New anticoagulants

Jack Hirsh, Martin O’Donnell, and Jeffrey I. Weitz

Anticoagulants are pivotal agents for prevention and treatment of thromboembolic disorders. Limitations of existing anticoagulants, vitamin K antagonist and heparins, have led to the development of newer anticoagulant therapies. These anticoagulants have been designed to target specific coagulation enzymes or steps in the coagulation pathway. New anticoagulants that are under evaluation in clinical trials include: (1) inhibitors of the factor VIIa/tissue factor pathway; (2) factor Xa inhibitors, both indirect and direct; (3) activated protein C and soluble thrombomodulin; and (4) direct thrombin inhibitors. Although most of these are parenteral agents, several of the direct inhibitors of factor Xa and thrombin are orally active. Clinical development of these therapies often starts with studies in the prevention of venous thrombosis before evaluation for other indications, such as prevention of cardioembolism in patients with atrial fibrillation or prosthetic heart valves. At present, the greatest clinical need is for an oral anticoagulant to replace warfarin for long-term prevention and treatment of patients with venous and arterial thrombosis. Ximelagatran, an oral direct thrombin inhibitor, is the first of a series of promising new agents that might fulfill this need. Large phase 3 trials evaluating ximelagatran for the secondary prevention of venous thromboembolism and prevention of cardioembolic events in patients with atrial fibrillation have been completed. (Blood. 2005;105:453-463)

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Introduction

Anticoagulants are pivotal agents for prevention and treatment of thromboembolic disorders. Heparin and coumarins were discovered more than 60 years ago, long before their mechanism of action was completely understood. Low-molecular-weight heparin (LMWH), a derivative of heparin, was in clinical development for at least a decade before its mechanistic advantages over heparin were elucidated. In contrast, the new anticoagulants have been developed to target specific coagulation enzymes or steps in the coagulation pathway (Figure 1). These anticoagulants have been developed from hematophagous organisms, by the application of recombinant DNA technology, or by structure-based drug design.

The characteristics of an ideal anticoagulant are listed in Table 1. Of these, by far the most important is a high efficacy-to-safety index. Despite claims that inhibition of 1 clotting enzyme may cause less bleeding than inhibition of another enzyme, these assertions have yet to be substantiated in humans.

The cost to develop a new anticoagulant is high, largely reflecting the expense of phase 3 clinical trials. Therefore, the selection of the first clinical indication is often based on cost considerations rather than unmet medical needs. For example, although the greatest need for new anticoagulants is for prevention of cardioembolism in patients with atrial fibrillation or prosthetic heart valves, drug development often starts with studies in the prevention of venous thrombosis because the required sample size is much smaller and the duration of follow-up is shorter. Such an approach presupposes that efficacy in the prevention of venous thromboembolism (VTE) predicts success for other indications.

Inhibitors of the factor VIIa/tissue factor pathway (extrinsic pathway)

Three compounds that target the factor VIIa/tissue factor pathway have been evaluated in clinical trials. These include recombinant tissue factor pathway inhibitor (TFPI), nematode anticoagulant peptide (NAPc2), and active-site blocked factor VIIa (factor VIIai).

TFPI

TFPI is a bivalent, naturally occurring inhibitor that modulates the initiation of coagulation by inhibiting the factor VIIa/tissue factor complex. TFPI first binds and inactivates factor Xa, and the resulting complex then inhibits factor VIIa within the factor VIIa/tissue factor complex. TFPI is found in plasma, in platelet α-granules and on the endothelial cell surface. TFPI levels increase after heparin or LMWH administration, but it is uncertain whether released TFPI contributes to the antithrombotic properties of these agents.
A dose of 3.0 mg NAPc2 is given subcutaneously 1 to 12 hours after surgery and every second day thereafter to a maximum of 4 doses.

Factor VIIa inhibitors

Factor VIIa inhibitors exert its anticoagulant effect by competing with factor VIIa for tissue factor binding.16 Factor VIIa (with or without adjunctive heparin) was reported to be no more effective than heparin alone in a phase 2 trial of 491 patients undergoing elective knee arthroplasty. Subcutaneous NAPc2 was given 1 to 12 hours after surgery and every second day thereafter to a maximum of 4 doses. A dose of 3.0 μg/kg given 1 hour after surgery was considered most effective.14

The safety of NAPc2 has been evaluated in a randomized, double-blind, placebo-controlled dose-escalation study of 154 subjects undergoing elective coronary angiography.15

Factor Xa inhibitors

Factor Xa inhibitors have been shown to be effective in animal models of thrombosis,18 but have yet to be evaluated in phase 2 clinical trials.

Contrast, direct factor Xa inhibitors bind to the enzyme with 1:1 stoichiometry and block the interaction of factor Xa with its substrates.20 Currently available direct factor Xa inhibitors are reversible and not only inhibit free factor Xa, but also inactivate factor Xa bound to platelets within the prothrombinase complex.21,22

Fondaparinux

Fondaparinux binds antithrombin with high affinity, has excellent bioavailability after subcutaneous injection, and has a plasma half-life of 17 hours that permits once-daily administration.22 The drug is excreted unchanged in the urine and is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min).22 Fondaparinux does not bind to platelet factor 4 (PF4); consequently, it should not cause heparin-induced thrombocytopenia.22,23 Unlike heparin, there is no antidote for fondaparinux. If uncontrolled bleeding occurs with fondaparinux, a procoagulant, such as recombinant factor VIIa, might be effective.24 Fondaparinux has been evaluated for prevention and treatment of VTE and for treatment of arterial thrombosis.

