Emerging anticoagulants for the treatment of venous thromboembolism

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Summary
Anticoagulant therapy is the cornerstone of treatment of venous thromboembolism (VTE). Such treatment is divided into two stages. Rapid initial anticoagulation is given to minimize the risk of thrombus extension and fatal pulmonary embolism, whereas extended anticoagulation is aimed at preventing recurrent VTE, thereby reducing the risk of postphlebitic syndrome. With currently available drugs, immediate anticoagulation can only be achieved with parenteral agents, such as heparin, low-molecular-weight heparin, or fondaparinux. Extended treatment usually involves the administration of vitamin K antagonists, such as warfarin. Emerging anticoagulants have the potential to streamline VTE treatment. These agents include idraparinux, a long-acting synthetic pentasaccharide that is given subcutaneously on a once-weekly basis, and new oral anticoagulants that target thrombin or factor Xa. This paper i) reviews the pharmacology of these agents, ii) outlines their potential strengths and weaknesses, iii) describes the results of clinical trials with these new drugs, and iv) identifies the evolving role of new anticoagulants in the management of VTE.

Keywords
Coagulation inhibitors, heparins / glycosaminoglycans, pulmonary embolism, deep vein thrombosis

Introduction
Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality. In the United States, it is estimated that two million people develop DVT each year. DVT progresses to PE in 600,000 of these patients and the PE is fatal in 200,000 (1). In addition to PE, DVT can lead to debilitating postphlebitic syndrome in up to one-third of patients (2). The risk of postphlebitic syndrome is highest in patients with extensive DVT and in those with recurrent disease.

Anticoagulant therapy remains the cornerstone of VTE treatment. Such treatment is usually divided into two stages. Rapid initial anticoagulation is given to minimize the risk of thrombus extension and subsequent fatal PE, whereas extended anticoagulation is administered to prevent recurrent VTE, thereby reducing the risk of postphlebitic syndrome. With currently available drugs, immediate anticoagulation can only be effected with parenteral anticoagulants, such as heparin, low-molecular-weight heparin (LMWH), or fondaparinux. Extended therapy usually involves the administration of an oral anticoagulant. Currently, the only orally available anticoagulants are the vitamin K antagonists, such as warfarin.

The introduction of LMWH has simplified the initial treatment of VTE. LMWH has better bioavailability after subcutaneous injection than heparin. LMWH also has a longer half-life than heparin and produces a more predictable anticoagulant response. These features permit once- or twice-daily subcutaneous dosing without coagulation monitoring (3). Consequently, the majority of patients with VTE can now be treated with LMWH as outpatients (4, 5), an approach that reduces healthcare costs (6, 7) and enhances patient satisfaction (8).

Although LMWH represents an important advance in VTE treatment, some difficulties persist. The need for once- or twice-daily subcutaneous injections renders LMWH problematic for some patients. In addition, the risk of heparin-induced thrombocytopenia is not eliminated with LMWH, although it is lower than that with heparin (9). These issues have not only prompted...
the introduction of longer acting parenteral agents that do not cause heparin-induced thrombocytopenia, but also have driven the development of novel oral anticoagulants with a rapid onset of action.

Warfarin also is problematic in the setting of VTE. With a slow onset of action, warfarin must be overlapped with a parenteral anticoagulant for at least five days (10). The therapeutic dose of warfarin varies from patient to patient reflecting, at least in part, differences in dietary vitamin K intake (10), genetic polymorphisms in the enzymes involved in warfarin metabolism (11, 12), and administration of concomitant medications that suppress or potentiate the anticoagulant effects of warfarin (13).

Frequent coagulation monitoring is necessary to ensure that a therapeutic anticoagulant response is achieved with warfarin, because a subtherapeutic response is associated with an increased risk of thrombosis whereas excessive anticoagulation increases the risk of hemorrhage (10). The requirement for frequent coagulation monitoring is burdensome for patients and physicians, and costly for the healthcare system. The difficulties surrounding warfarin administration have spurred the development of new oral anticoagulants that can be given in fixed doses with little or no coagulation monitoring. The need for oral anticoagulants that are more convenient to administer than warfarin has increased in recent years with emerging evidence that patients with unprovoked VTE require anticoagulation therapy for at least six months after their index event, and possibly for longer (14).

This article focuses on the new anticoagulants that are under investigation for VTE treatment. These include novel parenteral and orally active agents. Concentrating on drugs that have at least reached phase II clinical testing for VTE treatment, this paper i) reviews their pharmacology, ii) highlights the potential advantages of these novel agents over existing anticoagulants, iii) describes the results of the clinical trials evaluating these new agents for VTE treatment, iv) provides perspective on the opportunities for these drugs and their potential drawbacks, and v) identifies the evolving role of new anticoagulants in the management of VTE.

