergoing PCI. The newer indirect factor Xa inhibitors are second and third generation.
variants of fondaparinux. These include idraparinux, SSR126517E and SR123781A (Table 3).

**Idraparinux**: A hypermethylated derivative of fondaparinux, idraparinux binds antithrombin with such high affinity that its plasma half-life of 80 h is similar to that of antithrombin.\(^66\) Because of its long half-life, idraparinux can be given subcutaneously on a once-weekly basis. In a phase II dose-finding trial, idraparinux was compared with warfarin in 659 patients with proximal DVT.\(^67\) After a 5- to 7-day course of enoxaparin, patients were randomized to receive once-weekly subcutaneous idraparinux (2.5, 5.0, 7.5 or 10 mg) or warfarin for 12 weeks. The primary end point, thrombus burden, as assessed by measuring 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 given idraparinux with an unacceptably high frequency in those given the 10 mg dose. Two patients, both of whom received 5 mg of idraparinux once-weekly, suffered a fatal bleed. Patients given the lowest dose of idraparinux had less bleeding than those randomized to warfarin (p = 0.029). Based on these results, a once-weekly 2.5 mg dose of idraparinux was chosen for further trials.

The phase III Van Gogh DVT and PE trials\(^68\) randomized 2,904 patients with acute symptomatic DVT and 2,215 patients with PE to either a 3 to 6 month course of once-weekly subcutaneous idraparinux (at a dose of 2.5 mg) or to conventional therapy with LMWH or heparin followed by a vitamin K antagonist. Based on the results of these trials, idraparinux appears to have an acceptable safety profile compared with warfarin. The discordant results in the DVT and PE trials highlight the importance of adequate levels of anti-coagulation for initial PE treatment because the majority of the recurrences occurred early. These findings suggest that PE patients require higher initial doses of idraparinux than DVT patients.

The efficacy of long-term idraparinux was evaluated in the Van Gogh extension study.\(^69\) In this trial, 1215 patients who had completed 6 months of initial treatment of DVT or PE with either idraparinux or a vitamin K antagonist were randomized to an additional 6 months of treatment with either once-weekly subcutaneous idraparinux or with placebo. Compared with placebo, idraparinux produced a 72.9% relative reduction in the risk of recurrent VTE (p = 0.002), reducing recurrent events from 3.7% to 1%. Major bleeding occurred in 3.7% of those given idraparinux and included 3 fatal intracranial bleeds. In contrast, there were no major bleeds in the placebo group. These findings suggest that although effective compared with placebo, idraparinux causes excessive bleeding. Based on this information, it is unlikely that idraparinux will be developed further. Instead, attention has shifted to SSR12517E.

**SSR12517E**: A biotinylated form of idraparinux, SSR12517E exhibits the same pharmacokinetic and pharmacodynamic profile as idraparinux. Like idraparinux, SSR12517E is given subcutaneously on a once-weekly basis. The only difference is that the anticoagulant activity of SSR12517E can be rapidly neutralized by IV administration of avidin. A large tetrameric protein derived from egg white, avidin binds biotin with high affinity to form a 1:1 stoichiometric complex that is then cleared via the kidneys.

SSR12517E is now undergoing phase III evaluation in patients with symptomatic PE with or without evidence of DVT. Patients are given at least 5 days of

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idraparinux</td>
<td>Subcutaneous</td>
<td>Inhibits factor Xa in an antithrombin-dependent fashion</td>
<td>Completed phase III</td>
</tr>
<tr>
<td>SSR12517E</td>
<td>Subcutaneous</td>
<td>Biotinylated form of idraparinux</td>
<td>Phase III</td>
</tr>
<tr>
<td>SR123781A</td>
<td>Subcutaneous</td>
<td>Synthetic hexadecasaccharide that inhibits factor Xa and thrombin in an antithrombin-dependent fashion</td>
<td>Phase II</td>
</tr>
</tbody>
</table>
heparin or LMWH before being randomized to SSR12517E or to a vitamin K antagonist.

**SR123781A:** A synthetic hexadecasaccharide, SR123781A is composed of the antithrombin-binding synthetic pentasaccharide plus a thrombin binding sulfated tetrasaccharide joined together by a central nonsulfated heptasaccharide. SR123781A binds antithrombin with high affinity. In addition to catalyzing factor Xa inhibition by antithrombin, SR123781A is long enough to bridge antithrombin to thrombin, thereby enhancing thrombin inhibition. Like heparin, therefore, SR123781A catalyzes the inhibition of both factor Xa and thrombin. Unlike heparin, SR123781A does not bind platelet factor 4 (PF4) or fibrin. Because it does not bind PF4, heparin-induced thrombocytopenia is unlikely to occur with SR123781A. Without affinity for fibrin, SR123781A does not promote the formation of the ternary heparin/thrombin/fibrin complex that protects fibrin-bound thrombin from inhibition by the antithrombin/heparin complex. In contrast to heparin, therefore, SR123781A appears capable of inhibiting fibrin-bound thrombin.