Prevention of VTE

Fondaparinux has been shown to be more effective than enoxaparin in 4 large phase 3 trials for thromboprophylaxis in patients undergoing surgery for hip fracture or elective hip or knee arthroplasty and is licensed for these indications.25-28 (Table 2). In a meta-analysis of these studies that included a total of 7344 subjects (4510 undergoing hip arthroplasty, 1670 having surgery for hip fracture, and 1034 undergoing knee arthroplasty) randomly assigned to receive fondaparinux (2.5 mg once daily) or fixed-dose enoxaparin, fondaparinux reduced the risk of VTE by 55% compared with enoxaparin (Table 4).38 Major bleeding occurred more frequently in the fondaparinux-treated group (P = .008), but the incidence of bleeding leading to death, reoperation, or occurring in a critical organ was not significantly different between the 2 groups.38 In these trials the protocol specified that fondaparinux was to be started 4 to 8 hours after surgery, whereas enoxaparin therapy was to be initiated 12 to 24 hours after surgery, with or without a dose 12 hours prior to surgery (Table 3). Because of the asymmetric study design, it is not possible to conclude whether differences in efficacy and safety were drug-related or caused by differences in the timing of drug administration after surgery. It is noteworthy, however, that post-hoc subgroup analysis of pooled data from the 4 trials suggested that when the first dose of fondaparinux was administered 6 to 8 hours after surgery, the regimen currently approved by the Food and Drug Administration (FDA), the rate of major bleeding with fondaparinux was similar to that with enoxaparin.53

Extended fondaparinux thromboprophylaxis has been evaluated in a phase 3 trial (The PENTasaccharide in Hip-FRActure Surgery-Plus [PENTHIFRA-Plus]) in 656 patients undergoing surgery for contrast, direct factor Xa inhibitors bind to the enzyme with 1:1 stoichiometry and block the interaction of factor Xa with its substrates.20 Currently available direct factor Xa inhibitors are reversible and not only inhibit free factor Xa, but also inactivate factor Xa bound to platelets within the prothrombinase complex.21,22

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Extended fondaparinux thromboprophylaxis has been evaluated in a phase 3 trial (The PENTasaccharide in Hip-FRActure Surgery-Plus [PENTHIFRA-Plus]) in 656 patients undergoing surgery for
hip fracture. Patients received 2.5 mg fondaparinux subcutaneously once daily for 7 days and were then randomized to receive continuing fondaparinux or placebo for an additional 3 weeks, at which time routine venography was performed. Fondaparinux treatment decreased the rate of deep vein thrombosis (DVT) from 35% to 1.4%, (P < 0.001) and reduced the rate of symptomatic VTE from 2.7% to 0.3% (P = 0.021) (Table 3). These results support the notion that extended anticoagulant prophylaxis should be used in high-risk patients undergoing hip surgery. Accordingly, fondaparinux has been approved by regulatory authorities for extended prophylaxis after surgery for hip fracture.

Fondaparinux has also been evaluated in general surgery patients and in medical patients. In both trials, the primary outcome measure was a composite of venographically documented DVT, symptomatic DVT, and nonfatal and fatal pulmonary embolism (PE). In a double-blind trial of 2297 subjects undergoing major abdominal surgery, patients were randomly assigned to receive dalteparin (2500 IU 2 hours preoperatively and 6 hours postoperatively and then 5000 IU postoperatively [once daily]) or receive dalteparin (2500 IU 2 hours preoperatively and 6 hours postoperatively and then 5000 IU postoperatively [once daily]) or fondaparinux (2.5 mg subcutaneously once daily) for 5 to 9 days. The outcome, assessed at postoperative day 10, occurred in 4.6% of the fondaparinux group and 6.1% of those given dalteparin (P = 0.14). Symptomatic VTE occurred in 0.4% and 0.3% of patients, respectively, whereas major bleeding occurred in 3.4% and 2.4%, respectively; these differences are not statistically significant (Table 3).

In a double-blind study, 849 acutely ill, hospitalized, medical patients aged 65 years or older were randomly assigned to receive subcutaneous fondaparinux (2.5 mg once daily) or placebo for 6 to 14 days. VTE at day 15 was reported in 5.6% of the fondaparinux group and 10.5% of the placebo group (P = 0.03). Major bleeding while on therapy was infrequent and occurred in 0.2% of patients in both groups (Table 3).

### Treatment of VTE

Fondaparinux has been evaluated for initial treatment of VTE in 2 double-blind, noninferiority, randomized, phase 3 clinical trials. The MATISSE-DVT trial included 2205 patients with DVT who were assigned to receive either fondaparinux (7.5 mg subcutaneously once daily) or enoxaparin (1 mg/kg subcutaneously twice daily) for 5 days followed by a minimum of a 3-month course of treatment with a vitamin K antagonist. At 3 months, recurrent symptomatic VTE was observed in 3.9% and 4.1% of the fondaparinux or enoxaparin groups, respectively, whereas major bleeding rates were 1.1% and 1.2%, respectively (Table 4).

The MATISSE-PE trial was an open-label, noninferiority trial of 2213 patients with PE who were randomly assigned to receive either fondaparinux (5, 7.5, or 10 mg subcutaneously once daily, depending on patient weight) or unfractionated heparin (by continuous infusion) for 5 days followed by a minimum of a 3-month course of therapy with a vitamin K antagonist. At 3 months, recurrent symptomatic VTE was observed in 3.8% and 5.0% of the fondaparinux or unfractionated heparin groups, respectively, and major bleeding rates were 1.3% and 1.1%, respectively. Thus, fondaparinux is at least as effective and safe as LMWH or unfractionated heparin for initial treatment of VTE (Table 4).

### Acute coronary syndromes

Fondaparinux has been evaluated for treatment of acute coronary syndromes in 2 phase 2 studies. Bleeding was similar in all treatment groups. Based on these results, phase 3 trials with fondaparinux in patients with ST-elevation and non–ST-elevation myocardial infarction (MI) have been initiated.

### Idraparinux

Idraparinux is a hyper-methylated derivative of fondaparinux. Its plasma half-life is 80-130 hours. Consequently, idraparinux is given once weekly by subcutaneous injection.

Irdaparinux was compared with warfarin in a phase 2 trial of 659 patients with proximal DVT. The primary outcome measure rates were similar in all idraparinux groups and did not differ from those in the warfarin group. In contrast, there was a clear dose response for major bleeding in patients given idraparinux and there was less bleeding with the 2.5-mg idraparinux dose than with warfarin. A phase 3 trial with this dose of idraparinux is under way.

### DX-9065a

DX-9065a is a nonpeptidic arginine derivative that binds to the active site of factor Xa. In a small phase 2 safety study, DX-9065a given as a continuous intravenous infusion was compared with placebo in patients with stable coronary artery disease. There were no major bleeds with DX-9065a.