Pharmacology of new anticoagulants

New anticoagulants currently being evaluated for VTE treatment include inhibitors of factor Xa or thrombin. The factor Xa inhibitors encompass fondaparinux, idraparinux, and SSR126517E, parenteral drugs that target factor Xa in an antithrombin-dependent fashion, and rivaroxaban, apixaban, and other orally active agents that directly inhibit factor Xa. The new thrombin inhibitors, both of which are orally active, are ximelagatran, which, as discussed later, has recently been withdrawn from the market, and dabigatran etexilate.

Inhibitors of factor Xa block thrombin generation, whereas thrombin inhibitors block the activity of thrombin, the enzyme that catalyzes the conversion of fibrinogen to fibrin. Whether thrombin generation is attenuated or thrombin action is suppressed, the net effect is a reduction in thrombin activity and fibrin formation, events that result in inhibition of coagulation. Limiting thrombin generation or activity is critical, because, in addition to its role in fibrin formation, thrombin not only serves as a potent platelet agonist, but also amplifies its own generation by feedback activation of factors VIII and V, key cofactors involved in factor Xa and thrombin generation, respectively.

Focusing first on the factor Xa inhibitors and then covering the thrombin inhibitors, the pharmacology of these new anticoagulants will be discussed.

Fondaparinux

A synthetic analog of the antithrombin-binding pentasaccharide found in heparin or LMWH (Fig. 1), fondaparinux binds antithrombin with high affinity (15, 16). Fondaparinux has a higher specific anti-factor Xa activity than heparin or LMWH and a longer half-life (Table 1). As a defined chemical entity, fondaparinux has a molecular weight of 1,728 (15, 16). Like heparin and LMWH, fondaparinux has no intrinsic anticoagulant activity. Instead, it exerts its anticoagulant effects by binding to antithrombin and evoking a conformational change at the reactive site of antithrombin that enhances its reactivity with factor Xa. Because it is too short to bridge antithrombin to thrombin, fondaparinux does not increase the rate of thrombin inhibition by antithrombin. Consequently, fondaparinux is considered to be a specific antithrombin-dependent inhibitor of factor Xa, although it also catalyzes the inhibition of factor IXa by antithrombin (17).

Fondaparinux has almost complete bioavailability after subcutaneous injection and has a plasma half-life of 17 hours (15, 16). By contrast, the bioavailability of LMWH is about 90% and its half-life is four hours (3). Because of the long half-life of fondaparinux, the drug is administered by subcutaneous injection once daily. Fondaparinux produces a predictable anticoagulant response and exhibits linear pharmacokinetics when given in subcutaneous doses of 2–8 mg (15, 16). Because of these features, fondaparinux can be given without coagulation monitoring. If monitoring is required, anti-factor Xa levels can be measured using assays similar to those used to monitor heparin or LMWH. However, fondaparinux must be employed as a standard in these assays to establish drug concentrations (18). Fondaparinux has little or no effect on routine tests of coagulation, such as the activated partial thromboplastin time (aPTT) or the activated clotting time (19).

Fondaparinux is excreted unchanged in the urine. Therefore, the drug must be used with caution in patients with renal insufficiency. Fondaparinux is contraindicated in those with renal failure (15, 16).

Although fondaparinux may induce the formation of anti-platelet factor 4 (PF4)/heparin antibodies, fondaparinux is unlikely to cause heparin-induced thrombocytopenia, because it is poorly recognized by the generated antibodies (20). However, these findings raise the possibility that fondaparinux-treated patients may be at risk for heparin-induced thrombocytopenia if they are subsequently given heparin or LMWH. Small studies have shown no cross-reactivity of fondaparinux with sera from patients with heparin-induced thrombocytopenia (21, 22). Furthermore, in two small case series of patients treated with fondaparinux either, because they had acute heparin-induced thrombocytopenia (23) or had a prior history of heparin-induced thrombocytopenia and required parenteral anticoagulation (24), no patient developed clinically evident thrombosis. Although these findings suggest that fondaparinux may be a suitable anticoagulant for patients with heparin-induced thrombocytopenia...
Figure 1: Structures of natural pentasaccharide, fondaparinux and idraparinux.

Table 1: Comparison of the features of LMWH, fondaparinux, and idraparinux.

<table>
<thead>
<tr>
<th>Features</th>
<th>LMWH</th>
<th>Fondaparinux</th>
<th>Idraparinux</th>
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<tbody>
<tr>
<td>Route of administration</td>
<td>Subcutaneous or intravenous</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Target</td>
<td>Factor Xa and thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>90</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>4</td>
<td>17</td>
<td>80</td>
</tr>
<tr>
<td>Plasma protein-binding</td>
<td>Low</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk of heparin- induced thrombocytopenia</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Safe in pregnancy</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Neutralized by protamine sulfate</td>
<td>Partial</td>
<td>No</td>
<td>No</td>
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</table>
more data are required before its use can be recommended in this setting.