SR123781A is administered subcutaneously. It exhibits almost complete bioavailability after subcutaneous administration and produces a dose proportional increase in the activated partial thromboplastin time and anti-factor Xa activity. The drug is primarily cleared by the kidneys where it is excreted intact. SR123781A is currently undergoing phase II evaluation for prophylaxis in patients undergoing knee arthroplasty.

### 4.2.2.2 Direct Factor Xa Inhibitors

Direct factor Xa inhibitors include parenteral agents, such as DX9065a and otamixaban, as well as several orally active drugs. All of the direct factor Xa inhibitors are small molecules that reversibly block the active site of factor Xa (Table 4). The large number of oral factor Xa inhibitors highlights the continued focus on development of oral anticoagulants that can replace vitamin K antagonists, such as warfarin.

**DX-9065a:** A synthetic nonpeptidic direct FXa inhibitor, DX9065a is administered parentally, has a dose-dependent half-life that ranges from 40 min to 5 h, and is cleared by the kidneys. DX9065a was evaluated in patients with non–ST-elevation ACS and in patients undergoing PCI. In the ACS trial, 402 patients were randomized to weight-adjusted heparin or to low- or high-dose DX-9065a. The primary efficacy end point, a composite of death, MI, urgent revascularization, or ischemia, occurred in 33.6%, 34.3%, and 31.3% of patients, respectively.

**Otamixaban:** A noncompetitive inhibitor of FXa, this agent is administered IV and has a half-life of 2–3 h. It is excreted unchanged in the urine, whereas metabolites appear in the feces. A phase IIa study compared a 24-h otamixaban infusion with placebo in patients with stable coronary artery disease. The addition of otamixaban to usual medications did not cause bleeding and otamixaban produced a rapid and sustained increase in anti-factor Xa activity. A phase II trial comparing otamixaban with heparin in patients undergoing nonurgent percutaneous coronary interventions demonstrated greater reductions in the levels of prothrombin fragment 1 + 2 with otamixaban than with heparin and no difference in the rate of major bleeding.

**Razaxaban:** Razaxaban, a nonpeptidic oral FXa inhibitor, underwent phase II evaluation for thromboprophylaxis after knee arthroplasty. The primary end point, a composite of venographically-detected DVT and symptomatic venous thromboembolism, occurred in 8.6% of patients randomized to the lowest dose of razaxaban and in 15.9% of those given enoxaparin. Major bleeding occurred in 0.7% of patients given the lowest dose of razaxaban and in none of those treated with enoxaparin. The three higher dose razaxaban arms were stopped prematurely because of increased rates of major bleeding. Because of the narrow therapeutic index and phar-

### Table 4—Direct Factor Xa Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>DX-9065a</td>
<td>IV</td>
<td>Stopped at phase II</td>
</tr>
<tr>
<td>Otamixaban</td>
<td>IV</td>
<td>Phase II</td>
</tr>
<tr>
<td>Razaxaban</td>
<td>Oral</td>
<td>Stopped at phase II</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Oral</td>
<td>Phase III</td>
</tr>
<tr>
<td>LY-517717</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>YM-150</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>DU-176b</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
<tr>
<td>PRT054021</td>
<td>Oral</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Major bleeding occurred in 3.3% of those randomized to heparin and in < 1% of those who received DX-9065a. In the PCI trial, 175 patients were randomized to open-label DX-9065a or to heparin in one of four sequential phases. Although thrombotic events were rare in all phases of the study, enrollment in the phase evaluating the lowest dose of DX-9065 was stopped because of catheter thrombosis. Major bleeding events were uncommon and there was no apparent dose-response. Although promising, DX9065a has not undergone further clinical evaluation.
macological limitations, further development of raza-
xaban was halted in favor of apixaban.

**Apixaban:** A variant of razaxaban that has superior
pharmacologic properties, apixaban has high oral
bioavailability and a half-life of about 12 h. Food
has no effect on its absorption and the drug
produces a predictable anticoagulant effect. Apixa-
ban is cleared through both the fecal and renal route
with renal elimination accounting for about 25% of
drug clearance.

In a phase II trial in 1,238 patients undergoing
knee replacement surgery, apixaban was compared
with enoxaparin or with warfarin. Apixaban was
given in total daily doses of 5, 10 or 20 mg using a
once-daily or a bid regimen. The primary end point,
total venous thromboembolism and all-cause mortal-
ity, was lower with all doses of apixaban than with
enoxaparin or warfarin. At daily doses of 10 or 20 mg,
the efficacy of apixaban appeared to be better with
bid dosing than with once-daily treatment. Total
bleeding was less frequent with 5 mg apixaban qd or
with 2.5 mg bid than it was with enoxaparin or
warfarin. With higher doses of apixaban, there was
more bleeding than with enoxaparin or warfarin.
Based on these data, a dose of 2.5 mg apixaban bid
will be compared with enoxaparin in two phase III
trials in patients undergoing knee replacement sur-
surgery and in one trial in patients undergoing hip
replacement surgery. This dose also will be evaluated
for thromboprophylaxis in medical patients. Phase II
trials of apixaban for treatment of venous thrombo-
embolism, for secondary prevention in ACS patients,
and for thromboprophylaxis in cancer patients are
ongoing.

