

# New Anticoagulants for Treatment of Venous Thromboembolism

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**Abstract**—Treatment of venous thromboembolism (VTE) usually starts with concomitant administration of heparin or low-molecular-weight heparin (LMWH) and a vitamin K antagonist. The parenteral anticoagulant, which is given for at least 5 days, is stopped once the vitamin K antagonist produces a therapeutic level of anticoagulation. Although the introduction of LMWH has simplified the initial treatment of VTE, problems remain. LMWH must be given by daily subcutaneous (SC) injection and vitamin K antagonists require routine coagulation monitoring, which is inconvenient for patients and physicians. Recently, 3 new anticoagulants have been introduced in an attempt to overcome these limitations. These include fondaparinux and idraparinux, synthetic analogs of the pentasaccharide sequence that mediates the interaction of heparin and LMWH with antithrombin, and ximelagatran, an orally active inhibitor of thrombin. These agents produce a predictable anticoagulant response; thus, routine coagulation monitoring is unnecessary. Because they do not bind to platelets or platelet factor 4, fondaparinux and idraparinux do not cause heparin-induced thrombocytopenia (HIT). Unlike vitamin K antagonists, ximelagatran has a rapid onset of action, thereby obviating the need for concomitant administration of a parenteral anticoagulant when starting treatment. The lack of an antidote for these new agents is a drawback, particularly for idraparinux, which has a long half-life. (*Circulation*. 2004;110[suppl 1]:I-19-I-26.)

**Key Words:** venous thromboembolism ■ pulmonary embolism ■ deep venous thrombosis ■ anticoagulants ■ coagulation ■ pharmacology ■ thrombosis

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs in ≈1 in 1000 white individuals per year.<sup>1</sup> The primary goal of initial treatment of VTE is to limit thrombus extension.<sup>2</sup> This not only reduces the risk of PE, a complication that can be fatal, but also may minimize postphlebotic syndrome, a potentially debilitating long-term sequelae of extensive DVT.<sup>3</sup>

Anticoagulants remain the cornerstone of treatment of VTE. The landmark study by Barritt and Jordan<sup>4</sup> established the role of anticoagulants in this setting. These investigators randomized 35 patients with clinically diagnosed PE to treatment with heparin or to no treatment. There were no fatalities in the heparin-treated group. In contrast, 25% of those untreated died of autopsy-proven PE.

Rapid anticoagulation is necessary to minimize the risk of thrombus extension and PE in patients with VTE. This concept is supported by the placebo-controlled study of Brandjes et al,<sup>5</sup> which randomized 120 patients with proximal DVT to treatment with heparin plus a vitamin K antagonist or to a vitamin K antagonist alone. The study was stopped prematurely because the rate of symptomatic recurrent VTE was lower in those given heparin plus a vitamin K antagonist than in those treated only with a vitamin K antagonist (6.7%

and 20%, respectively;  $P=0.058$ ), as was the rate of VTE extension (8.2% and 39.6%, respectively;  $P<0.001$ ).

With currently available drugs, rapid anticoagulation can only be effected with parenteral anticoagulants, such as heparin or LMWH. The introduction of LMWH has simplified the initial treatment of VTE. Compared with heparin, LMWH exhibits greater bioavailability after SC injection, has a longer half-life, and produces a more predictable anticoagulant response.<sup>6</sup> Consequently, LMWH can be given subcutaneously once or twice daily without coagulation monitoring. Meta-analyses of trials comparing SC LMWH with continuous intravenous (IV) heparin for initial treatment of VTE demonstrate that LMWH is at least as effective and safe as heparin.<sup>7,8</sup> Because LMWH is more convenient to administer, however, it is ideally suited for outpatient treatment of VTE,<sup>9,10</sup> an approach that reduces health care costs<sup>9-12</sup> and improves patient satisfaction.<sup>13</sup>