The safety of fondaparinux in pregnant women is uncertain. Although no placental transfer of fondaparinux was observed in a dually perfused human cotyledon model (26), limited clinical experience suggests that fondaparinux may pass the placental barrier in vivo, resulting in low but measurable anti-factor Xa activity in umbilical cord blood (27).

**Idraparinux and SSR12617E**

A second generation synthetic pentasaccharide, idraparinux is a hypermethylated derivative of fondaparinux (Fig. 1) that binds antithrombin with such high affinity that it assumes a plasma half-life of 80 hours (28, 29), similar to that of antithrombin. Idraparinux exhibits complete bioavailability after subcutaneous injection, binds only to antithrombin in plasma and produces a predictable anticoagulant response. Consequently, idraparinux is given by subcutaneous injection once-weekly without coagulation monitoring (28, 29).

Like fondaparinux, idraparinux is not metabolized and is excreted unchanged via the kidneys. Therefore, the dose of idraparinux must be reduced in patients with renal insufficiency and idraparinux is contraindicated in those with renal failure. The safety of idraparinux in pregnancy is uncertain (28, 29).

SSR126517E is a biotinylated form of idraparinux. The advantage of biotinylated idraparinux is that it can be neutralized with intravenous recombinant avidin. Avidin binds biotinylated fondaparinux with high affinity, and the complex is then rapidly cleared.

**Rivaroxaban**

An oxazolidinone derivative (Fig. 2), rivaroxaban (formerly known as BAY59–7939), which has a molecular weight of 436, is a potent and selective inhibitor of factor Xa (30). It binds to the active site of factor Xa and inhibits the enzyme in a reversible and competitive fashion regardless of whether factor Xa is free in solution or bound within the prothrombinase complex (30). Rivaroxaban is well absorbed from the gastrointestinal tract and plasma levels of the drug peak in about three hours (31). The terminal half-life is about nine hours at steady state so the drug is given orally twice daily (32, 33), although once-daily administration may be sufficient when rivaroxaban is used in the prophylactic setting (34). Food prolongs the time to peak plasma concentration and increases drug exposure by 25 to 35%.

Rivaroxaban exhibits a dual mechanism of excretion. About 65% is excreted via the kidneys, while the remainder is excreted in the feces (30). Because of this dual excretion mechanism, the drug may be less likely to accumulate in patients with renal insufficiency.

Rivaroxaban is metabolized in the liver and shows some interaction with potent inhibitors of CYP3A4, such as ketoconazole. However, its potential for other drug-drug interactions is expected to be low.

Like other direct factor Xa inhibitors, rivaroxaban prolongs the international normalized ratio (INR) and aPTT but its effects on these tests are relatively small at therapeutic doses, with the INR being more sensitive than the aPTT (30). An anti-factor Xa assay can be used to measure drug concentrations in plasma (30).

**Apixaban**

A small molecule inhibitor that targets the active site of factor Xa, apixaban has a molecular weight of 460 (Fig. 2). Apixaban is a selective and reversible inhibitor of factor Xa and, like rivaroxaban, it inhibits factor Xa bound within the prothrombinase complex as well as the free enzyme. The drug is well absorbed from the gastrointestinal tract and peak plasma levels are achiev-
ed in about three hours. With repeated doses, the terminal half-life is between nine and 14 hours. Therefore, once-daily administration may be possible.

Apixaban is oxidized to a phenol metabolite in the liver and CYP3A4 may be involved in this metabolism. However, the potential for drug-drug interactions with apixaban is expected to be low. Like rivaroxaban, apixaban exhibits a dual mechanism of excretion. About 25% is excreted via the kidneys, while the remainder appears in the feces. Table 2 compares and contrasts the features of apixaban and rivaroxaban.

Apixaban prolongs the INR and aPTT in a concentration-dependent fashion. However, its effect on these tests is minimal at concentrations that are likely to be therapeutic.

Other oral factor Xa inhibitors
Promising phase II results with LY-517717 (35) and YM-150 (36), two other oral factor Xa inhibitors, were recently reported. These agents were evaluated in the setting of VTE prophylaxis after major orthopedic surgery. Additional phase II studies will be needed to establish optimal doses and to determine the potential utility of these agents for VTE treatment.

Ximelagatran
The first orally available direct thrombin inhibitor, ximelagatran is a prodrug of melagatran (Fig. 2), a 429 Dalton dipeptide analog of the portion of fibrinopeptide A that fits within the active site cleft of thrombin and blocks its interaction with substrates (37). In contrast to melagatran, which has poor oral bioavailability, ximelagatran, whose molecular weight is 474, is well absorbed from the gastrointestinal tract with a bioavailability of approximately 20% (37, 38). Once absorbed, ximelagatran undergoes rapid biotransformation to melagatran, the level of which peaks within two hours. Melagatran has a plasma half-life of 3–4 hours in healthy volunteers and 4–5 hours in patients. Because of its short half-life, ximelagatran is administered orally twice daily (37, 38).