**Rivaroxaban:** An oxazolidone derivative, rivaroxa-
ban has oral bioavailability of 80%, inhibits FXa with
a Ki of 0.4 nM and has a half-life of about 9 h. It is
cleared by the kidneys and the gut. Rivaroxaban has
been evaluated for thromboprophylaxis in pa-
tients undergoing knee or hip arthroplasty in four
phase II trials. Proof of principle was established in
an open-label study in patients undergoing hip ar-
throplasty. This was followed by two double-blind
dose-finding studies, one in patients undergoing hip
arthroplasty and one in those undergoing knee
arthroplasty. Both studies compared twice-daily
oral rivaroxaban at total daily doses of 5, 10, 20, 40 or
60 mg started 6 to 8 h after surgery, with subcuta-
neous enoxaparin (40 mg qd starting the evening
before surgery in patients undergoing hip arthro-
plasty or 30 mg bid starting 12–24 h after surgery
in those having knee arthroplasty). A pooled anal-
ysis of results from two of these studies failed to
demonstrate a statistically significant dose-re-
sponse for efficacy with rivaroxaban, although the
point estimates for both the primary efficacy
outcome (DVT, PE and all-cause mortality) and
secondary efficacy outcome (proximal DVT, PE, and
venous thromboembolism-related mortality) in all of
the rivaroxaban dosing arms were lower than those in
enoxaparin-treated controls. There was a signifi-
cant dose response for major bleeding with the 10,
20, and 30 mg bid rivaroxaban regimens producing
more bleeding than enoxaparin.

A follow-up double blind randomized dose-finding
study in 873 patients undergoing hip arthroplasty
compared once-daily rivaroxaban (in 5 doses ranging
from 5 to 40 mg started 6 to 8 h postoperatively)
with enoxaparin (40 mg qd started the evening
before surgery and given postoperatively at least 6 to
8 h after skin closure). The frequencies of both the
primary efficacy outcome (a composite of venographi-
cally-detected DVT, symptomatic venous thromboem-
bolism and all-cause mortality) and the secondary
efficacy outcome (proximal DVT, PE, and venous
thromboembolism-related mortality) were lower
with all but the 5 mg daily dose of rivaroxaban than
with enoxaparin. Once again, there was no clear
dose-response relationship for efficacy. Compared
with enoxaparin, the point estimates for major bleed-
ing were higher with rivaroxaban than with enoxapa-
rin with all doses except 10 mg. On the basis of these
results, the phase III trials in major orthopedic
surgery used a 10 mg qd dose.

The REgulation of Coagulation in major Orthope-
dic surgery reducing the Risk of DVT and PE (RECORD)-3 trial compared oral rivaroxaban (10
mg qd started 6–8 h after surgery) with subcutane-
ous enoxaparin (40 mg qd started the evening before
surgery) in 2,531 patients undergoing knee replace-
ment surgery. Both regimens were continued for
10 to 14 days. The primary efficacy end point, a
composite of DVT, nonfatal PE and all-cause mor-
tality, occurred in 9.6% of patients receiving rivar-
oxaban and in 18.9% of those given enoxaparin.
Thus, rivaroxaban was associated with a 49% reduc-
tion in relative risk, a difference that was statistically
significant (p < 0.001). Major VTE, a composite of
proximal DVT, nonfatal PE and VTE-related mor-
tality, occurred in 1.0% of patients given rivaroxaban
and in 2.6% of those treated with enoxaparin; a
difference that was statistically significant (p = 0.01).
Symptomatic VTE occurred in 1.0% and 2.7% of
those given rivaroxaban or enoxaparin, respectively.
Major bleeding rates were 0.6% and 0.5% in the
rivaroxaban and enoxaparin-treated groups, respec-
tively, whereas any bleeding occurred in 4.9% and
4.8%, respectively. Three other phase III orthopedic
trials have been conducted with rivaroxaban. Two are completed and the third is underway.

Rivaroxaban also has been evaluated for treatment of proximal DVT in two dose-ranging studies. The first trial randomized 613 patients to a 3-month course of rivaroxaban (at doses of 10, 20 or 30 mg twice daily or 40 mg qd), or to LMWH followed by a vitamin K antagonist. The primary efficacy outcome, reduced thrombus burden based on repeated ultrasound evaluation at 21 days without evidence of recurrent VTE, was achieved in 43.8% to 59.2% of patients given rivaroxaban and in 45.9% of those treated with LMWH followed by a vitamin K antagonist.

In the second study, 543 patients with proximal DVT were randomized to a 3-month course of once-daily rivaroxaban (at doses of 20, 30 or 40 mg) or to heparin or LMWH followed by a vitamin K antagonist. The primary end point, a composite of symptomatic events (VTE-related death, DVT or PE) plus an increase in thrombus burden (as detected by repeated ultrasound and ventilation-perfusion lung scanning), occurred in 6% of those given rivaroxaban and in 9.9% of those receiving conventional therapy. There was no apparent dose-response with rivaroxaban. In both trials, rates of major bleeding were low with rivaroxaban and with conventional therapy. Phase III studies evaluating rivaroxaban for treatment of VTE and for stroke prevention in atrial fibrillation are underway. A 20 mg qd dose of rivaroxaban is being evaluated for these indications.

