

# New Anticoagulants: An Update

**Mark Crowther, MD, and Jeffrey I. Weitz, MD**

Dr. Crowther is Head of the Division of Hematology at St. Joseph's Hospital and Associate Professor of Medicine at McMaster University, in Hamilton, Ontario, Canada. Dr. Weitz is Professor of Medicine and Biochemistry at McMaster University and Director of the Henderson Research Centre.

Address correspondence to: Dr. Jeffrey Weitz, Henderson Research Centre, 711 Concession Street, Hamilton, Ontario, L8V 1C3, Canada, Tel: (905) 574-8550, Fax: (905) 575-2646; E-mail: [jweitz@thrombosis.hhscr.org](mailto:jweitz@thrombosis.hhscr.org).

## Abstract

There has been an explosion of new anticoagulants in recent years. New parenteral anticoagulants have been developed to overcome the limitations of heparin and low molecular weight heparin, whereas novel orally active anticoagulants have been designed to provide more streamlined therapy than vitamin K antagonists. Focusing on drugs in more advanced stages of clinical testing, this review identifies the molecular targets of new anticoagulants, describes the results of clinical trials, and provides perspective on the opportunities for new anticoagulants.

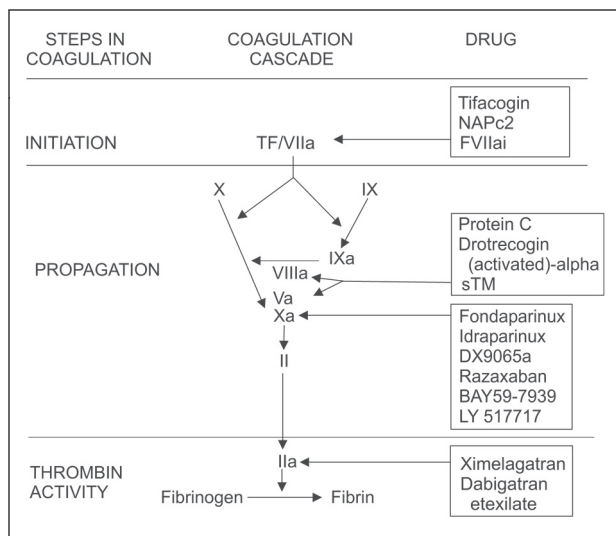
Anticoagulants are used for prevention and treatment of venous and arterial thrombosis. New parenteral anticoagulants have been developed to overcome the limitations of heparin and low molecular weight heparin (LMWH), whereas novel orally active anticoagulants have been designed to provide more streamlined therapy than vitamin K antagonists (VKAs). These advances are possible because of an improved understanding of the molecular mechanisms underlying blood coagulation, the introduction of recombinant DNA technology, isolation, and characterization of anticoagulants from hematophagous organisms, and advances in structure-based drug design. Building on these developments, new anticoagulants that target specific clotting enzymes or steps in coagulation are now available (Figure 1).

When considering new anticoagulants, it is convenient to divide coagulation into 3 steps: initiation, propagation, and fibrin formation. Initiation of coagulation is triggered by the factor VIIa/tissue factor (TF) complex, which activates factors IX and X. Coagulation is propagated by factors IXa and Xa together with their activated cofactors, factors VIIIa and Va, respectively. The final step, fibrin formation, is effected by thrombin, which converts fibrinogen to fibrin and activates factor XIII, the enzyme that stabilizes the fibrin network by covalently crosslinking adjacent fibrin monomers. Thrombin also amplifies coagulation by activating factors V and VIII, and serves as a potent platelet agonist.

The first step in the clinical evaluation of new anticoagulants often involves their assessment in high-risk orthopedic patients. This approach is used because patients undergoing surgery for hip fracture or elective hip or knee arthroplasty have high rates of venographically detected deep vein thrombosis (DVT) after surgery, despite currently accepted anticoagulant thromboprophylactic regimens. Although most of these thrombi are asymptomatic, regulatory agencies usually accept this endpoint as a surrogate for clinically important venous thromboembolism (VTE). Furthermore, patients undergoing major orthopedic surgery are at risk for postoperative bleeding if the level of anticoagulation is excessive. Consequently, studies in orthopedic patients provide an efficient method for identifying effective and safe doses of new anticoagulants and for comparing their benefit-to-risk profile with those of established agents. Once the efficacy of new anticoagulants has been established in thromboprophylaxis studies, additional studies are often done to evaluate their utility in the treatment of VTE and, in the case of orally active drugs, as alternatives to warfarin in patients with atrial fibrillation.