### Razaxaban

Razaxaban (DPC 906), an orally active agent, has been compared with enoxaparin 30 mg twice daily in a phase 2 dose-finding study in 656 patients following elective knee arthroplasty. Razaxaban was given at 25-, 50-, 75-, and 100-mg doses twice daily. There was
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Study</th>
<th>No. of patients</th>
<th>Population</th>
<th>Regimen</th>
<th>Control</th>
<th>Outcome measure</th>
<th>Main results</th>
<th>Major bleeding</th>
</tr>
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<tbody>
<tr>
<td>Fondaparinux</td>
<td>EPHESUS</td>
<td>25</td>
<td>THR</td>
<td>2.5 mg SC OD postoperatively</td>
<td>Enoxaparin 40 mg OD preoperatively</td>
<td>Venographically detected DVT and symptomatic VTE to d 11</td>
<td>Fond: 37/908 (4.1%) Enox: 85/919 (9.2%), P &lt; .0001</td>
<td>Fond: 47/1140</td>
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<tr>
<td></td>
<td>25</td>
<td>2309</td>
<td>THR</td>
<td></td>
<td></td>
<td></td>
<td>(4.1%) Enox: 32/1133 (2.8%) NS</td>
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<tr>
<td></td>
<td>PENTATHLON-2000</td>
<td>2275</td>
<td>THR</td>
<td>2.5 mg SC OD, postoperatively</td>
<td>Enoxaparin 30 mg bid postoperatively</td>
<td></td>
<td>Fond: 48/787 (6.1%) Enox: 66/797 (8.3%) NS</td>
<td>Fond: 20/1128</td>
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<tr>
<td></td>
<td>25</td>
<td>2275</td>
<td>THR</td>
<td></td>
<td></td>
<td></td>
<td>(1.7%) Enox: 11/1129 (0.9%) NS</td>
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<tr>
<td></td>
<td>PENTAMAKS</td>
<td>1049</td>
<td>TKR</td>
<td>2.5 mg SC OD postoperatively</td>
<td>Enoxaparin 30 mg bid postoperatively</td>
<td></td>
<td>Fond: 45/361 (12.5%) Enox: 101/363 (27.8%), P &lt; .001</td>
<td>Fond: 10/517</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>2275</td>
<td>TKR</td>
<td></td>
<td></td>
<td></td>
<td>(1.9%) Enox: 1/517 (0.2%) P = .006</td>
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<tr>
<td></td>
<td>PENTHIFRA</td>
<td>1711</td>
<td>Hip fracture</td>
<td>2.5 mg SC OD postoperatively</td>
<td>Enoxaparin 40 mg OD preoperatively</td>
<td></td>
<td>Fond: 52/626 (8.3%) Enox: 119/624 (19.1%), P &lt; .001</td>
<td>Fond: 11/831</td>
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<tr>
<td></td>
<td>25</td>
<td>1711</td>
<td>Hip fracture</td>
<td></td>
<td></td>
<td></td>
<td>(1.3%) Enox: 19/842 (2.3%) NS</td>
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<td>PENTHIFRA-Plus</td>
<td>656</td>
<td>Hip fracture</td>
<td>2.5 mg SC OD × 3 wk after initial 7 d of fondaparinux</td>
<td>Placebo after initial 7 d of fondaparinux</td>
<td>Venographically detected DVT and symptomatic VTE at 3 wk</td>
<td>Fond: 3/208 (1.4%) Placebo: 77/220 (35%), P &lt; .001</td>
<td>Fond: 8/327</td>
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<tr>
<td></td>
<td>25</td>
<td>656</td>
<td>Hip fracture</td>
<td></td>
<td></td>
<td></td>
<td>(2.4%) Placebo: 2/329 (0.6%) NS</td>
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<td></td>
<td>PEGASUS</td>
<td>2927</td>
<td>General surgery</td>
<td>2.5 mg SC OD × 5-9 d postoperatively</td>
<td>Dalteparin 2500 IU preoperatively and 1st dose postoperatively, then 5000 IU × 5-9 d</td>
<td>Venographically detected DVT and symptomatic VTE to d 10</td>
<td>Fond: 4.6%* Dalteparin: 6.1% NI</td>
<td>Fond: 3.4%* Dalteparin: 2.4% NS</td>
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<tr>
<td></td>
<td>25</td>
<td>2927</td>
<td>General surgery</td>
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<td></td>
<td>ARTEMIS</td>
<td>849</td>
<td>Medical</td>
<td>2.5 mg SC OD × 6-14 d</td>
<td>Placebo × 6-14 d</td>
<td>Venographically detected DVT and symptomatic VTE and PE to d 15</td>
<td>Fond: 5.6%* Placebo: 10.5%, P &lt; .03</td>
<td>Fond: 0.2%* Placebo: 0.2% NS</td>
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<tr>
<td></td>
<td>25</td>
<td>849</td>
<td>Medical</td>
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<tr>
<td></td>
<td>Ximelagratran</td>
<td>METHRO-III</td>
<td>THR/TKR</td>
<td>Melagatran 3 mg SC postoperatively, then ximelagratran 24 mg bid × 8-11 d</td>
<td>Enoxaparin 40 mg OD SC preoperatively, then × 8-11 d</td>
<td>Venographically detected DVT and symptomatic VTE to d 15</td>
<td>Xim: 355/1146 (31%) Enox: 306/1122 (27.3%) NS</td>
<td>Xim: 20/1399</td>
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<tr>
<td></td>
<td>25</td>
<td>2788</td>
<td>THR/TKR</td>
<td></td>
<td></td>
<td></td>
<td>(1.7%) Enox: 23/1389 (0.9%) NS</td>
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<td></td>
<td>Platinum-hip</td>
<td>1838</td>
<td>THR</td>
<td>Ximelagratran 24 mg bid × 7-12 d postoperatively</td>
<td>Enoxaparin 30 mg bid SC × 7-12 d postoperatively</td>
<td>Venographically detected DVT and symptomatic VTE to d 11</td>
<td>Xim: 62/782 (7.9%) Enox: 36/775 (4.6%), P &lt; .05, NNI</td>
<td>Xim: 7/906 (0.8%)</td>
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<tr>
<td></td>
<td>25</td>
<td>1838</td>
<td>THR</td>
<td></td>
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<td></td>
<td>Platinum-knee</td>
<td>680</td>
<td>TKR</td>
<td>Ximelagratran 24 mg bid × 7-12 d postoperatively</td>
<td>Warfarin INR 2-3.0 × 7-12 d postoperatively</td>
<td>Venographically detected DVT and symptomatic VTE to d 12</td>
<td>Xim: 53/261 (19.2%) Warfarin: 67/261 (25.7%) NS</td>
<td>Xim: 6/345</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>680</td>
<td>TKR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1.7%) Warfarin: 3/330 (0.9%) NS</td>
</tr>
<tr>
<td></td>
<td>EXULT A</td>
<td>2301</td>
<td>TKR</td>
<td>Ximelagratran 24 mg OR 36 mg bid × 7-12 d postoperatively</td>
<td>Warfarin INR 2-3.0 × 7-12 d postoperatively</td>
<td>Total VTE and all-cause mortality to d 12</td>
<td>Xim 36 mg: 128/629 (20%) Xim 24 mg: 153/614 (25%) Warfarin: 168/608 (28%), P = .003</td>
<td>Xim 36 mg: 6/769 (0.8%)</td>
</tr>
</tbody>
</table>
a dose response both for efficacy and safety. There was a trend for the lowest dose (25 mg twice daily) to be more effective than enoxaparin, with similar low rates of major bleeding. The 3 higher dose groups receiving razaxaban were stopped prematurely because of excessive major bleeding.51