LY-517717: With oral bioavailability of 25 to 82%, LY-517717 inhibits FXa with a Ki of 5 to 7 nM. LY-517717 has a half-life of about 25 h and is given once daily. LY-517717 was evaluated in a phase II noninferiority study that randomized 511 patients undergoing hip or knee arthroplasty to one of six doses of LY-517717 (25, 50, 75, 100, 125 or 150 mg started 6 to 8 h after wound closure) or to once-daily subcutaneous enoxaparin (40 mg started the evening before surgery). Both treatments were administered for a total of 6 to 10 doses. Randomization to the three lower doses of LY-517717 was stopped early due to lack of efficacy. The three higher doses of LY-517717 had efficacy similar to that of enoxaparin (17.1 to 24.0% and 22.2%, respectively). Adjudicated major bleeding events were uncommon in all study arms. Additional studies are needed to determine the efficacy and safety of this agent.

YM 150: An oral inhibitor that inhibits FXa with a Ki of 31 nM, YM 150 is given once daily. YM 150 was evaluated in 174 patients undergoing elective hip arthroplasty. YM 150, at once-daily doses of 3, 10, 30 or 60 mg produced a statistically significant dose-response for efficacy. No major bleeds were reported and there was no dose-response trend for clinically relevant nonmajor bleeding. Although the point estimates for DVT appeared to favor the two highest doses of YM 150 over enoxaparin, the small study sample size precludes any firm conclusions. A second phase II trial in patients undergoing elective hip arthroplasty is ongoing.

DU-176b: An oral FXa inhibitor, DU-176b inhibits FXa with a Ki of 0.56 nM. Building on preclinical evidence of antithrombotic efficacy in animal models, DU-176b is currently undergoing phase II evaluation in hip arthroplasty patients.

PRT 054021: With oral bioavailability of 47% and a half-life of 19 h, PRT 054021 inhibits factor Xa with a Ki of 0.12 nM. PRT 054021 exhibited antithrombotic activity in animal models and was well tolerated in humans in a phase I trial that included 64 subjects. In the phase II EXPERT trial, oral PRT 054021, at doses of 15 or 40 mg bid, was compared with subcutaneous enoxaparin (30 mg bid) for postoperative thromboprophylaxis in 215 patients undergoing elective knee arthroplasty. Randomization was done in a 2:2:1 fashion and treatment was given for 10 to 14 days. DVT and nonfatal PE occurred in 20% and 15% of patients given 15 or 40 mg of PRT 054021, respectively, and in 10% of those given enoxaparin. There were no major bleeds in the 171 patients given PRT 054021 and there was one major bleed in the 43 patients given enoxaparin.

4.3 Factor Va Inhibitors

Factor Va is the major target of activated protein C. Activated protein C acts as an anticoagulant by proteolytically degrading and inactivating factor Va, a key cofactor in thrombin generation. Factor Va is directly inhibited by drotrecogin alfa (activated), a recombinant form of activated protein C. ART-123, a recombinant analog of the extracellular domain of thrombomodulin, binds thrombin and enhances its capacity to activate protein C (Table 5).

4.3.1 Drotrecogin Alfa (Activated)

A recombinant form of activated protein C, drotrecogin is licensed for treatment of patients with severe sepsis. Approval for this indication was based on a trial comparing drotrecogin with placebo in 1,690 patients with severe sepsis. When given as an infusion of 24 μg/kg/h > 96 h, drotrecogin C produced a 19% reduction in mortality at 28 days (from
30.8% to 24.7%; \( p = 0.005 \)). The rate of major bleeding was higher with drotrecogin than with placebo (3.5% and 2%, respectively; \( p = 0.06 \)). Since approval, two additional clinical trials, one in adults with sepsis and a low risk of death and the other in children with sepsis, were stopped prematurely due to lack of efficacy and the potential to cause harm because of bleeding.98

4.3.2 ART-123

A recombinant analog of the extracellular domain of thrombomodulin,99 ART-123 binds thrombin and converts it from a procoagulant enzyme into a potent activator of protein C. ART-123 has nearly 100% bioavailability after subcutaneous administration and a half-life of 2 to 3 days. In a phase IIa dose-ranging study in patients undergoing elective hip arthroplasty, the primary end point (a composite of venographically-detected DVT and symptomatic PE) occurred in 4.3% of the 94 patients given lower dose ART-123 and in none of the 99 patients receiving the higher dose.100 Major bleeding occurred in 1.6% and 5.7% of patients receiving low or high dose ART-123, respectively. Plans for further development of this agent are uncertain.

4.4 Inhibitors of Fibrin Formation

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

Direct thrombin inhibitors have properties that give them potential mechanistic advantages over indirect inhibitors.101,102 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.101,102

Three parenteral direct thrombin inhibitors (hirudin, argatroban and bivalirudin) have been licensed in North America for limited indications. Hirudin and argatroban are approved for treatment of patients with heparin-induced thrombocytopenia, whereas bivalirudin is licensed as an alternative to heparin in PCI patients with or without heparin-induced thrombocytopenia. Because these drugs are already licensed, they will not be discussed here. Two new parenteral direct thrombin inhibitors are currently undergoing phase II evaluation. These are flovagatran and pegmusirudin. There also are three new oral thrombin inhibitors; odiparcil, an indirect inhibitor, and ximelagatran and dabigatran etexilate, which are direct thrombin inhibitors (Table 6).