## Keywords

Anticoagulants, antithrombotic drugs, heparin, low molecular weight heparin, vitamin K antagonists, warfarin



**Figure 1.** Sites of action of new anticoagulant drugs. The coagulation cascade is initiated by the tissue factor/factor VIIa complex (TF/VIIa), which activates factors IX and X, respectively. Coagulation is propagated by activated factor X (Xa), which together with its activated cofactor, factor Va, converts prothrombin (factor II) to thrombin (factor IIa). Factor Xa generation is amplified by factor IXa, which together with its activated cofactor, factor VIIIa, also activates factor X. In the final step of coagulation, thrombin converts fibrinogen to fibrin. Thrombin also amplifies its own generation by feedback activation of factors V and VIII. New anticoagulant drugs can target any of these steps in coagulation. Drugs that inhibit the initiation of coagulation include tifacogin, nematode anticoagulant protein (NAPc2), and active site-blocked factor VIIa (FVIIai). Agents that inhibit the propagation of coagulation can target the activated cofactors (factors Va and VIIIa) or factor Xa. Drotrecogin (activated)-alpha (recombinant activated protein C) inactivates factors Va and VIIIa. In contrast, protein C and soluble thrombomodulin (sTM) promote protein C activation. Drugs that target factor Xa include synthetic pentasaccharides (fondaparinux and idraparinux) and small molecules, such as DX9065a, razaxaban, BAY 59-7939, and LY 51,7717. Finally, ximelagatran and dabigatran etexilate attenuate fibrin formation by inhibiting thrombin.

Focusing on agents that have at least reached phase II clinical testing, this review identifies the step in coagulation that is inhibited by new anticoagulants, describes the results of clinical trials, and provides clinical perspective on the opportunities for new anticoagulants.

### Inhibitors of Initiation of Coagulation

Drugs targeting the factor VIIa/TF complex that are in more advanced stages of development include tifacogin (recombinant tissue factor pathway inhibitor), nematode anticoagulant peptide (NAPc2), and active-site blocked factor VIIa (FVIIai).

#### *Tifacogin*

A 2-step inhibitor, tifacogin first binds and inactivates factor Xa and the tifacogin/factor Xa complex, then inhibits TF-bound factor VIIa.<sup>1</sup> Because tifacogin has a short half-life, the drug must be given by continuous intravenous infusion. Despite promising phase II data,<sup>1</sup> a phase III trial comparing tifacogin with placebo in patients with severe sepsis failed to demonstrate a significant reduction in all-cause mortality

at 28 days.<sup>2</sup> An ongoing phase II trial is comparing tifacogin with placebo as an adjunct to antibiotics in patients with severe community-acquired pneumonia.

#### *NAPc2*

Originally isolated from the canine hookworm, NAPc2 binds to a noncatalytic site on factor X/factor Xa,<sup>3</sup> and this complex then inhibits TF-bound VIIa. Because it binds factor X, NAPc2 has a half-life of 50 hours after subcutaneous injection. Consequently, NAPc2 is more convenient to administer than tifacogin.

In a phase II trial,<sup>4</sup> subcutaneous NAPc2, started 1 hour after surgery and given on alternate days thereafter, was associated with low rates of DVT and major bleeding. These findings have yet to be confirmed in a phase III trial. Instead, NAPc2 is now undergoing evaluation in patients with acute coronary syndromes.

#### *FVIIai*

By competing with factor VIIa for TF binding, FVIIai attenuates the initiation of coagulation. Promising results in animal models of thrombosis<sup>5,6</sup> prompted a phase II trial in patients undergoing elective percutaneous coronary interventions (PCI) with or without adjunctive heparin.<sup>7</sup> Compared with heparin alone, FVIIai with or without adjunctive heparin had no significant effect on the primary endpoint, a composite of death, myocardial infarction (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. Because of these results, further development of FVIIai as an anticoagulant has been halted.

### Inhibitors of Propagation of Coagulation

Propagation of coagulation can be inhibited by drugs that target factors IXa or Xa, or by agents that inactivate their respective cofactors, factors VIIIa and Va. TTP889, an orally active factor IXa inhibitor, has completed phase I evaluation, but has not yet reached phase II testing. Factor Xa inhibitors include fondaparinux (Arixtra, GlaxoSmithKline) and idraparinux (Sanofi-Aventis), parenteral agents that catalyze factor Xa inhibition by antithrombin, and DX-9065a (Daiichi Pharmaceutical), razaxaban (Bristol-Myers Squibb), BAY 59-7939 (Bayer), and LY 51,7717 (Eli Lilly), which are direct factor Xa inhibitors. Inhibition of factors VIIIa and Va can be effected directly by drotrecogin (activated)- $\alpha$  (recombinant activated protein C), an agent that proteolytically degrades and inactivates these cofactors. Alternatively, protein C or recombinant soluble thrombomodulin can be given to promote the generation of activated protein C.

#### *Fondaparinux*

A synthetic analog of the pentasaccharide sequence that mediates the interaction of heparin and LMWH with antithrombin, fondaparinux promotes factor Xa inhibition by antithrombin.<sup>8</sup> Because it is too short to bridge antithrombin to thrombin, fondaparinux has no effect on the rate of thrombin inhibition. Fondaparinux exhibits complete bioavailability after subcutaneous injection, and with a plasma half-life of 17 hours, the drug is administered once daily. Fondaparinux

is excreted unchanged in the urine and is contraindicated in patients with a creatinine clearance less than 30 mL/min.

Because it does not bind to platelet factor 4 (PF4) to form the heparin/PF4 complexes that are the antigenic target for the antibodies that cause heparin-induced thrombocytopenia (HIT), fondaparinux does not cause this problem. Although there are case reports of successful use of fondaparinux in HIT patients, its utility in this setting requires evaluation in clinical trials.