Inhibitors of factors Va and VIIIa

Activated protein C (APC) modulates thrombin generation by inactivating factors Va and VIIIa.52 An increase of APC can be produced by direct administration of recombinant APC or by administration of recombinant soluble thrombomodulin.

Activated protein C

In a phase 3 clinical trial, recombinant APC, drotrecogin alfa (activated), given as an infusion over 96 hours, was compared with placebo in 1690 patients with severe sepsis.11 APC reduced mortality at 28 days by 19% (from 30.8% to 24.7%; \( P = .005 \)) but produced a 1.5% increase in major bleeding (from 2.0% to 3.5%; \( P = .06 \); Table 2).11 It is unclear whether the benefits of APC are due exclusively to its anticoagulant effect or whether other non-anticoagulant mechanisms play a role. A number of non-anticoagulant effects of ACP have been reported including its ability to down-regulate inflammatory cytokines (tumor necrosis factor and interleukin 6).53 Based on these results, recombinant APC has been licensed in North America as an adjunct for treatment of severe sepsis.

Soluble thrombomodulin

Soluble thrombomodulin binds thrombin and induces a conformational change in the active site of the enzyme that renders it a potent activator of protein C.54 A recombinant analog of the extracellular domain of thrombomodulin has been developed that binds thrombin and induces its anticoagulant effects.55 Soluble thrombomodulin has been shown to reduce mortality, major bleeding, and thromboembolic complications in patients with acute severe sepsis.56

Table 3. Phase 3 trials of new anticoagulants for thromboprophylaxis (continued)

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Study</th>
<th>No. of patients</th>
<th>Population</th>
<th>Regimen</th>
<th>Control</th>
<th>Outcome measure</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPRESS35</td>
<td>2835</td>
<td>THR/TKR</td>
<td>Melagatran 2 mg SC preoperatively, 3 mg SC postoperatively, then ximelagatan 24 mg bid × 8-11 d</td>
<td>Enoxaparin 40 mg OD SC × 8-11 d preoperatively</td>
<td>Venographically detected proximal DVT, symptomatic VTE, and death where PE could not be excluded to d 12</td>
<td>Xim: 26/1138 (2.3%) Enox: 74/1178 (6.3%) ( p = .001 ) Enox: 18/1387 (1.2%) ( P = \text{NA} )</td>
<td></td>
</tr>
<tr>
<td>EXULT B37</td>
<td>2303</td>
<td>TKR</td>
<td>Ximelagatan 36 mg bid × 7-12 d postoperatively</td>
<td>Warfarin INR 2-3.0 × 7-12 d postoperatively</td>
<td>Total VTE and all-cause mortality to d 14</td>
<td>Xim: 22.5%* Warfarin: 31.9% ( P &lt; .001 ) Warfarin: 0.4% NS</td>
<td></td>
</tr>
</tbody>
</table>

THR indicates total hip replacement; SC, subcutaneously; OD, once daily; bid, twice daily; TKR, total knee replacement; NI, noninferiority criteria were met; NNI, noninferiority criteria were not met; NA, not available.

* Results published in abstract only, raw data unavailable.
† Value refers to comparison between ximelagatan 36 mg/d and warfarin.
‡ Estimated cumulative risk.

Inhibitors of factors Va and VIIIa

Activated protein C (APC) modulates thrombin generation by inactivating factors Va and VIIIa.52 An increase of APC can be produced by direct administration of recombinant APC or by administration of recombinant soluble thrombomodulin.

Activated protein C

In a phase 3 clinical trial, recombinant APC, drotrecogin alfa (activated), given as an infusion over 96 hours, was compared with placebo in 1690 patients with severe sepsis.11 APC reduced mortality at 28 days by 19% (from 30.8% to 24.7%; \( P = .005 \)) but produced a 1.5% increase in major bleeding (from 2.0% to 3.5%; \( P = .06 \); Table 2).11 It is unclear whether the benefits of APC are due exclusively to its anticoagulant effect or whether other non-anticoagulant mechanisms play a role. A number of non-anticoagulant effects of ACP have been reported including its ability to down-regulate inflammatory cytokines (tumor necrosis factor and interleukin 6).53 Based on these results, recombinant APC has been licensed in North America as an adjunct for treatment of severe sepsis.