After initial treatment with heparin or LMWH, ongoing anticoagulant therapy is needed to prevent recurrent VTE.<sup>14,15</sup> Extended therapy usually involves administration of a vitamin K antagonist,<sup>2</sup> although long-term LMWH may be a better choice in cancer patients with VTE.<sup>16</sup> A 3-month course of anticoagulant treatment is adequate for patients with VTE complicating a transient risk factor, such as surgery. In contrast, more extended therapy is needed in

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patients with unprovoked VTE.<sup>17–24</sup> Long-term anticoagulation therapy is problematic because vitamin K antagonists are not easy to administer.<sup>25</sup> Routine coagulation monitoring is essential to ensure that a therapeutic response is obtained because vitamin K antagonists have a narrow therapeutic window. Thus, a subtherapeutic response does not effectively reduce the risk of thrombosis, whereas excessive anticoagulation increases the risk of bleeding.<sup>25</sup> Furthermore, interactions with a range of drugs can reduce or enhance the anticoagulant effects of vitamin K antagonists, as can variable intake of foods containing vitamin K. In addition, genetically determined polymorphisms in the cytochrome P450C9 enzyme influence the metabolism of vitamin K antagonists.<sup>26,27</sup> These phenomena contribute to the need for routine coagulation monitoring. Even when coagulation monitoring is performed, patients using vitamin K antagonists have a therapeutic anticoagulant response less than half the time,<sup>25</sup> a situation that places them at risk for complications.

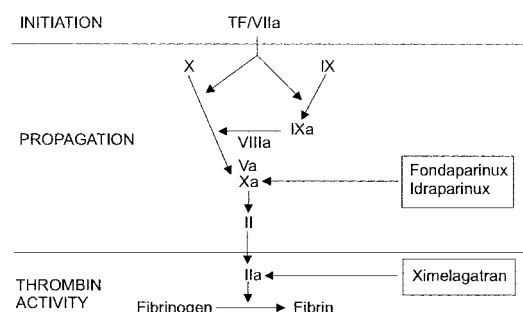
Recently, 2 new parenteral and 1 novel oral anticoagulant have been evaluated in patients with VTE. Parenteral agents with longer half-lives than heparin or LMWH have the potential to simplify initial or extended treatment of VTE, whereas rapidly acting oral anticoagulants provide an opportunity for streamlined therapy by eliminating the need for parenteral agents for initial VTE treatment and by obviating the requirement for coagulation monitoring and dose adjustment. Focusing on new drugs that have been evaluated in patients with VTE, this article (1) reviews their pharmacology, (2) outlines the potential advantages of these agents over existing anticoagulants, (3) describes the results of clinical trials evaluating new anticoagulants for treatment of VTE, (4) provides perspective as to strengths and potential drawbacks of these new agents, and (5) identifies their evolving role in VTE management.

### Pharmacology of New Anticoagulants

The new anticoagulants that have been evaluated for the treatment of VTE include 2 parenteral antithrombin-dependent inhibitors of activated factor X (factor Xa), fondaparinux and idraparinux, and ximelagatran, the first oral direct thrombin inhibitor. By targeting factor Xa, fondaparinux and idraparinux block thrombin generation. In contrast, ximelagatran inhibits thrombin, the enzyme that catalyzes the conversion of fibrinogen to fibrin (Figure 1). Thrombin also activates platelets and amplifies its own generation by feedback activation of factors VIII and V, key cofactors in factor Xa and thrombin generation, respectively. The pharmacology of fondaparinux, idraparinux, and ximelagatran is briefly discussed.

#### Fondaparinux

A synthetic analog of the antithrombin-binding pentasaccharide sequence found on heparin or LMWH (Figure 2), fondaparinux binds antithrombin with high affinity. Once bound, fondaparinux evokes conformational changes in the reactive center loop of antithrombin that enhance its reactivity with factor Xa.<sup>28,29</sup> Fondaparinux is a catalytic inhibitor; thus, after promoting the formation of the factor Xa/anti-