There is no antidote for fondaparinux. If uncontrolled bleeding occurs, recombinant factor VIIa may be effective.<sup>9</sup> However, recombinant factor VIIa is not available in all hospitals, and the drug is expensive and can cause thrombotic complications.

Fondaparinux is licensed for thromboprophylaxis in orthopedic patients and as an alternative to heparin or LMWH for initial treatment of venous thromboembolism. The drug also has been evaluated for thromboprophylaxis in medical and surgical patients and for acute coronary syndromes, but is not yet approved for these indications.

**Thromboprophylaxis in orthopedic surgery patients:** In 4 large phase III trials that compared fondaparinux with enoxaparin (Lovenox, Aventis) for thromboprophylaxis in patients undergoing surgery for hip fracture or elective hip or knee arthroplasty, fondaparinux reduced the risk of VTE by 55%.<sup>10</sup> Although major bleeding was more frequent with fondaparinux, there was no increase in fatal bleeding, bleeding into critical organs, or bleeding leading to reoperation.<sup>10</sup> The efficacy of extended fondaparinux thromboprophylaxis was evaluated in the PENTHIFRA-Plus trial.<sup>11</sup> In this study, 656 patients undergoing surgery for hip fracture received 2.5 mg of fondaparinux subcutaneously once daily for 7 days after surgery and were then randomized to continue fondaparinux or placebo for an additional 3 weeks. Fondaparinux decreased the rate of DVT detected by routine venography at 1 month from 35% to 1.4% ( $P < .001$ ) and reduced the rate of symptomatic VTE from 2.7% to 0.3% ( $P = .021$ ). These findings add to mounting evidence that patients remain at risk for DVT for several weeks after hip fracture surgery and benefit from extended thromboprophylaxis.<sup>12-15</sup>

**Thromboprophylaxis in medical patients:** In the ARTEMIS trial,<sup>16</sup> 849 medical patients aged 65 years or older were randomly assigned to receive subcutaneous fondaparinux (2.5 mg once daily) or placebo for 6–14 days. The primary endpoint, a composite of venographically detected DVT, symptomatic DVT, and nonfatal and fatal pulmonary embolism (PE) at day 15, occurred in 5.6% of patients randomized to fondaparinux and 10.5% of those given placebo ( $P = .03$ ). Major bleeding occurred in 0.2% of patients in both groups.

**Thromboprophylaxis in general surgery patients:** In the PEGASUS trial,<sup>17</sup> 2,297 patients undergoing abdominal surgery were randomly assigned to receive subcutaneous fondaparinux (2.5 mg once daily) or dalteparin (Fragmin, Pfizer; 2,500 U preoperatively and 5,000 U once daily postoperatively) for 5–9 days. The primary endpoint, a composite of venographically documented DVT, symptomatic DVT, and nonfatal and fatal PE at postoperative day 30, occurred in 4.6% of patients ran-

domized to fondaparinux and in 6.1% of those given dalteparin ( $P = .14$ ). In the subgroup of patients with cancer, fondaparinux reduced this composite endpoint from 7.7% to 4.6% ( $P = .02$ ). Symptomatic VTE occurred in 0.4% and 0.3% of those given fondaparinux and dalteparin, respectively, whereas major bleeding occurred in 3.4% and 2.4%, respectively; these differences were not statistically significant.

**Treatment of venous thromboembolism:** In the double-blind MATISSE DVT trial,<sup>18</sup> 2,205 patients with DVT were randomized to receive either fondaparinux (5 mg, 7.5 mg, or 10 mg subcutaneously once daily depending on body weight) or enoxaparin (1 mg/kg subcutaneously twice daily) for 5 days followed by at least a 3-month course of treatment with a VKA. At 3 months, rates of recurrent symptomatic VTE with fondaparinux and enoxaparin/VKA were 3.9% and 4.1%, respectively, whereas rates of major bleeding were 1.1% and 1.2%, respectively. None of these differences were statistically significant.

In the open-label MATISSE PE trial,<sup>19</sup> 2,213 patients with PE were randomized to receive either fondaparinux (5 mg, 7.5 mg, or 10 mg subcutaneously once daily depending on body weight) or heparin (by continuous intravenous infusion) for 5 days followed by at least a 3-month course of treatment with a VKA. At 3 months, rates of recurrent symptomatic VTE with fondaparinux and heparin/VKA were 3.9% and 4.1%, respectively, whereas major bleeding rates were 1.1% and 1.2%, respectively; these differences were not statistically significant. Based on the results of these 2 trials, fondaparinux is as effective and safe as LMWH or heparin for initial treatment of VTE.

**Treatment of arterial thrombosis:** The phase II PENTUA trial randomized patients with unstable angina to fondaparinux, in various doses, or to enoxaparin.<sup>20</sup> The primary outcome, a composite of death, MI, or recurrent angina at day 9, occurred in 37% of patients given fondaparinux (any dose) and in 40.2% of those treated with enoxaparin. The lowest dose of fondaparinux (2.5 mg) appeared to produce the best results. Bleeding was similar in all treatment groups.