Soluble thrombomodulin

Soluble thrombomodulin binds thrombin and induces a conformational change in the active site of the enzyme that renders it a potent activator of protein C.54 A recombinant analog of the extracellular domain of thrombomodulin has been developed that binds thrombin and induces its anticoagulant effects.55 Soluble thrombomodulin has been shown to reduce mortality, major bleeding, and thromboembolic complications in patients with acute severe sepsis.56

Table 3. Phase 3 trials of new anticoagulants for thromboprophylaxis (continued)

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Study</th>
<th>No. of patients</th>
<th>Population</th>
<th>Regimen</th>
<th>Control</th>
<th>Outcome measure</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPRESS35</td>
<td>2835</td>
<td>THR/TKR</td>
<td>Melagatran 2 mg SC preoperatively, 3 mg SC postoperatively, then ximelagatan 24 mg bid × 8-11 d</td>
<td>Enoxaparin 40 mg OD SC × 8-11 d preoperatively</td>
<td>Venographically detected proximal DVT, symptomatic VTE, and death where PE could not be excluded to d 12</td>
<td>Xim: 26/1138 (2.3%) Enox: 74/1178 (6.3%) ( p = .001 ) Enox: 18/1387 (1.2%) ( P = \text{NA} )</td>
<td></td>
</tr>
<tr>
<td>EXULT B37</td>
<td>2303</td>
<td>TKR</td>
<td>Ximelagatan 36 mg bid × 7-12 d postoperatively</td>
<td>Warfarin INR 2-3.0 × 7-12 d postoperatively</td>
<td>Total VTE and all-cause mortality to d 14</td>
<td>Xim: 22.5%* Warfarin: 31.9% ( P &lt; .001 ) Warfarin: 0.4% NS</td>
<td></td>
</tr>
</tbody>
</table>
days after subcutaneous injection, has been evaluated in a phase 2 dose-escalating study in 312 subjects undergoing elective hip arthroplasty. Although there was no control group, soluble thrombomodulin reduced the rate of DVT in a dose-dependent fashion.55

### Thrombin inhibitors

All of the new thrombin inhibitors bind directly to thrombin and block its interaction with substrates. Unlike heparin, direct thrombin inhibitors inactivate fibrin-bound thrombin, as well as fluid-phase thrombin.56,57 Three parenteral direct thrombin inhibitors (hirudin, argatroban, and bivalirudin) and 1 oral direct thrombin inhibitor (ximelagatran) have been evaluated in phase 3 clinical trials. Specific antidotes are not available to neutralize these compounds.56,57 The parenteral thrombin inhibitors 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 patients undergoing PCI. Ximelagatran is still under investigation.

### Hirudin

Hirudin is a bivalent inhibitor; its amino-terminal domain interacts with the active site of thrombin and its carboxy-terminal tail binds to exosite 1.58 Binding is essentially irreversible. The plasma half-life of hirudin is 60 minutes after intravenous injection and 120 minutes after subcutaneous injection.59 Hirudin is cleared via the kidneys so its dose must be adjusted in patients with renal insufficiency.60

Although hirudin has been evaluated in acute coronary syndromes61-70 and for prevention and treatment of DVT,71-73 its development for these indications is no longer being pursued. For acute coronary indications hirudin was marginally more effective than heparin but caused more bleeding (Table 5).61-70 In contrast, at the lower doses used for the prevention of DVT in patients undergoing elective hip arthroplasty, hirudin was more effective than LMWH and heparin and was not associated with an increased risk of bleeding.71,72 The approval for use of hirudin for treatment of patients with heparin-induced thrombocytopenia is based largely on 2 prospective cohort studies that evaluated hirudin in this setting and reported a significant reduction in the incidence of a composite of death, amputation, and thromboembolic events when compared with historical controls.77,78

### Table 5. Phase 3 trials of new anticoagulant for acute coronary syndrome and percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>No. of patients</th>
<th>Population</th>
<th>Regimen</th>
<th>Control</th>
<th>Outcome measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirudin</td>
<td>OASIS-2</td>
<td>10 141</td>
<td>ACS non-ST</td>
<td>0.4 mg/kg bolus and infusion 0.15 mg/kg/h × 72 h</td>
<td>IV UFH × 72 h</td>
<td>Cardiovascular death, MI, or refractory angina at d 7</td>
<td>Hirudin: 284/5083 (5.6%)&lt;br&gt;UFH: 340/5058 (6.7%)&lt;br&gt;P = .01&lt;br&gt;Hirudin: 59/5083 (1.2%)&lt;br&gt;UFH: 34/5058 (0.7%)&lt;br&gt;P = .01</td>
</tr>
<tr>
<td></td>
<td>TIMI-9B</td>
<td>3002</td>
<td>STEMI-all received thrombolysis</td>
<td>0.1 mg/kg bolus and infusion 0.1 mg/kg/h × 96 h</td>
<td>IV UFH × 96 h</td>
<td>Death, recurrent nonfatal MI, severe CCF, or cardiogenic shock at 30 d</td>
<td>Hirudin: 195/1511 (12.9%)&lt;br&gt;UFH: 178/1491 (11.9%)&lt;br&gt;NS&lt;br&gt;Hirudin: 68/1474 (4.6%)&lt;br&gt;UFH: 77/1456 (5.3%)&lt;br&gt;NS</td>
</tr>
<tr>
<td></td>
<td>GUSTO-2B</td>
<td>12 142</td>
<td>ACS*</td>
<td>0.1 mg/kg bolus and infusion 0.1 mg/kg/h × 72 h IV infusion</td>
<td>IV UFH × 72 h</td>
<td>Death and nonfatal MI at 30 d</td>
<td>Hirudin: 8.9%<em>&lt;br&gt;UFH: 9.8%&lt;br&gt;NS&lt;br&gt;Hirudin: 1.2%</em>&lt;br&gt;UFH: 1.1%†&lt;br&gt;NS</td>
</tr>
<tr>
<td></td>
<td>HELVETICA</td>
<td>1141</td>
<td>PCI after ACS non-ST</td>
<td>IV bolus 40 mg then IV infusion 0.1 mg/kg/h × 24 h then either hirudin 40 mg SC bid or placebo × 3 d</td>
<td>IV UFH × 24 h then placebo × 3 d</td>
<td>Event-free survival at 7 mo</td>
<td>Hir IV: 242/381 (64%)&lt;br&gt;Hir IV/SC: 257/378 (68%)&lt;br&gt;UFH IV: 257/382 (67%)&lt;br&gt;NS&lt;br&gt;Hir IV: 18/381 (4.7%)&lt;br&gt;Hir IV/SC: 28/378 (7.4%)&lt;br&gt;UFH IV: 24/382 (6.2%)&lt;br&gt;NS</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Bittl et al</td>
<td>4098</td>
<td>PCA for unstable or postinfarct angina</td>
<td>IV bolus (1 mg/kg) then IV infusion × 24 h</td>
<td>IV UFH × 24 h</td>
<td>Death, MI, abrupt vessel closure, and cardiac clinical deterioration in-hospital</td>
<td>Biv: 235/2059 (11.4%)&lt;br&gt;UFH: 249/2039 (12.2%)&lt;br&gt;NS&lt;br&gt;Biv: 82/2161 (3.8%)&lt;br&gt;UFH: 210/2151 (9.8%)&lt;br&gt;P = .001</td>
</tr>
<tr>
<td></td>
<td>REPLACE-2</td>
<td>6010</td>
<td>PCI</td>
<td>IV 0.75 mg/kg bolus then infusion 1.75 mg/kg/h +/- GPIib/IIIa inh†</td>
<td>IV UFH + GPIib/IIIa inh†</td>
<td>Death, MI, urgent revascularization or major bleeding at 30 d</td>
<td>Biv: 275/2975 (9.2%)&lt;br&gt;UFH: 299/2991 (10%)&lt;br&gt;NS&lt;br&gt;Biv: 71/2993 (2.4%)&lt;br&gt;UFH: 123/3008 (4.1%)&lt;br&gt;P = .001</td>
</tr>
<tr>
<td></td>
<td>HERO-2</td>
<td>17 073</td>
<td>STEMI-all received thrombolysis</td>
<td>IV 0.25 mg/kg bolus then infusion × 48 h</td>
<td>IV UFH × 48 h</td>
<td>Death at 30 d</td>
<td>Biv: 919/8516 (10.8%)&lt;br&gt;UFH: 931/8557 (10.9%)&lt;br&gt;NS&lt;br&gt;Biv: 58/8516 (0.7%)&lt;br&gt;UFH: 40/8557 (0.5%)†&lt;br&gt;NS</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; STEMI, ST-elevation MI; CCF, congestive cardiac failure; PCA, percutaneous coronary angioplasty inh, inhibitor.