No foods or drugs have been documented to influence the absorption of ximelagatran. Ximelagatran does not inhibit cytochrome P450 enzymes (39) and, therefore, has a low potential for drug-drug interactions. Ximelagatran produces a predictable anticoagulant response after oral administration rendering coagulation monitoring unnecessary (37, 38).

Melagatran is eliminated via the kidneys. Therefore, dose adjustments are needed in patients with severe renal insufficiency (40, 41). The half-life of melagatran is slightly prolonged in the elderly, likely reflecting their reduced creatinine clearance.

The major off-target side effect of ximelagatran is elevation of liver transaminases (42). Elevations in alanine aminotransferase of greater than three times the upper limit of normal occur in about 8% of patients receiving ximelagatran for more than a month, versus 2% in those treated with enoxaparin or warfarin. Concomitant two-fold or greater elevations in serum bilirubin occur in 0.5% of patients (42). Typically, changes in liver enzymes occur after six weeks to four months of therapy and are asymptomatic and reversible, even if the medication is continued. One death due to hepatorenal failure, along with two other deaths from hepatic failure contributed to the decision of the Food and Drug Administration (FDA) to reject an initial application for approval of ximelagatran for prophylactic and treatment indications (43). In Europe and Argentina, the drug was approved for short-term thromboprophylaxis after orthopedic surgery (44). Recently, ximelagatran was withdrawn from the global market when a patient given a one-month course of ximelagatran treatment for thromboprophylaxis after orthopedic surgery developed hepatic insufficiency several weeks after stopping the drug. The mechanism of the liver enzyme abnormalities with ximelagatran is unknown. A second generation version of ximelagatran, AZD0837, is currently undergoing phase II evaluation. Based on data available to-date, this drug does not appear to produce the increase in hepatic transaminases that were seen with ximelagatran.

Dabigatran etexilate (BIBR 1048)
Another oral direct thrombin inhibitor (45, 46), dabigatran etexilate is a double prodrug (Fig. 2) that is converted by esterases into its active metabolite, dabigatran (BIBR 953), once it is absorbed from the gastrointestinal tract. The molecular weight of dabigatran etexilate is 628, whereas dabigatran has a molecular weight of 471 (45, 46). Because bioconversion of dabigatran etexilate to dabigatran begins in the gut, the drug enters the portal vein as a combination of prodrug and active compound. Once in the liver, bioconversion of the prodrug is completed and about 20% is conjugated and excreted via the biliary system. The cytochrome P450 system plays no part in the metabolism of dabigatran etexilate. Therefore, the risk of drug-drug interactions is low.

The bioavailability of dabigatran etexilate is only about 4%, so relatively high doses of dabigatran etexilate must be given to ensure that adequate plasma concentrations are achieved (47). The absorption of dabigatran etexilate in the stomach and small intestine is dependent on an acid environment. To maintain such a microenvironment, dabigatran etexilate is provided in tartaric acid-containing capsules. Nonetheless, drug absorption is reduced by 20 to 25% if dabigatran-treated patients are given proton pump inhibitors. Levels of dabigatran peak in the blood about two hours after dabigatran etexilate administration. The half-life of dabigatran is approximately eight hours after single-dose administration and up to 14 to 17 hours after multiple doses have been given. With the long terminal half-life, once-daily administration may be possible for some indications.

Table 2: Comparison of the features of rivaroxaban and apixaban.

<table>
<thead>
<tr>
<th>Features</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>436</td>
<td>460</td>
</tr>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP450 metabolism</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td>Time to peak drug level (h)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9</td>
<td>9–14</td>
</tr>
<tr>
<td>Biliary excretion (%)</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>65</td>
<td>25</td>
</tr>
</tbody>
</table>
Dabigatran is excreted unchanged via the kidneys (45, 46). Consequently, plasma concentrations can increase in patients with renal insufficiency. The drug has not been studied in patients with renal failure.

Table 3 compares and contrasts the features of dabigatran etexilate with those of ximelagatran. Dabigatran etexilate prolongs the aPTT, but its effects are not dose-dependent. It has minimal effect on the INR, but prolongs the ecarin clotting time in a concentration-dependent fashion (45, 46).

Limited clinical information is available with dabigatran etexilate (48, 49). Based on findings from a small number of patients treated with the drug for at least six months, the incidence of three-fold or higher elevations in serum levels of alanine aminotransferase appears to be about 1.5%. Concomitant elevations in bilirubin of two-fold or higher have yet to be seen. However, more long-term data are required to assess the hepatic liability of this agent.