The PENTALYSE trial was an open-label, phase II trial that randomized patients with evolving ST-elevation MI to receive either fondaparinux, in various doses, or unfractionated heparin as adjuncts to alteplase (Activase, Genentech) plus aspirin.<sup>21</sup> The primary endpoint, patency of the infarct-related artery at 90 minutes, was similar with fondaparinux (all groups combined) and heparin (60% and 68%, respectively); rates of bleeding also were similar. Based on the results of the PENTUA and PENTALYSE studies, phase III trials of fondaparinux in patients with ST-elevation and non-ST-elevation MI are underway.

### **Idraparinix**

A more negatively charged derivative of fondaparinux, idraparinix binds antithrombin with higher affinity than does fondaparinux. This property endows idraparinix with a plasma half-life of 80 hours, similar to that of antithrom-

**Table 1.** Comparison of the Properties of Fondaparinux, Idraparinux, and Low Molecular Weight Heparin (LMWH)

Property	Fondaparinux	Idraparinux	LMWH
Factor Xa Inhibition	Yes	Yes	Yes
Thrombin inhibition	No	No	Yes
Half-life (hours)	17	80	4
Clearance	Renal	Renal	Renal
Reversal with protamine sulphate	No	No	Partial

bin.<sup>22</sup> Consequently, idraparinux is given subcutaneously on a weekly basis. Table 1 compares the properties of idraparinux with those of fondaparinux and LMWH.

In the phase II PERSIST trial,<sup>23</sup> patients with proximal DVT were treated with LMWH for 5–7 days prior to randomization to warfarin or to 1 of 4 doses of idraparinux for 12 weeks. The primary endpoint, change in thrombus burden determined by repeated compression ultrasound examination and perfusion lung scanning, was similar in all idraparinux groups and did not differ from that in the control group. However, there was a clear dose response for major bleeding in patients given idraparinux. Two patients, both of whom received 5 mg of idraparinux, suffered fatal bleeds. Patients given the lowest dose of idraparinux (2.5 mg once weekly) had less bleeding than those randomized to warfarin ( $P=.029$ ). Based on these data, this dose of idraparinux is being evaluated in phase III trials. Thus, once-weekly idraparinux is being compared with enoxaparin/VKA or heparin/VKA for treatment of DVT and PE, respectively. Once-weekly idraparinux is also being compared with adjusted-dose warfarin for prevention of cardioembolic events in patients with nonvalvular atrial fibrillation.

### ***DX-9065a***

DX-9065a is a synthetic, nonpeptidic parenteral factor Xa inhibitor that binds reversibly to the active site of factor Xa. In the XaNADU-PCI pilot study,<sup>24</sup> which randomized 175 patients undergoing elective PCI to different doses of DX9065a or to heparin, DX-9065a appeared to be an effective alternative to heparin in this setting.

### ***Razaxaban***

A synthetic, nonpeptidic, orally active factor Xa inhibitor, razaxaban was evaluated in a phase II trial that enrolled 656 patients undergoing elective knee arthroplasty.<sup>25</sup> Patients were randomized to oral razaxaban (in doses ranging from 25 mg to 100 mg twice daily starting 8 hours postoperatively) or subcutaneous enoxaparin (30 mg twice daily start-

ing 12–24 hours postoperatively) for 10 days. The primary endpoint, a composite of venographically detected DVT and symptomatic VTE, occurred in 8.6% of patients randomized to the lowest dose of razaxaban and in 15.9% of those given enoxaparin. Rates of major bleeding in these 2 groups were 0.7% and 0%, respectively. The 3 higher-dose razaxaban arms of the study were stopped prematurely because of increased bleeding. Based on these results, additional studies are needed to determine the optimal dose of razaxaban.

### ***BAY 59-7939 and LY 51,7717***

These oral, small-molecule, direct factor Xa inhibitors are currently undergoing phase II evaluation for thromboprophylaxis after hip and knee arthroplasty and for treatment of DVT.

### ***Protein C***

Both plasma-derived and recombinant forms of protein C are available. Promising results with protein C concentrates have been reported in patients with meningococemia.<sup>26,27</sup>

### ***Drotrecogin (Activated)-Alpha***

Drotrecogin (activated)- $\alpha$  is licensed for the treatment of adults with severe sepsis based on the results of the PROWESS trial, which demonstrated that, compared with placebo, drotrecogin (activated)- $\alpha$  reduced 28-day mortality in adults with severe sepsis.<sup>28</sup> Studies are now underway to assess and determine whether this agent also reduces mortality in children with severe sepsis.

### ***Soluble Thrombomodulin***

A recombinant analog of the extracellular domain of thrombomodulin, soluble thrombin (sTM) binds thrombin and alters its substrate specificity, thereby converting it from a procoagulant into a potent activator of protein C. In a phase II study,<sup>29</sup> patients undergoing elective hip arthroplasty were given subcutaneous sTM (either 0.3 mg/kg or 0.45 mg/kg) 2–4 hours after surgery; those given the lower dose received a second dose 5 days later. The primary endpoint, a composite of venographically detected DVT and symptomatic VTE, occurred in 4.3% of the 94 patients given the lower dose of sTM and in none of the 99 patients receiving the higher dose. Major bleeding occurred in 1.6% and 5.7% of patients receiving low or high doses of sTM, respectively. Additional studies are needed to compare sTM with other forms of thromboprophylaxis.