* Included STEMI and ACS non-ST elevation.

† Defined as severe bleeding, does not include intracranial hemorrhage.

‡ Administered for duration of procedure.
Bivalirudin

Bivalirudin is a 20-amino acid synthetic polypeptide analog of hirudin. The amino-terminal D-Phe-Pro-Arg-Pro sequence, which binds to the active site of thrombin, is connected via 4 Gly residues to a carboxy-terminal dodecapeptide that interacts with exosite 1 on thrombin. Once bound, thrombin cleaves the Pro-Arg bond within the amino terminal of bivalirudin, thereby reducing its antithrombin activity. Bivalirudin has been evaluated in patients undergoing PCI and as an adjunct to streptokinase in patients with ST-elevation MI.

Coronary angioplasty

The first phase 3 study compared bivalirudin with heparin in 4098 patients undergoing coronary angioplasty for unstable or postinfarction angina. The frequency of the primary outcome measure, a composite of in-hospital death, MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin, was not significantly lower in the bivalirudin group (Table 5; 11.4% versus 12.2%), whereas bleeding was significantly lower with bivalirudin than with heparin (3.8% and 9.8%, respectively; P < .001). In a prospectively stratified, high-risk subgroup of 704 patients with postinfarction angina, bivalirudin significantly reduced the primary outcome (from 14.2% to 9.1%; P = .04).

Bivalirudin has also been evaluated in Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) a phase 3 clinical trial of 6010 PCI patients who were randomly assigned to bivalirudin plus provisional glycoprotein (GP) IIb/IIIa antagonist (either abciximab or eptifibatide), or heparin plus a GPIIb/IIIa antagonist. The primary outcome measure, a composite of death, MI, urgent revascularization, or major bleeding at 30 days, occurred in 9.2% of the patients treated with bivalirudin and in 10% of those given heparin (P = .32). A GPIIb/IIIa antagonist was required in only 7% of patients randomized to bivalirudin. Rates of major bleeding were significantly lower in patients given bivalirudin than in those treated with heparin (2.4% and 4.1%, respectively; P < .001; Table 5).

Adjunct to thrombolysis

Bivalirudin has been compared with heparin as adjuncts to thrombolytic therapy in a phase 3 randomized trial (Hirulog and Early Reperfusion or Occlusion [HERO-2]) of 17 073 patients with acute ST-elevation MI. Patients were randomly assigned to an intravenous bolus followed by a 48-hour infusion of either fixed-dose bivalirudin (n = 8516) or adjusted-dose heparin (n = 8557) in conjunction with streptokinase. The primary outcome measure was 30-day mortality, and secondary outcome measures included reinfarction within 96 hours and bleeding. Mortality at 30 days was similar in patients randomized to bivalirudin or heparin (10.8% and 10.9%, respectively; P = .85), but in contrast to the other 2 randomized trials, the rate of bleeding was significantly higher with bivalirudin. In addition, there was a trend for higher major bleeding rates (including severe bleeding) with bivalirudin (Table 5).

Argatroban

Argatroban, a competitive inhibitor of thrombin, binds noncovalently to the active site of thrombin to form a reversible complex. The plasma half-life of argatroban is 45 minutes and the drug is metabolized in the liver. Argatroban is licensed for treatment of heparin-induced thrombocytopenia with or without thrombosis. Argatroban has not been evaluated in appropriately designed randomized controlled trials in this setting and, like hirudin, evidence supporting its use is confined to 2 prospective cohort studies of patients treated with argatroban compared with historical controls.

Although trials have evaluated argatroban for treatment of unstable angina, as an adjunct to thrombolysis, and as an alternative to heparin in patients undergoing coronary angioplasty, the studies are small and none has shown definitive advantages of argatroban over heparin.