4.4.1 Flovagatran

A synthetic active site-directed small molecule, formerly designated TGN 255, flovagatran reversibly inhibits thrombin (trigen.co.uk). The drug exhibits predictable and dose-dependent pharmacokinetics after IV injection and has a short half-life. Because

<table>
<thead>
<tr>
<th>Table 5—Inhibitors of Factor Va</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Drotrecogin</td>
</tr>
<tr>
<td>ART-123</td>
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<table>
<thead>
<tr>
<th>Table 6—Thrombin Inhibitors</th>
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</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Odiparcil</td>
</tr>
<tr>
<td>Ximelagatran</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
</tr>
</tbody>
</table>
flowagatran is mainly cleared via an extra-renal mechanism, its pharmacokinetic profile in patients with renal failure is reported to be similar to that in patients with normal renal function. Building on this property, flowagatran is being investigated as an alternative to heparin during hemodialysis in patients with end stage renal disease who have antibodies to the heparin/PF4 complex. A small phase II study in 38 such patients demonstrated that the drug produces a predictable anticoagulant effect that permits successful hemodialysis. Plans for future development of flowagatran are uncertain.

4.4.2 Pegmusirudin

A chemically modified hirudin derivative, pegmusirudin is manufactured by coupling two polyethylene glycol side chains to recombinant hirudin. These side chains prolong the half-life of hirudin from 60 min after IV bolus injection to about 12 h in patients with normal renal function. Like hirudin, pegmusirudin is cleared by the kidneys and its half-life is prolonged in patients with renal insufficiency. Capitalizing on this feature, the drug is undergoing phase II evaluation in patients with end stage renal disease who are receiving routine hemodialysis (www.speedel.com). Given IV prior to each dialysis session, pegmusirudin not only provides anticoagulation during dialysis, but produces continued anticoagulant between dialysis sessions. With this prolonged anticoagulant effect, pegmusirudin is being evaluated as a strategy to reduce the risk vascular access graft occlusion.

4.4.3 Odiparcil

An oral β-D-xyloside, odiparcil primes the synthesis of circulating dermal skin-like glycosaminoglycans. These glycosaminoglycans indirectly inhibit thrombin by catalyzing heparin cofactor II. Steady state levels of glycosaminoglycans are achieved after 2 to 3 days of odiparcil administration. Like warfarin, therefore, odiparcil has a delayed onset of action. The anticoagulant activity of odiparcil can be partially reversed with protamine sulfate. In a phase II dose-finding trial, 3 different doses of oral odiparcil were compared with warfarin for thromboprophylaxis in patients undergoing knee arthroplasty. Because of lack of efficacy, further development of odiparcil has been halted.

4.4.4 Ximelagatran

A prodrug of melagatran, ximelagatran is absorbed from the GI tract with a bioavailability of 20%. Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran via two intermediate metabolites, H338/57 and H415/04. Melagatran has a half-life of 4 to 5 h and is administered twice daily.

Ximelagatran does not interact with food, has a low potential for drug interactions, and produces a predictable anticoagulant response. Ximelagatran underwent extensive evaluation for prevention and treatment of VTE, prevention of cardioembolic events in patients with nonvalvular atrial fibrillation, and prevention of recurrent ischemia in patients with recent MI. Initial studies led to its temporary licensing in Europe for thromboprophylaxis in patients undergoing major orthopedic surgery. However, the drug was not approved in North America and was eventually withdrawn from the world market because of potential hepatic toxicity. Thus, in a total of 6,948 patients randomized to ximelagatran, there was one death from heporenal failure and two other deaths from hepatic failure. Added to this was a patient who developed severe hepatic injury several weeks after receiving a 4-week course of ximelagatran for thromboprophylaxis after orthopedic surgery. AZD0837, a follow-up compound to ximelagatran that appears to have a lower risk of hepatic toxicity, is currently undergoing phase II evaluation.

4.4.5 Dabigatran Etexilate

A double prodrug, dabigatran etexilate is absorbed from the GI tract with a bioavailability of 5% to 6%. Absorption requires an acid microenvironment and is reduced by acid suppression therapy. Once absorbed, dabigatran etexilate is converted by esterases into its active metabolite, dabigatran (BIBR 953). Plasma levels of dabigatran peak at 2 h and dabigatran has a half-life of 8 h after single dose administration and up to 17 h after multiple doses. Consequently, it may be possible to administer dabigatran etexilate once daily for some indications. At least 80% of dabigatran is excreted unchanged via the kidneys; therefore, the drug is contraindicated in patients with renal failure.

Dabigatran etexilate has been evaluated for thromboprophylaxis in patients undergoing hip or knee arthroplasty in phase II and III trials and for prevention of stroke in patients with atrial fibrillation in phase II trials. In the phase II arthroplasty trial, 1,973 patients were randomized to receive one of four doses of dabigatran etexilate for 6 to 10 days after surgery (with the first dose administered 1 to 4 h postoperatively) or enoxaparin 40 mg qd started 12 h prior to surgery. The primary efficacy outcome was a composite of venographically-detected DVT or symptomatic VTE. The three highest dabigatran etexilate dose regimens produced a statistically significant reduction in the incidence of venous
thromboembolism compared with enoxaparin. However, this was balanced by a trend for more major bleeding with higher dabigatran doses than with enoxaparin.