Potential advantages of new anticoagulants

Fondaparinux was developed to replace heparin and LMWH, whereas idraparinux and direct factor Xa and thrombin inhibitors were designed to compete with warfarin for long-term anticoagulation. Because of their rapid onset of action, however, idraparinux and the new oral agents may also be useful for initial treatment of VTE, as well as for extended therapy.

Fondaparinux and idraparinux have potential safety advantages over heparin and LMWH. Synthetic pentasaccharides are likely to eliminate the risk of heparin-induced thrombocytopenia provided that there is no concomitant use of heparin or LMWH. In addition, osteoporosis, which can complicate long-term treatment with heparin, is unlikely to occur with fondaparinux or idraparinux. Thus, in studies using cultured osteoblasts, fondaparinux had no effect on cellular activity, whereas heparin, and to a lesser extent LMWH, suppressed their activity (50, 51). Finally, fondaparinux and idraparinux are less likely to cause urticarial reactions at the site of subcutaneous injection than heparin or LMWH. In support of this concept, there are reports of the successful use of fondaparinux in patients who experienced urticarial reactions to LMWH (52, 53).

Oral direct factor Xa or thrombin inhibitors have potential advantages over warfarin. These new agents have a rapid onset of action, which could obviate the need for overlap with a parenteral anticoagulant when starting treatment in a patient with VTE. With no food interactions, no genetic variations in metabolism and minimal potential for drug-drug interactions, oral factor Xa or thrombin inhibitors can be given in fixed doses with little or no coagulation monitoring. These features render them more convenient to administer than warfarin. Building on their potential advantages, these new agents have been compared with conventional anticoagulants in patients with VTE.

Clinical trials with new anticoagulants

Fondaparinux, idraparinux and ximelagatran have completed phase III clinical trials for VTE treatment, but the results with idraparinux have yet to be reported. Phase III trials with dabigatran etexilate in patients with VTE have started. A phase II trial with rivaroxaban has been completed, while a phase II trial with apixaban is underway. No results have been reported so far.

Fondaparinux

Two phase III trials evaluated the utility of fondaparinux for initial treatment of VTE. In the MATISSE-DVT study (54), 2,205 patients with DVT were randomized, in a double-blind fashion, to receive either fondaparinux (at a dose of 7.5 mg subcutaneously once daily for those weighing 50 to 100 kg; those under 50 kg were given 5 mg, while those over 100 kg received 10 mg) or enoxaparin (at a dose of 1 mg/kg subcutaneously twice daily). Study drug was given for at least five days and was followed by a minimum of a three-month course of treatment with a vitamin K antagonist. At three months, the rates of recurrent VTE were 3.9% and 4.1% with fondaparinux and enoxaparin, respectively, while the rates of major bleeding were 1.1% and 1.2%, respectively.

In the open-label MATISSE-PE trial (55), 2,213 patients with PE were randomized to receive either once-daily subcutaneous fondaparinux (at the same doses used in the MATISSE-DVT trial) or heparin, which was given by continuous intravenous infusion. Study drug was given for at least five days, and patients were then given a minimum three-month course of treatment with a vitamin K antagonist. At three months, the rates of recurrent VTE were 3.8% and 5.0% with fondaparinux and heparin, respectively, while the rates of major bleeding were 1.3% and 1.1%, respectively.

The results of the MATISSE studies suggest that fondaparinux is as effective and safe, in terms of the risk of bleeding, as LMWH or heparin for initial VTE treatment. Based on these studies, fondaparinux has been licensed for this indication.

Iдрапарinux

Although idraparinux has completed phase III evaluation for VTE treatment, only the phase II data have been reported. In a phase II dose-finding trial of 659 patients with proximal DVT, participants were randomized to warfarin or one of four doses of once-weekly subcutaneous idraparinux after 5–7 days of initial therapy with enoxaparin (56). The rates of normalization and de-
terioration of ultrasonography and perfusion lung scanning were similar in all idraparinux dosing groups, and did not differ from those in the warfarin control group. However, there was a clear dose-response relationship with respect to major bleeding in patients given idraparinux, with an unacceptably high frequency of bleeding in those given 10 mg of idraparinux. Two patients, both of whom received 5 mg of idraparinux, suffered a fatal bleed. Patients given the lowest dose of 2.5 mg had less bleeding than those randomized to warfarin (p=0.029). Phase III trials comparing 2.5 mg of idraparinux subcutaneously once weekly with enoxaparin or heparin followed by warfarin for treatment of patients with DVT or PE, respectively, have been completed, but the results have yet to be reported. Clinical trials with SSR126517E in patients with DVT are underway.