### ***Inhibitors of Fibrin Formation***

Three parenteral direct thrombin inhibitors—hirudin, argatroban (Argatroban, Encysive), and bivalirudin (Angiomax, Medicines Co.)—are licensed in North America for limited indications. Ximelagatran (Exanta, AstraZeneca) and dabigatran etexilate (BIBR 1048; Boehringer Ingelheim), both of which are oral direct thrombin inhibitors, are new agents under development.

### ***Ximelagatran***

Ximelagatran is a prodrug of melagatran, a dipeptide mimetic of the portion of fibrinopeptide A that interacts with the active site of thrombin and blocks the enzyme's interaction with its substrates. To overcome melagatran's poor bioavailability after oral administration, ximelagatran

**Table 2.** Potential Advantages of Ximelagatran Over Warfarin and Their Consequences

Advantage	Consequence
Rapid onset of action	No need for overlap with a parenteral anticoagulant when initiating treatment in patients with established thrombosis or at high risk for thrombosis
No drug, food, or alcohol interactions	Can be given in fixed doses
Wide therapeutic window	No need for routine coagulation monitoring
Short half-life	Limits need for an antidote

has an ester and hydroxyl group added to the carboxyl and amidine groups of melagatran, respectively. By rendering the drug more lipophilic, these modifications result in absorption of ximelagatran in the small intestine with a bioavailability of 20%.<sup>30</sup>

Ximelagatran levels in the blood peak 30 minutes after oral administration. Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran, a process that involves hydrolysis of the ester group and reduction of the hydroxyl group. Intermediates with one or the other of these side groups removed can be transiently found in the plasma, but levels of melagatran peak within 2 hours. Melagatran has a half-life of 4–5 hours in patients. Because of its relatively short half-life, ximelagatran is administered twice daily.

Food, drugs, and alcohol do not influence the absorption or metabolism of ximelagatran. Because it produces a predictable anticoagulant response, ximelagatran can be given without coagulation monitoring. Melagatran is eliminated unchanged via the kidneys. Consequently, dose adjustments may be necessary in patients with a creatinine clearance less than 30 mL/min.<sup>30</sup>

Because there is no specific antidote for ximelagatran, its short half-life works to its advantage. If serious bleeding complications occur, they can be managed symptomatically. Although not well studied, dialysis or hemoperfusion likely removes melagatran from the circulation. Recombinant factor VIIa overcomes the anticoagulant activity of melagatran in animals<sup>31</sup> and in humans,<sup>32</sup> but the effect of such treatment on ximelagatran-induced bleeding has yet to be assessed.

Based on its pharmacological properties, ximelagatran has potential advantages over warfarin (Table 2). Building on these features, ximelagatran has been evaluated for thromboprophylaxis in orthopedic surgery patients, for treatment of VTE, for prevention of cardioembolic events in patients with atrial fibrillation, and for prevention of recurrent ischemia after MI.

**Thromboprophylaxis in orthopedic surgery patients:** In METHRO II,<sup>33</sup> a phase II study, ximelagatran, in combi-

nation with subcutaneous melagatran, was shown to be safe and effective when used for venous thromboprophylaxis in patients undergoing elective hip or knee arthroplasty. The phase III EXPRESS trial indicated that a regimen of preoperative subcutaneous melagatran (2 mg), followed by postoperative subcutaneous melagatran (3 mg) and then by oral ximelagatran (24 mg twice daily), is more effective than a standard enoxaparin regimen in reducing the risk of VTE, but may cause more bleeding.<sup>34</sup>

When started postoperatively, unmonitored ximelagatran, at a dose of 36 mg twice daily, is more effective than warfarin (target international normalized ratio [INR] of 1.8–3.0) for the prevention of VTE after knee replacement surgery, and does not significantly increase the risk of major bleeding.<sup>35,36</sup> A lower dose of ximelagatran (24 mg twice daily) initiated postoperatively was less effective than enoxaparin in patients undergoing hip arthroplasty.<sup>37</sup> The higher dose ximelagatran regimen has yet to be tested against enoxaparin in this setting.

**Treatment of venous thromboembolism:** Based on the results of the phase II THRIVE I trial,<sup>38</sup> the phase III THRIVE treatment study<sup>39</sup> randomized 2,489 patients with acute DVT to receive ximelagatran (36 mg twice daily) or enoxaparin (1 mg/kg twice daily for a minimum of 5 days) followed by warfarin (targeted to an INR of 2.0–3.0) for 6 months. Rates of recurrent VTE with ximelagatran and enoxaparin/warfarin were 2.1% and 2.0%, respectively, whereas rates of major bleeding were 1.3% and 2.2%. There was no significant difference in all-cause mortality. This study suggests that ximelagatran is as effective as conventional anticoagulation with enoxaparin followed by warfarin for treatment of DVT.

**Long-term prevention of venous thromboembolism:** In the THRIVE III study,<sup>40</sup> 1,233 patients who had completed a 6-month course of anticoagulant therapy for VTE treatment were randomized to ximelagatran (24 mg twice daily) or placebo for an additional 18 months. VTE recurred in 2.8% of patients receiving ximelagatran and in 12.6% of those given placebo (hazard ratio 0.16;  $P < .001$ ). Major bleeding rates were similar with ximelagatran and placebo (1.1% and 1.3%, respectively; hazard ratio 1.16), and there were no fatal or intracranial bleeds. This trial indicates that, compared with placebo, a lower-dose ximelagatran regimen prevents recurrent VTE without increasing the risk of bleeding.