In the phase III RE-MODEL trial, \(^{113}\) 2,076 patients undergoing knee arthroplasty were randomized to receive either dabigatran etexilate (at doses of 150 or 220 mg qd starting with a half dose given 1 to 4 h after surgery) or enoxaparin (given subcutaneously once daily at a dose of 40 mg starting 12 h prior to surgery). The primary end point, a composite of VTE and all-cause mortality, occurred in 40.5% and 36.4% of patients given 150 and 220 mg of dabigatran etexilate, respectively, and in 37.7% of those randomized to enoxaparin. Major bleeding occurred in 1.3%, 1.5% and 1.3% of those given 150 mg dabigatran etexilate, 220 mg dabigatran etexilate and enoxaparin, respectively, while rates of major bleeding plus clinically relevant, nonmajor bleeding were 7.1%, 7.4% and 6.6%, respectively. None of these differences was statistically significant. Levels of alanine aminotransferase > 3 times the upper limit of normal were observed in 3.7% and 2.8% of patients receiving 150 and 220 mg of dabigatran etexilate, respectively, compared with 4.0% of those given enoxaparin.

Dabigatran etexilate has been evaluated in two other phase III orthopedic trials. The RE-NOVATE trial randomized 3,494 patients undergoing hip replacement surgery to oral dabigatran etexilate (either 150 mg or 220 mg qd starting with a half dose given 1 to 4 h after surgery) or subcutaneous enoxaparin (40 mg qd starting 12 h prior to surgery) for an average of 33 days. \(^{114}\) The primary efficacy end point, a composite of DVT, nonfatal PE and all-cause mortality, occurred in 8.6% and 6.0% of patients given dabigatran etexilate 150 or 220 mg, respectively, and in 6.7% of those treated with enoxaparin. Major bleeding occurred in 1.3% and 2.0% of patients treated with dabigatran etexilate 150 and 220 mg, respectively, and in 1.6% of those given enoxaparin. None of these differences was statistically significant.

In the North American RE-MOBILIZE trial, patients undergoing knee replacement surgery were randomized to oral dabigatran etexilate (either 150 or 220 mg once daily starting with a half dose give 8 to 12 h after surgery) or subcutaneous enoxaparin (30 mg bid starting 12 to 24 h after surgery) for 10 to 14 days. \(^{115}\) The primary efficacy end point, a composite of DVT, nonfatal PE and all-cause mortality, occurred in 33.7% and 31.1% of patients treated with dabigatran 150 or 220 mg, respectively and in 25.3% of those given enoxaparin. Major bleeding occurred in 0.6% of patients treated with either dose of dabigatran and in 1.4% of those given enoxaparin, differences that were not statistically significant. Unlike the other two phase III trials, dabigatran was inferior to enoxaparin in this trial. This difference may reflect the higher dose enoxaparin regimen used as a comparator and/or the delayed start of dabigatran etexilate.

A phase II trial in 502 patients with atrial fibrillation compared a 3-month course of treatment with three different doses of dabigatran etexilate (50, 150 or 300 mg bid) or with warfarin (with doses adjusted to achieve a target INR of 2 to 3). \(^{116}\) Using a factorial design, patients also were randomized to aspirin (81 or 325 mg daily) or to placebo. Recruitment into the high dose dabigatran etexilate plus aspirin arm was stopped early because of 4 GI bleeds in 63 patients. Addition of aspirin in the other groups did not appear to increase the risk of bleeding. In the low dose dabigatran etexilate arm, 2 of 105 patients suffered a thromboembolic event. Building on these data, 361 of the 432 patients randomized to dabigatran etexilate continued open-label treatment at doses of 50, 100 or 300 mg bid or 150 or 300 mg qd for at least 16 months. The two lowest doses of dabigatran etexilate (50 bid or 150 qd) were discontinued early because of annual stroke rates of 8.4 and 8.1%, respectively. The annual stroke rate with the 300 mg qd dose was 9.5%, whereas rates were lower with the other doses. The cumulative frequency of elevations in alanine aminotransferase of > 3 times the upper limit of normal was 2% in patients receiving dabigatran etexilate for at least 12 months compared with 1% in those given warfarin. Based on these data, the ongoing phase III RELY trial is comparing dabigatran etexilate doses of 110 or 150 mg bid with dose-adjusted warfarin for stroke prevention in 18,000 patients with nonvalvular atrial fibrillation. In addition, dabigatran etexilate also is undergoing phase III evaluation for treatment of VTE.