Ximelagatran also was evaluated for secondary prevention of VTE in the THRIVE III trial (58). In this double-blind study, 1,233 patients who had completed a six-month course of conventional anticoagulant therapy for VTE were randomized to receive ximelagatran (at a dose of 24 mg twice daily) or placebo for an additional 18 months. The primary efficacy endpoint, objectively documented recurrent VTE, occurred in 2.8% of those given ximelagatran and in 12.6% of those randomized to placebo (hazard ratio 0.16; P<0.001). Major bleeding rates were similar in the ximelagatran and placebo treated groups (1.1% and 1.3%, respectively; hazard ratio 1.16) and there were no fatal or intracranial bleeds. This study demonstrated that lower-dose ximelagatran reduced the risk of recurrent VTE without increasing the risk of major bleeding.

**Oral factor Xa inhibitors**

A phase II trial evaluating rivaroxaban for treatment of acute DVT treatment has been completed, but the results have yet to be reported. This study randomized patients with objectively documented, symptomatic proximal DVT to treatment with one of four doses of rivaroxaban (either 10, 20, or 30 mg twice daily or 40 mg once-daily) or to enoxaparin (at a dose of 1 mg/kg subcutaneously twice daily) for a minimum of five days followed by warfarin (with doses adjusted to achieve an INR of 2.0 to 3.0). Investigators were blinded as to rivaroxaban dose, but the study was open-label between enoxaparin/warfarin and rivaroxaban.

The main treatment period was for 21 days. At this point, efficacy was assessed by measuring the rates of normalization or deterioration on repeat compression ultrasonography and lung scanning compared with the baseline tests. Treatment was then extended for an additional three months, and the tests were repeated. The primary safety endpoint was bleeding. A total of 600 patients were entered into the study; 120 per treatment arm.

A phase II study with apixaban in patients with DVT also is underway. This study is comparing apixaban (at doses of 5 or 10 mg twice daily or 20 mg once daily) with LMWH or fondaparinux followed by a vitamin K antagonist. Again, efficacy will be assessed using a composite of symptomatic recurrent VTE plus deterioration in thrombus burden as assessed by repeat compression ultrasonography and lung scanning. This study is expected to enroll 520 patients.

**Dabigatran etexilate**

An extensive phase III program is underway with dabigatran etexilate. This program includes evaluation of dabigatran etexilate for treatment of VTE. Two studies are underway. The first, designated Re-COVER, will focus on patients with objectively diagnosed VTE. After conventional treatment with a parenteral anticoagulant for at least five days, patients will be randomized, in a double-blind fashion, to a six-month course of dabigatran etexilate (at a dose of 150 mg twice daily) or warfarin (with dose adjustments to achieve an INR between 2.0 and 3.0). The primary efficacy outcome will be objectively documented recurrent VTE, whereas the primary safety endpoint will be bleeding. An estimated 2,550 patients will be entered and the trial is powered for non-inferiority.

No phase II dose-finding studies have been done with dabigatran etexilate in the acute VTE setting. The dose of dabigatran etexilate chosen for the Re-COVER trial was one that showed efficacy in phase II evaluation both for prophylaxis of VTE after major orthopedic surgery and for stroke prevention in atrial fibrillation. Because of limited dose-finding information, a decision was made to delay treatment with dabigatran etexilate until after an initial course of therapy with a parenteral anticoagulant. Therefore, this trial will compare fixed-dose unmonitored dabigatran etexilate with dose-adjusted warfarin for treatment of acute VTE after an initial course of a parenteral anticoagulant.

The second phase III trial with dabigatran etexilate, which is designated Re-MEDY, will focus on secondary VTE prevention. Patients who have completed a three- to six-month course of conventional anticoagulation therapy for VTE will be randomized, in a double-blind fashion, to an 18-month course of treatment with dabigatran etexilate (at a dose of 150 mg twice daily) or warfarin (with doses adjusted to achieve an INR between 2.0 and 3.0). The primary efficacy endpoint will be the rate of objectively-documented recurrent VTE, whereas bleeding will be the primary safety endpoint. This study, which is expected to enroll about 2,000 patients, is powered for non-inferiority.

**Opportunities for new anticoagulants in VTE treatment**

The introduction of LMWH was a major advance in the initial management of VTE. With once- or twice-daily subcutaneous
injection and no need for coagulation management, LMWH shifted the initial management of most VTE patients from the hospital to the outpatient setting. The new anticoagulants have the potential to further streamline care and may offer safety advantages over existing agents. In contrast to heparin or LMWH, fondaparinux and idraparinux eliminate the risk of heparin-induced thrombocytopenia. Whereas fondaparinux must be given by daily subcutaneous injection, idraparinux has the advantage of once-weekly dosing. Therefore, a single subcutaneous injection of idraparinux at the time of VTE diagnosis would provide adequate parenteral anticoagulation while waiting for a therapeutic response with warfarin. This approach could simplify management of patients incapable of self-injection with LMWH or fondaparinux. SSR126517E has an advantage over idraparinux in that an antidote is available should rapid reversal be required.