**Atrial fibrillation:** Based on promising phase II data,<sup>41</sup> 2 phase III trials randomized patients with atrial fibrillation and at least 1 additional risk factor for stroke to receive fixed-dose ximelagatran (36 mg twice daily) or adjusted-dose warfarin (target INR 2.0–3.0) for 12–26 months.<sup>42</sup> In the open-label SPORTIF III study,<sup>43</sup> which enrolled 3,407 patients, the primary event rate (all strokes, both ischemic and hemorrhagic, and systemic embolic events) was similar in those given ximelagatran and warfarin (1.6%/year and 2.3%/year, respectively;  $P = .10$ ). Rates of major bleeding also were similar with ximelagatran and warfarin (1.3%/year and 1.8%/year, respectively), whereas the rate of major plus minor bleeding was significantly lower with ximelagatran than with warfa-

rin (25.5%/year and 29.5%/year, respectively;  $P=.003$ ). All-cause mortality was 3.2%/year in both treatment groups.

In the double-blind SPORTIF V trial,<sup>44</sup> which enrolled 3,922 patients, the primary event rate was similar with ximelagatran and warfarin (1.6%/year and 1.2%/year, respectively;  $P=.13$ ), as was the rate of major bleeding (2.4%/year and 3.1%/year, respectively;  $P=.16$ ). The rate of combined major plus minor bleeding was lower with ximelagatran than with warfarin (37%/year and 47%/year, respectively;  $P<.001$ ).

When the results from the SPORTIF III and SPORTIF V studies are combined, the absolute difference in the primary event rate between ximelagatran and warfarin is 0.3% ( $P=.94$ ). There is a 0.6% absolute difference in the rate of major hemorrhage favoring ximelagatran ( $P=.05$ ). Thus, these studies indicate that in patients with atrial fibrillation, ximelagatran, administered in fixed doses without coagulation monitoring, is as effective as dose-adjusted warfarin in preventing stroke and systemic embolic events.

It is important to note that the control of warfarin anticoagulation in these studies was excellent. The INR values were within the range of 1.8–3.2 for 81% and 83% of the time in SPORTIF III and SPORTIF V, respectively. By contrast, in the community setting, it is estimated that INR values are within this range less than 50% of the time. Consequently, the SPORTIF trials may overestimate the efficacy and safety of warfarin when the drug is given outside the clinical trial setting.

**Acute coronary syndromes:** The phase II ESTEEM trial<sup>45</sup> compared ximelagatran with placebo for prevention of recurrent ischemia after acute MI. All patients received aspirin. The primary outcome, a composite of all-cause mortality, nonfatal MI, and severe recurrent ischemia at 6 months, occurred in 12.7% of patients randomized to ximelagatran and 16.3% of those given placebo (hazard ratio 0.76;  $P=.036$ ). There was no evidence of a dose response among the different ximelagatran groups. Major bleeding occurred in 1.8% of patients given ximelagatran and 0.9% of those randomized to placebo (hazard ratio 1.97; 95% CI, 0.80–4.84). The rate of major plus minor bleeding was higher with ximelagatran than with placebo (22% and 13%, respectively). Mortality was low and similar between the groups. A post-hoc analysis demonstrated a reduction in all-cause mortality, MI, and stroke, with ximelagatran compared with placebo (11.1% and 7.4%, respectively; hazard ratio 0.66; 95% CI, 0.48–0.90).

**Other considerations:** The most troublesome side effect of ximelagatran is elevation of liver enzymes. Overall, 6.7% of patients treated with long-term ximelagatran have an increase in alanine aminotransferase (ALT) levels over 3 times the upper limit of normal. Typically, this occurs 1–6 months after the start of treatment, and it is usually asymptomatic and reversible, even if the medication is continued. Although the increase in ALT levels appears to be benign and is only associated with elevated levels of bilirubin in 0.5% of patients, more data on patients treated over the long term are needed.

Availability of this information may delay the licensing of ximelagatran for long-term use. If ximelagatran is approved, liver function monitoring will be necessary when initiating treatment and during the first 6 months of therapy.

### ***Dabigatran Etxilate***

An oral prodrug of BIBR 953,<sup>46,47</sup> dabigatran etxilate is absorbed in the small intestine. When formulated as a capsule, dabigatran has a half-life of 15 hours, which permits once-daily administration. This agent has been evaluated for thromboprophylaxis in phase II trials, and is undergoing phase II evaluation for stroke prevention in atrial fibrillation.

### **Conclusions**

Although several promising new anticoagulants are in development, few have been approved. Fondaparinux is licensed for thromboprophylaxis in patients undergoing major orthopedic surgery and as an alternative to heparin or LMWH for initial treatment of patients with VTE. Ongoing studies will determine the utility of fondaparinux in patients with acute coronary syndromes. The results of these studies are important because evidence of effectiveness in multiple clinical settings is an important determinant for inclusion of new drugs in many hospital formularies.