### 5.0 Fibrinolytic Therapy

Although traditional antithrombotic strategies have been aimed at inhibiting platelet function or blocking coagulation, a better understanding of fibrinolysis has identified potential methods to enhance endogenous fibrinolytic activity and has led to the development of new fibrinolytic agents. Strategies to enhance endogenous fibrinolysis include inhibitors of type 1 plasminogen activator (PAI-1), activated thrombin activatable fibrinolysis inhibitor (TAFIa) or activated factor XIII (factor XIIIa). New fibrinolytic agents include alfitanerase, BB10153 and desmoteplase.
5.1 Strategies to Enhance Endogenous Fibrinolysis

5.1.1 PAI-1 Inhibitors

PAI-1 is the major physiologic inhibitor of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (u-PA). Consequently, inhibition of PAI-1 results in increased endogenous fibrinolytic activity. PAI-1 activity can be reduced by (i) decreasing PAI-1 gene expression, or (ii) by reducing the activity of PAI-1. Lipid-lowering drugs, such as niacin and fibrates, 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 insertion of the reactive center loop into the body of the inhibitor after cleavage by the target protease, or by converting PAI-1 into its latent conformation. 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.

5.1.2 TAFIa Inhibitors

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

5.1.3 Factor XIIIa Inhibitors

A thrombin-activated transglutaminase, factor XIIIa, cross-links the α- and γ-chains of fibrinogen to form α-polymers and γ-dimers, respectively. Cross-linking stabilizes the fibrin polymer and renders it more refractory to degradation by plasmin. Inhibition of factor XIIIa, therefore, has the potential to increase the susceptibility of the thrombus to lysis.

Tridegin, a peptide isolated from the giant Amazon leech, Haementeria ghilanti, is a specific inhibitor of factor XIIIa and enhances fibrinolysis in vitro when added before clotting of fibrinogen. Desstabilase, a leech enzyme that hydrolyzes cross-links, provides an alternative approach to reversing the consequences of factor XIIIa-mediated fibrin crosslinking. Neither of these agents has been tested in humans.

5.2 New Fibrinolytic Agents

Existing fibrinolytic agents are plasminogen activators that act by converting plasminogen to plasmin. tPA and u-PA, which are enzymes, do this directly by converting single-chain plasminogen into two-chain plasmin. In contrast, streptokinase accomplishes this indirectly. Streptokinase, which is not an enzyme, binds to plasminogen and the streptokinase/plasminogen complex then serves as the plasminogen activator. More recently licensed plasminogen activators are variants of tPA. These include reteplase, a truncated tPA variant with a longer half-life, and tenecteplase, a bioengineered tPA variant that not only has a longer half-life than tPA, but also exhibits enhanced fibrin specificity and resistance to inhibition by PAI-1. Because of their longer half-lives, reteplase and tenecteplase can be given by bolus injection, thereby simplifying administration.

New fibrinolytic agents under development build on advances with tPA derivatives. Direct acting fibrinolytics, such as alfimeprase, have been developed in an attempt to accelerate lysis, whereas BB10153 and desmoteplase have been developed because of their enhanced fibrin-specificity (Table 7).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Mechanism of Action</th>
<th>Stage of Development as of 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfimeprase</td>
<td>IV</td>
<td>Directly degrades fibrin and fibrinogen</td>
<td>Phase III</td>
</tr>
<tr>
<td>BB10153</td>
<td>IV</td>
<td>Thrombin activatable plasminogen variant</td>
<td>Phase II</td>
</tr>
<tr>
<td>Desmoteplase</td>
<td>IV</td>
<td>A variant of tPA with enhanced fibrin specificity</td>
<td>Phase III</td>
</tr>
</tbody>
</table>
Agkistrodon contortrix contortrix. Like fibrolase, alfimeprase directly degrades the α-chain of fibrin and fibrinogen. Because there is no need for plasmin generation, alfimeprase has the potential to degrade fibrin more rapidly than tPA. Furthermore, the action of alfimeprase is independent of the plasminogen content of the thrombus and alfimeprase is not inhibited by PAI-1. Finally, by degrading fibrinogen as well as fibrin, alfimeprase not only degrades preformed fibrin, but also has the potential to inhibit fibrin generation.

In the circulation, alfimeprase is rapidly inhibited by α2-macroglobulin. Neutralization by α2-macroglobulin limits the systemic effects of alfimeprase and may reduce its hemorrhagic potential. To bypass circulating α2-macroglobulin, alfimeprase must be administered directly into the thrombus. Therefore, clinical trials of alfimeprase have focused on catheter-directed lysis of peripheral arterial occlusions or on local delivery to restore flow in indwelling catheters blocked by thrombus. Phase III studies with alfimeprase for these indications have been halted, at least temporarily, because key efficacy end points were not met. The full results of these trials have not yet been published.

5.2.2 BB10153

A variant form of plasminogen, BB10153 has the plasminogen activator cleavage site replaced with a thrombin cleavage site. Like plasminogen, BB10153 binds to fibrin. Once bound to fibrin, BB10153 is converted to plasmin by fibrin-bound thrombin and not by plasminogen activators. After IV injection, BB10153 has a half-life of about 4.4 h in humans. In a phase II dose-escalation study in 50 patients with acute MI, a single IV bolus of BB10153 produced a dose-dependent increase in drug levels and, at doses in the 5 to 10 mg/kg range, 34% of patients achieved complete flow in the infarct-related artery. Major bleeding occurred in 3 patients, while minor bleeding occurred in 6. There were no intracranial bleeds. Based on these data, BB10153 is undergoing continued investigation for treatment of acute ischemic stroke and peripheral arterial occlusion.