Ximelagatran

Ximelagatran is the first orally active thrombin inhibitor. It is a produg of the active site-directed thrombin inhibitor, melagatran. After ingestion, ximelagatran is absorbed from the small intestine and undergoes rapid biotransformation to melagatran, the active agent. Melagatran has been evaluated for thromboprophylaxis in high-risk orthopedic patients, treatment of VTE, and prevention of cardioembolic events in patients with nonvalvular atrial fibrillation. Based on its predictable anticoagulant response, ximelagatran was administered in fixed doses without coagulation monitoring.

Venous thromboprophylaxis

Ximelagatran has been evaluated for the prevention of VTE in 6 phase 3 trials in patients undergoing either elective hip surgery, major knee surgery, or both in 3 studies (Table 3). The comparator was enoxaparin in 3 studies and warfarin in the other. In the 2 European trials, melagatran/ximelagatran showed similar efficacy and safety to preoperative enoxaparin. In the Platinum Hip study, postoperative enoxaparin was more effective and showed a similar incidence of bleeding to the postoperative melagatran/ximelagatran regimen, whereas in the EXPlained PRophylaxis Evaluation Surgery Study (EXPRESS) trial (hip and knee replacement surgery), the combination of preoperative melagatran and postoperative ximelagatran was more effective than preoperative enoxaparin, but at the cost of more bleeding.

In the 3 North American trials in which warfarin was the comparator, it was started postoperatively in a dose adjusted to produce an international normalized ratio (INR) of 2.0 to 3.0. Ximelagatran was commenced postoperatively in a dose of either 24 mg or 36 mg twice daily. In the North American studies, ximelagatran was started on the day after surgery (ie, 12-24 hours postoperatively) in the 2 European trials and the other 2 randomized trials, the rate of bleeding was significantly higher with bivalirudin. In addition, there was a trend for higher major bleeding rates (including severe bleeding) with bivalirudin (Table 5).
The results of these studies indicate that ximelagatran administered postoperatively is as safe and marginally less effective than enoxaparin and more effective than warfarin, for the prevention of venous thrombosis in patients undergoing elective orthopedic surgical procedures. However, when combined with preoperative melagatran, the prophylactic regimen is associated with an increase in perioperative bleeding (Table 3). At present, melagatran/ximelagatran has been approved in France for prevention of VTE after major orthopedic surgery, based on the results of the METHRO III and EXPRESS trials.32,36

Treatment of VTE

Ximelagatran has been evaluated in 2 phase 3 trials. In the THRonbin Inhibitor in Venuous thromboEmbolism (THRIVE III) trial,41 1233 patients, who had completed a 6-month course of anticoagulant therapy for treatment of VTE, were randomized to ximelagatran (24 mg twice daily) or placebo for an additional 18 months. The cumulative risk of an event during the 18 months was 2.8% in the ximelagatran group and 12.6% in the placebo group (hazard ratio 0.16; P < .001). Major bleeding occurred in 1% of patients in each group. There was no difference between groups in death from any cause (Table 4).

The THRIVE II/V42 trial was a double-dummy, randomized noninferiority trial of 2491 patients with acute VTE. Participants were randomized to receive oral ximelagatran (36 mg twice daily) or subcutaneous enoxaparin (1 mg/kg twice daily for a minimum of 5 days) followed by warfarin (target INR, 2.0-3.0). Treatment was given for 6 months and patients were followed up for an additional 40 days. Recurrent VTE occurred in 2.1% of ximelagatran-treated patients and 2.0% in the enoxaparin/warfarin group and all-cause mortality occurred in 2.3% and 3.4%, respectively. Major bleeding occurred in 1.3% of those given ximelagatran and 2.2% of those treated with enoxaparin/warfarin, a trend that was not significant. These results suggest that ximelagatran is an effective and safe alternative to LMWH followed by warfarin for acute treatment of VTE (Table 4).

Atrial fibrillation

Two phase 3 trials have compared ximelagatran (36 mg twice daily) to warfarin for the prevention of cardioembolic events in patients with nonvalvular atrial fibrillation93,94 (Table 6). The Stroke Prevention and warfarin for the prevention of cardioembolic events in patients with nonvalvular atrial fibrillation (SPORTIF III) study randomized 3407 such subjects, in an open-label fashion, to receive either ximelagatran or adjusted-dose warfarin (targeted to an INR of 2.0-3.0).93 The primary outcome, all strokes and systemic embolic events, was reported in 40 subjects (1.6%/year) assigned to ximelagatran and 56 (2.3%/year) assigned to warfarin in an intention-to-treat analysis following a mean duration of follow-up of 21 months. Rates of major and intracranial hemorrhage were comparable in both groups, although major and minor bleeds were reduced in the ximelagatran group (25.5% compared with 29.5%; P = .007). All-cause mortality was 3.2%/year in both groups.

The SPORTIF V trial randomized 3922 participants with nonvalvular atrial fibrillation (and more than 1 additional vascular risk factor) to receive ximelagatran 36 mg twice daily or adjusted-dose warfarin (INR, 2.0-3.0). SPORTIF V was a double-blind, double-dummy trial.94 The primary outcome measure of all strokes (ischemic or hemorrhagic) and systemic embolic events was reported in 51 subjects (1.6%/year) assigned to ximelagatran and 37 (1.2%/year) assigned to warfarin (intention-to-treat analysis) following a mean duration of follow-up of 24 months (P = .13). Rates of major bleeding were 3.1% in those receiving adjusted-dose warfarin and 2.4% in those receiving ximelagatran (P = .16). Intracranial hemorrhage occurred in 0.06% of participants in both groups. The rate of major plus minor bleeding was lower in the ximelagatran group (37% compared with 47%).94 When the results of SPORTIF III and V were combined, ximelagatran was associated with a 16% relative risk reduction in the composite outcome measure of all strokes (ischemic or hemorrhagic), systemic embolic events, major bleeding, and death (P = .038).94

Acute coronary syndrome

In the Efficacy and Safety of oral direct Thrombin inhibitor ximelagatran in patiEnms with rEcent Myocardial infarction (ESTEEM) study,95 1883 patients with ST-elevation or non–ST-elevation MI within the past 14 days were randomly assigned to receive oral ximelagatran (24, 36, 48, or 60 mg twice daily) or placebo. All patients received aspirin. The primary outcome measures, all-cause mortality, nonfatal MI, and severe recurrent ischemia, were significantly reduced in the ximelagatran group (16.3% and 12.7%, respectively; P = .036). Within the ximelagatran groups, efficacy was comparable among the various dosage groups, but the lowest rate of major bleeding was reported with a dose of 24 mg twice-daily.