Ximelagatran is superior to warfarin for prevention of VTE after knee replacement surgery. Thus, ximelagatran has the potential to simplify oral thromboprophylaxis because it can be given in fixed doses without coagulation monitoring. Ximelagatran may be particularly useful for extended prophylaxis in these patients, a concept that has yet to be tested. The THRIVE treatment study suggests that ximelagatran is as effective and safe as LMWH followed by warfarin for VTE treatment. If these results are confirmed by other studies, ximelagatran has the potential to streamline anticoagulant therapy by obviating the need for initial treatment with a parenteral anticoagulant and by eliminating the coagulation monitoring that is required with warfarin administration.

Based on the results of the SPORTIF III and V trials, ximelagatran also is a promising alternative to warfarin for prevention of cardioembolic events in patients with atrial fibrillation. With no need for coagulation monitoring, ximelagatran is more convenient than warfarin, a feature that may increase anticoagulant use in high-risk atrial fibrillation patients. The success of ximelagatran, however, will depend on better definition of the risk of hepatic injury with long-term use. This complication appears to be idiosyncratic in origin and its mechanism has yet to be established. Until the long-term safety of ximelagatran is known, the need for routine monitoring of liver enzymes limits the convenience of this agent.

The extensive clinical trial program with ximelagatran validates thrombin as a target for new oral anticoagulants. Clinical trials with idraparinux, a long-acting parenteral agent that targets factor Xa, and orally active factor Xa inhibitors are well under way. How these agents compare with ximelagatran remains to be established. However, with the plethora of new anticoagulants under development, our list of agents to prevent and treat venous and arterial thrombosis is likely to soon be expanded.

## Acknowledgements

Dr. Crowther is the recipient of a New Investigator Award from the Canadian Institutes of Health Research. Dr. Weitz is the recipient of a Career Investigator Award from the Heart and Stroke Foundation of Canada and holds the Heart and Stroke Foundation of Ontario/J. Fraser Mustard Chair in Cardiovascular Research and the Canada Research Chair (Tier 1) in Thrombosis at McMaster University.