All of the new oral inhibitors of factor Xa or thrombin have a rapid onset of action with peak plasma levels achieved within two to four hours. Thus, these agents will produce an anticoagulant response in the same timeframe as subcutaneously injected LMWH, fondaparinux or idraparinux. With this rapid onset of action, the new oral anticoagulants have the potential to obviate the need for a parenteral anticoagulant for initial VTE management. This concept is confirmed by the results of the THRIVE treatment trial (57), which demonstrated that monotherapy with ximelagatran was as effective and safe for the treatment of DVT as conventional therapy with enoxaparin followed by warfarin. In addition to eliminating the need for daily injection of LMWH or fondaparinux for the initial treatment of VTE, the new oral anticoagulants also offer advantages over warfarin for extended VTE treatment. With fixed dosing and no coagulation monitoring, the new agents will be simpler to administer than warfarin.

The novel agents may also be safer than warfarin. Thus, in the THRIVE III trial (58), which entered patients who had completed a six-month course of conventional anticoagulation therapy for VTE treatment, a lower-doseage ximelagatran regimen (24 mg twice daily rather than 36 mg twice daily) produced an 84% reduction in the rate of recurrent VTE compared with placebo without significantly increasing the risk of major bleeding. Furthermore, in the pooled analysis of data from the SPORTIF III and V trials (59), which compared higher-dose ximelagatran (36 mg twice daily) with warfarin (in doses adjusted to achieve an INR of 2.0 to 3.0) for stroke prevention in patients with atrial fibrillation, the combined rates of major and minor bleeding were significantly lower with ximelagatran than with warfarin (32% and 39% per year, respectively; P<0.0001). Whether other oral direct thrombin or factor Xa inhibitors will have the same safety profile in terms of hemorrhagic risk as ximelagatran remains to be established. However, the results with ximelagatran validate thrombin as a target for new oral anticoagulants and highlight the convenience and potential safety advantages of these types of agents over warfarin.

Although the data from the phase III trials with idraparinux for VTE treatment have yet to be reported, the results of the MA-TISSE-DVT and MATISSE-PE trials (54, 55) with fondaparinux illustrate that a drug that targets factor Xa is as effective and safe for initial VTE management as heparin or LMWH, agents that inhibit both thrombin and factor Xa. These findings, together with the promising data emerging from the phase II trials with oral factor Xa inhibitors, suggest that, like thrombin, factor Xa also is a good target for new parenteral or oral anticoagulants.

With once-weekly subcutaneous injection and no need for coagulation monitoring, idraparinux and SSR126517E may have a place in the long-term management of VTE provided that their efficacy and safety are confirmed in the phase III trials. These agents certainly would be easier to administer than warfarin. However, the availability of shorter-acting oral thrombin or factor Xa inhibitors may limit the need for long-acting parenteral anticoagulants.

Potential drawbacks of new anticoagulants

The major complication of all anticoagulants is bleeding. When a patient receiving anticoagulant therapy presents with a major bleed, it is desirable to have a safe rapidly-acting antidote to reverse the anticoagulant effects. An antidote also is useful when anticoagulant-treated patients require urgent surgery or suffer from major blunt trauma. Aside from SSR126517E, none of the new agents has a specific antidote. Protamine sulfate, which completely neutralizes the anticoagulant effects of heparin and partially reverses those of LMWH, has no activity against fondaparinux or idraparinux because it fails to bind to the pentasaccharide sequence. The lack of an antidote is particularly problematic for idraparinux because of its 80 hour half-life. This was the impetus for development of SSR126517E. Although recombinant factor VIIa has been reported to reverse the anticoagulant effects of fondaparinux, idraparinux and ximelagatran in healthy volunteers (60–61), factor VIIa has not been evaluated in patients who are bleeding. Furthermore, factor VIIa is not available in all hospitals and the drug is expensive, particularly if multiple doses are required. Finally, factor VIIa may induce thrombotic complications in patients with underlying VTE (62). Although not well studied, dialysis is likely to clear the direct factor Xa or thrombin inhibitors, all of which are small molecules. In contrast, dialysis will not eliminate fondaparinux or idraparinux.

In some animal models, direct factor Xa inhibitors produce less bleeding than direct thrombin inhibitors when given in doses with similar antithrombotic activity (63). Whether these findings will translate into a safety advantage for direct factor Xa inhibitors in humans is uncertain. Although ximelagatran modestly prolonged the bleeding time in healthy volunteers (64) and rivaroxaban did not (31), both agents increased major bleeding in a dose-dependent fashion when given after major orthopedic surgery. Head-to-head trials will be needed to determine whether, as a class, direct factor Xa inhibitors produce less bleeding than direct thrombin inhibitors.