Nonhemorrhagic side effects of ximelagatran

Between 6% and 9.6% of patients treated with long-term ximelagatran develop a 3-fold or greater increase in alanine aminotransferase.31,42,93,94 Typically, this side effect occurs between 6 weeks and 6 months of treatment.41,42,93,94 The increase in alanine aminotransferase is usually asymptomatic and reversible, even if the medication is continued. Based on data from clinical trials, the increase in transaminases with ximelagatran has been benign. However, this side effect is of potential concern and, if the drug is approved, its
long-term impact on liver function will need to be carefully monitored in clinical practice after the drug is marketed. It is likely that liver function tests will need to be monitored, at least during the initial 6 months of ximelagatran therapy.

### Summary of results by clinical indication

#### Venous thromboprophylaxis

Both LMWH and warfarin are safe and effective agents for thromboprophylaxis in high-risk orthopedic patients. Fondaparinux is a new alternative and is approved for this indication. Although ximelagatran also appears to be effective, it is not yet approved in North America. In the 3-month period after a 7- to 10-day course of postoperative prophylaxis with either agent, the incidence of symptomatic VTE is about 2.5% and 1.4% for hip and knee arthroplasty, respectively, and the incidence of fatal PE is about 0.05%. The main clinical need in this setting is a thromboprophylactic approach that is safe, effective, and convenient for use after hospital discharge, particularly in patients having hip surgery. LMWH is effective for extended thromboprophylaxis after hip and knee surgery, whereas fondaparinux is effective for extended prophylaxis in patients undergoing surgery for hip fracture. Neither agent requires coagulation monitoring, but both must be given by subcutaneous injection. The efficacy of ximelagatran in this setting has yet to be determined.

#### Treatment of VTE

LMWH is effective and safe for the initial treatment of acute VTE. The recently completed MATISSE trials indicate that fondaparinux is as effective and safe as heparin or LMWH for initial treatment of patients with VTE. The most pressing clinical need in the treatment VTE is for longer-term secondary prevention after the acute event. Although long-term warfarin therapy markedly reduces the risk of recurrence, its benefit is offset by the risk of major bleeding, and the inconvenience of frequent monitoring. Ximelagatran does not require coagulation monitoring, and based on the results of the THRIVE trials, ximelagatran has the potential to replace warfarin for secondary prevention of VTE. Still to be determined is the clinical impact of the abnormalities in liver function tests on the utility of this drug.

#### Prevention of cardioembolic events

Although warfarin is more effective than aspirin at reducing the risk of embolization in high-risk patients with atrial fibrillation, it has limitations. Even with monitoring in specialized clinics, the level of anticoagulation with vitamin K antagonists is outside the therapeutic range almost half of the time. Furthermore, the risk of major bleeding with long-term treatment increases in the elderly, the population where atrial fibrillation presents the greatest risk. Because of these problems, it is estimated that warfarin is not given to almost half of the eligible patients with atrial fibrillation. Ximelagatran has the potential to replace warfarin for this indication if the effects of ximelagatran on liver function tests are not limiting.

### Acute coronary syndromes

Parenteral anticoagulants continue to have a role in the treatment of acute coronary syndromes. The results of the REPLACE-2 trial suggest that bivalirudin obviates the need for GPIIb/IIIa antagonists in low-risk to moderate-risk patients undergoing PCI and reduces the risk of bleeding. The role of fondaparinux, NAPC2, and DX9065a for these indications remains to be established. Long-term treatment with the combination of aspirin and clopidogrel is more effective at reducing the risk of recurrent ischemia than aspirin alone, but at the cost of more bleeding. The relative efficacy and safety of aspirin plus clopidogrel versus warfarin is unknown. The initial results with ximelagatran are promising; eventually, ximelagatran will have to be compared with warfarin or the combination of aspirin and clopidogrel.

### Mechanistic insights

Based on the results of these randomized trials it is not possible to conclude with certainty that any 1 anticoagulant has a better efficacy-to-safety index than another. All of the anticoagulants evaluated for the prevention of VTE cause excessive bleeding if given in the immediate perioperative period. Although fondaparinux was more effective than enoxaparin in patients undergoing major orthopedic surgery, it was started sooner after surgery and, if started too soon, was associated with increased bleeding. In patients undergoing percutaneous coronary interventions, bivalirudin was associated with less bleeding than heparin in 2 studies. However, when used as adjuncts to streptokinase, there was more bleeding with bivalirudin than with heparin. Consequently, the difference in the efficacy-to-safety index between these 2 anticoagulants remains uncertain. Ximelagatran showed a similar efficacy to safety index to dose-adjusted warfarin. Because anticoagulant control with warfarin is likely to be better in the clinical trial setting than in routine practice, ximelagatran may prove to be safer, with respect to bleeding, than warfarin. There are now newer parenteral anticoagulants that are more convenient to use than heparin because they produce a more predictable anticoagulant response, thereby obviating the need for routine monitoring. The introduction of fondaparinux and bivalirudin also provides an opportunity to eliminate heparin-induced thrombocytopenia. Although these new agents are a step forward, the greatest clinical need is for an oral anticoagulant that is safe and effective when used in fixed or weight-adjusted doses without routine coagulation monitoring. As the first such agent, ximelagatran is promising. With other oral direct thrombin and factor Xa inhibitors in development, we soon will have a number of oral anticoagulants that have the potential to replace warfarin. So, more than 60 years since the introduction of the coumarins, this class of compounds will likely be replaced by new and more convenient oral anticoagulation in the very near future.

### References


New anticoagulants

Jack Hirsh, Martin O'Donnell and Jeffrey I. Weitz