## References

- Abraham E, Reinhart K, Svoboda P, et al. Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: a multicenter, randomized, placebo-controlled, single-blind, dose escalation study. *Crit Care Med*. 2001;29:2081-2089.
- Abraham E, Reinhart K, Opal S, for the OPTIMIST Trial Study Group. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: a randomized controlled trial. *JAMA*. 2003;290:238-247.
- Stassens P, Bergum PW, Gansemans Y, et al. Anticoagulant repertoire of the hookworm *Ancylostoma caninum*. *Proc Natl Acad Sci U S A*. 1996;93:2149-2154.
- Lee A, Agnelli G, Buller H, et al. Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein C2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. *Circulation*. 2001;104:74-78.
- Taylor FB Jr. Role of tissue factor and factor VIIa in the coagulant and inflammatory response to LD100 *Escherichia coli* in the baboon. *Haemostasis*. 1996;26:83-91.
- Jang Y, Guzman LA, Lincoff AM, et al. Influence of blockade at specific levels of the coagulation cascade on restenosis in a rabbit atherosclerotic femoral artery injury model. *Circulation*. 1995;92:3041-3050.
- Lincoff AM. First clinical investigation of a tissue-factor inhibitor administered during percutaneous coronary revascularization: a randomized, double-blinded, dose-escalation trial assessing safety and efficacy of FFR-FVIIa in percutaneous transluminal coronary angioplasty (ASIS) trial [abstract]. *J Am Coll Cardiol*. 2000;36:312.
- Boneu B, Necciari J, Cariou R, et al. Pharmacokinetics and tolerance of the natural pentasaccharide (SR90107/ORG31540) with high affinity to antithrombin III in man. *Thromb Haemost*. 1995;74:1468-1473.
- Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation*. 2002;106:2250-2254.
- Turpie AG, Eriksson BI, Bauer KA, Lassen MR. New pentasaccharides for the prophylaxis of venous thromboembolism: clinical studies. *Chest*. 2003;124:371S-378S.
- Eriksson BI, Lassen MR, PENTasaccharide in Hip-FRActure Surgery Plus Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. *Arch Intern Med*. 2003;163:1337-1342.
- Prandoni P, Bruchi O, Sabbion P, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. *Arch Intern Med*. 2002;162:1966-1971.
- Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. North American Fragmin Trial Investigators. *Arch Intern Med*. 2000;160:2208-2215.
- Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty – a meta-analysis. *Thromb Haemost*. 2001;85:940-941.
- Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. *Lancet*. 2001;358:9-15.
- Cohen AT, Gallus AS, Lassen MR, et al. Fondaparinux vs. placebo for the prevention of venous thromboembolism in acutely ill medical patients (ARTEMIS) [abstract]. *J Thromb Haemost*. 2003;(suppl 1):P2046.
- Agnelli G, Bergqvist D, Cohen A, et al. A randomized double-blind study to compare the efficacy and safety of fondaparinux with dalteparin in the prevention of venous thromboembolism after high-risk abdominal surgery: the PEGASUS Study. *J Thromb Haemost* [abstract]. 2003;1(suppl 1):OC006.
- Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for initial treatment of symptomatic deep vein thrombosis: a randomized trial. *Ann Intern Med*. 2004;140:867-873.
- The MATISSE Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695-1702.
- Ferguson JJ. Meeting highlights – American Heart Association Scientific Sessions. *Circulation*. 2001;2002;105:e37-e41.
- Coussement PK, Bassand JP, Convens C, et al. A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction. The PENTALYSE study. *Eur Heart J*. 2001;22:1716-1724.
- Herbert JM, Herault JB, Bernat A, et al. Biochemical and pharmacological properties of SANORG 34006, a potent and long-acting synthetic pentasaccharide. *Blood*. 1998;91:4197-4205.
- PERSIST Investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis: a phase II evaluation. *J Thromb Haemost*. 2004;2:47-53.
- Alexander JH, Dyke CK, Yang H, et al. Initial experience with factor Xa inhibition in percutaneous coronary intervention: the XaNADU-PCI Pilot. *J Thromb Haemost*. 2004;2:234-241.
- Lassen MR, Davidson BL, Gallus A, et al. A phase II randomized, double-blind, five-arm parallel-group, dose-response study of a new oral directly-acting factor Xa inhibitor, razaxaban, for the prevention of deep vein thrombosis in knee replacement surgery [abstract]. *Blood*. 2003;102:41.
- Ertingshausen CE, Veldmann A, Beeg T, et al. Replacement therapy with protein C concentrate in infants and adolescents with meningococcal sepsis and purpura fulminans. *Semin Thromb Haemost*. 1999;25:537-541.
- White B, Livingstone W, Murphy C, et al. An open-label study of the role of adjuvant hemostatic support with protein C replacement therapy in purpura fulminans-associated meningococemia. *Blood*. 2000;96:3719-3724.
- Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344:699-709.
- Kearon C, Comp C, Douketis JD, et al. A dose-response study of a recombinant human soluble thrombomodulin (ART-123) for prevention of venous thromboembolism after unilateral total hip replacement [abstract]. *J Thromb Haemost* 2003;1(suppl 1):OC330.
- Gustafsson D, Nystrom JE, Carlsson S, et al. The direct thrombin inhibitor melagatran and its oral prodrug H376/95: intestinal absorption properties, biochemistry and pharmacodynamic effects. *Thromb Res*. 2001;101:171-181.
- Elg M, Borjesson I, Pehrsson S, et al. Feiba™ reversed bleeding times prolonged by high doses of a thrombin inhibitor and was not prothrombotic [abstract]. *Blood*. 2000;96:13911.
- Ulvinge J-C, Berntsson P, Bostrom SL. Melagatran-induced inhibition of thrombin generation is reversed by Feiba™. *Blood*. 2000;96:13917.
- Eriksson BI, Bergqvist D, Kalebo P, et al. Melagatran for thrombin inhibition in orthopedic surgery. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. *Lancet*. 2002;360:1441-1447.
- Eriksson BI, Agnelli G, Cohen AT, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. *J Thromb Haemost*. 2003;1:2490-2496.
- Francis CW, Berkowitz SD, Comp PC, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. *N Engl J Med*. 2003;349:1703-1712.
- Colwell CW, Berkowitz SD, Comp PC, et al. Randomized, double-blind comparison of ximelagatran, an oral direct thrombin inhibitor, and warfarin to prevent venous thromboembolism (VTE) after total knee replacement (TKR): EXULT B [abstract]. *Blood*. 2003;102:14.
- Colwell CW, Berkowitz SD, Davidson BL, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. *J Thromb Haemost*. 2003;1:2119-2130.
- Eriksson H, Wahlander K, Gustafsson D, et al. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. *J Thromb Haemost*. 2003;1:41-47.
- Huisman MV, on behalf of the THRIVE Investigators. Efficacy and safety of the oral direct thrombin inhibitor ximelagatran compared with current standard therapy for acute symptomatic deep vein thrombosis, with or without pulmonary embolism: a randomized, double-blind, multinational study [abstract]. *J Thromb Haemost*. 2003;1(suppl 1):OC003.
- Schulman S, Wahlander K, Lundstrom T, et al.; THRIVE III Investigators. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. *N Engl J Med*. 2003;349:1713-1721.
- Petersen P, Grind M, Adler J; SPORTIF II Investigators. Ximelagatran versus warfarin for stroke prevention in patients with non-valvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol*. 2003;41:1445-1451.
- Halperin JL; Executive Steering Committee, SPORTIF III and V Study Investigators. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J*. 2003;146:431-438.
- Olsson B; SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362:1691-1698.
- Halperin J. 2003. Stroke prevention using the oral DTI ximelagatran in patients with non-valvular AF (SPORTIF V) trial. Presented at American Heart Association Meeting, November 9-12, 2003; Orlando, Fla.
- Wallentin L, Wilcox R, Weaver D, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. *Lancet*. 2003;362:789-797.
- Gustafsson D. Oral direct thrombin inhibitors in clinical development. *J Intern Med*. 2003;254:322-334.
- Mungall D. BIBR-1048 Boehringer Ingelheim. *Curr Opin Investig Drugs*. 2002;3:905-907.