5.2.3 Desmoteplase

A recombinant analog of the full-length plasminogen activator isolated from the saliva of the vampire bat, Desmodus rotundus, desmoteplase has >70% homology to tPA. Like tPA, desmoteplase binds to fibrin via its fibronectin finger-like domain and its catalytic activity is enhanced in the presence of 2-macroglobulin. Neutralization by 2-macroglobulin limits the systemic effects of alfimeprase and may reduce its hemorrhagic potential. To bypass circulating 2-macroglobulin, alfimeprase must be administered directly into the thrombus. Therefore, clinical trials of alfimeprase have focused on catheter-directed lysis of peripheral arterial occlusions or on local delivery to restore flow in indwelling catheters blocked by thrombus. Phase III studies with alfimeprase for these indications have been halted, at least temporarily, because key efficacy end points were not met. The full results of these trials have not yet been published.

6.0 Conclusions and Future Directions

Aspirin and clopidogrel have an established role in the prevention and treatment of arterial thrombosis. Although effective, breakthrough thrombosis remains a problem, even when the drugs are used in combination. This has prompted the development of new antiplatelet drugs. The variable antiplatelet effects of fixed-doses of clopidogrel have led to the development of new thienopyridines, such as prasugrel, which produce more consistent inhibition of ADP-induced platelet aggregation. Direct acting P2Y12 inhibitors not only overcome the slow onset and offset of the thienopyridines, but may also offer more potent ADP receptor blockade. The challenge with these new agents will be safety. Adding clopidogrel to aspirin increases the risk of major bleeding and the use of more potent P2Y12 inhibitors appears to further increase this risk. PAR-1 antagonists represent a novel class of antiplatelet agents. These drugs are unique in that, unlike other antiplatelet drugs, they do not prolong the bleeding time. Phase II results are promising and ongoing studies will determine the efficacy and safety of these drugs as adjuncts to current antiplatelet agents.

The greatest unmet need in anticoagulation therapy is replacement of warfarin with an orally active agent that can be given in fixed doses without routine
coagulation monitoring. Consequently, most of the current attention is focused on new oral anticoagu-
lants. Those in the most advanced stages of develop-
ment are the oral direct thrombin or factor Xa
inhibitors.

Which is the best target for new oral anticoagu-
lants? By blocking thrombin activity, thrombin
inhibitors attenuate fibrin formation and thrombin-
mediated platelet activation. However, factor Xa inhib-
itors also affect these processes by impairing thrombin
generation. Therefore, the net effect of blockade at the
level of factor Xa or thrombin is reduced fibrin forma-
tion.

We do not yet know whether upstream inhibition
is any safer than downstream blockade at the level of
thrombin. Studies with ximelagatran validate throm-
bin as a target for new anticoagulants. In addition, these
trials demonstrate that fixed dosing and no coagulation
monitoring are achievable properties for new oral agents. The unexpected hepatic toxicity was
the downfall for ximelagatran. At present, it is un-
clear whether hepatic toxicity is unique to ximelaga-
tran, or whether it represents a class effect. Ongoing
studies with dabigatran etexilate and the oral factor
Xa inhibitors will clarify this issue.

Emerging results from clinical trials with fondapa-
rinux confirm the concept that factor Xa also is a
good target for new anticoagulants. Although the
utility of factor Xa inhibitors for thromboprophylaxis
was expected, the clinical trial data with fondapa-
rinux indicate that factor Xa inhibitors also are
effective for treatment of established thrombosis.
Therefore, thrombin inhibition is not essential when
treating thrombosis, provided that ongoing thrombin
generation is interrupted.

A large number of oral factor Xa inhibitors are now
in phase II trials and several have moved on to phase
III. Dose-finding studies in orthopedic patients sug-
gest that these agents are effective. Like oral throm-
bin inhibitors, however, the factor Xa inhibitors also
produce a dose-dependent increase in bleeding.
Therefore, as yet, there is no evidence that factor Xa inhibitors cause less bleeding than thrombin inhibi-
tors. Direct head-to-head comparisons will be needed
to evaluate the relative benefit-to-risk ratios of the
two classes of agents. Such studies are unlikely to be
conducted for many years. In the interim, parallel
clinical trial programs will assess the utility of oral
direct thrombin or factor Xa inhibitors for prevent-
ton and treatment of venous and arterial thrombo-
embolism.

The lack of specific antidotes remains a challenge
for the new anticoagulants. This is particularly prob-
lematic for drugs with a long half-life, such as
idraparinux. Development of a biotinylated version
of idraparinux may overcome this limitation provided
that avidin, the antidote, is readily available and its
safety established.

With the plethora of new antithrombotic drugs
under development, we are at the beginning of a new
era in antithrombotic therapy. In addition to assessing
the antithrombotic efficacy and the hemorrhagic
potential of these new agents, the experience with
ximelagatran mandates careful attention to off-target
side-effects, particularly hepatic toxicity. The next
few years are likely to bring new classes of anti-
thrombotic drugs to the clinic.

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