The experience with ximelagatran highlights the challenges of bringing new anticoagulants to the clinic. The unexpected effect of ximelagatran on hepatic enzymes led to its ultimate withdrawal. Because the mechanism responsible for this side effect has yet to be identified, it is difficult to predict whether other oral direct thrombin or factor Xa inhibitors will have the same problem. The limited long-term experience with dabigatran etexilate suggests that a three-fold or greater elevation in alanine aminotransferase occurs in about 1.5% patients, a rate not dissimilar to that seen with warfarin in previous studies that compared long-
term ximelagatran with warfarin. These encouraging data argue against a class effect of oral direct thrombin inhibitors. Nonetheless, careful monitoring of liver enzymes will be an important part of the development strategy for all of the new anticoagulants.

Although the new anticoagulants have been designed to be given without coagulation monitoring, there are instances where monitoring may be helpful. For example, an INR is routinely measured when a warfarin-treated patient presents with a major bleed. If the INR is markedly elevated, the bleed is often attributed to excessive anticoagulation. In contrast, major bleeding that occurs with an INR in the therapeutic range usually prompts a search for an underlying source of blood loss. Likewise, the INR also is measured when a patient receiving warfarin for VTE treatment presents with recurrent VTE. In this setting, the INR helps to distinguish between an event that occurred on the background of an inadequate level of anticoagulation and one reflecting a warfarin failure. This is an important distinction because patients whose events occurred in the setting of a subtherapeutic INR can eventually be treated with higher doses of warfarin. In contrast, those who develop recurrent VTE despite a therapeutic INR often require treatment with an alternative anticoagulant.

Monitoring of the new anticoagulants is problematic. Although fondaparinux and idraparinux can be monitored using anti-factor Xa assays, the tests must be performed using these drugs as standards. Even if this is done, the therapeutic ranges for these agents have yet to be established. Monitoring is more complicated for the oral factor Xa and thrombin inhibitors. These agents have variable effects on routine tests of coagulation and none of the routine tests provides a good estimate of drug level. Although the ecarin clotting time may be useful to monitor direct thrombin inhibitors, the test is not available in all laboratories and it has yet to be standardized. Anti-factor Xa assays may prove useful to monitor oral factor Xa inhibitors. However, these assays also have not been standardized and the therapeutic anti-factor Xa level is likely to vary among the different agents. These issues will need to be addressed as the development of new anticoagulants moves forward.

In the absence of coagulation monitoring, compliance with new anticoagulants may be difficult to assess. Careful attention to drug packaging and ongoing supervision of patients will help to minimize this problem.

Finally, the cost of new anticoagulants will impact on their uptake, even if these drugs prove as safe and effective as existing agents. Although difficult to administer in an effective fashion, warfarin is relatively inexpensive, even with its attendant cost of coagulation monitoring. Unless the cost of the new agents is comparable, it is likely that they will be reserved for patients who cannot be adequately controlled on warfarin, or for those without ready access to a laboratory.

Conclusions and future directions

New anticoagulants have the potential to further refine VTE treatment. Still unknown is the role of these agents in the management of high-risk VTE patients, such as those with underlying cancer. The safety of these agents in pregnancy also is uncertain.

Recent studies showing an advantage of long-term LMWH over warfarin for patients with VTE in the setting of cancer (65, 66) have prompted some clinicians to use LMWH for such patients. There has also been a suggestion that LMWH improves survival in cancer patients (67), although this hypothesis requires confirmation. Shorter-acting oral direct thrombin or factor Xa inhibitors may be more convenient than LMWH in this setting, a concept that deserves exploration.

Currently, heparin or LMWH is used for VTE treatment during pregnancy. The safety of fondaparinux, idraparinux, or SSR126517E in this setting has yet to be established. If they are safe, idraparinux or SSR126517E may have advantages because they need only be given on a once-weekly basis. The availability of a safe oral anticoagulant would represent an even greater advance.

Never before have we been in a situation where so many anticoagulants are available for study. Emerging data suggest that factor Xa and thrombin are both good targets for new anticoagulants. Whether thrombin generation is attenuated or thrombin activity is suppressed, the relative efficacy and safety appear to be similar. Eventually, head-to-head trials comparing factor Xa inhibitors with thrombin inhibitors will be needed to identify the optimal target. Such studies are unlikely to be conducted in the near future. Instead, we will see parallel development of these two classes of anticoagulants. Although ximelagatran missed the mark, it provided convincing evidence that new oral anticoagulants have the potential to replace warfarin. With the large number of new oral anticoagulants in phase II and III development, one or more is likely to emerge a winner, offering new options for initial and long-term VTE management.

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