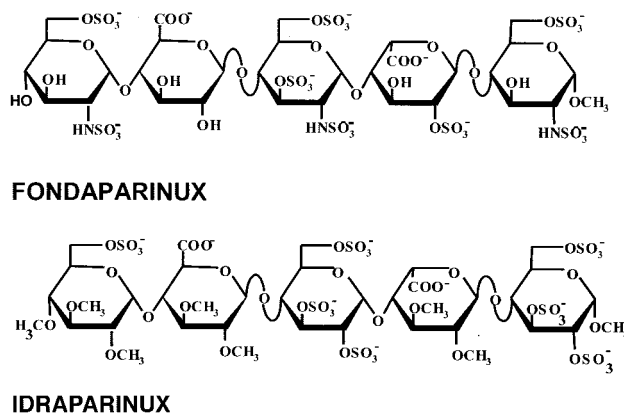


**Figure 1.** Sites of action of fondaparinux, idraparinux, and ximelagatran. Coagulation is initiated by the tissue factor/factor VIIa (TF/VIIa) complex, which activates factors IX and X. Activated factor X (Xa) converts small amounts of prothrombin (II) to thrombin (IIa), which then feeds back to activate factors VIII and V, key cofactors in coagulation. The process is propagated by activated factor IX (IXa), which together with activated factor VIII (VIIIa) assembles on the surface of activated platelets to form intrinsic tenase, a complex that efficiently activates factor Xa. Xa, together with activated factor V (Va), assembles on the surface of activated platelets to form prothrombinase. This complex generates a burst of thrombin that, in the final stage of the coagulation process, converts fibrinogen to fibrin. By inhibiting factor Xa in an antithrombin-dependent fashion, fondaparinux and idraparinux block thrombin generation. In contrast, ximelagatran undergoes biotransformation to melagatran, which then blocks thrombin activity by binding directly to the active site of the enzyme.

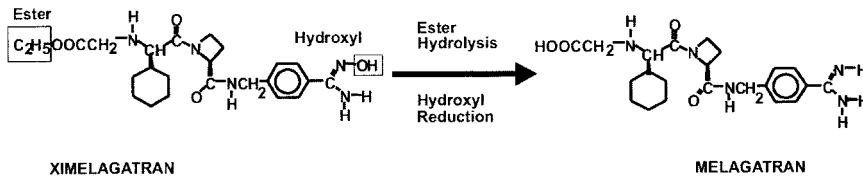
bin and is available to activate additional antithrombin molecules.

With excellent bioavailability after SC administration and a plasma half-life of 17 hours,<sup>30</sup> fondaparinux is administered subcutaneously once daily. Systemic fondaparinux is excreted unchanged via the kidneys. Therefore, fondaparinux must be used with caution in patients with renal insufficiency.<sup>28,29</sup>

When given SC in fixed doses, fondaparinux produces a predictable anticoagulant response. Consequently, routine coagulation monitoring is unnecessary. If necessary, fondaparinux can be monitored with antifactor Xa levels using a chromogenic assay.<sup>31</sup> Fondaparinux has no effect on routine tests of coagulation, such as the activated partial thromboplastin time or activated clotting time.<sup>32</sup>



**Figure 2.** Structures of fondaparinux and idraparinux. Fondaparinux is a synthetic analog of the natural pentasaccharide found in heparin and LMWH heparin. To enhance its affinity for anti-



**Figure 3.** Structures of ximelagatran and melagatran. Ximelagatran has ester and hydroxyl groups added to the carboxyl and amidine groups of melagatran. Bioconversion of ximelagatran to melagatran involves hydrolysis of the ester by esterases and reduction of the hydroxyl group. Intermediates with one or the other of these protecting groups removed can be found transiently in the plasma.

### Idraparinux

A second-generation synthetic pentasaccharide, idraparinux is more negatively charged than fondaparinux (Figure 2). Consequently, idraparinux binds to antithrombin with an affinity higher than that of fondaparinux.<sup>33</sup> Because it binds antithrombin so tightly, idraparinux has a plasma half-life similar to that of antithrombin,  $\approx 80$  hours. With this long half-life, idraparinux is administered SC on a once-weekly basis. Like fondaparinux, idraparinux exhibits excellent bioavailability after SC injection and produces a predictable anticoagulant response, thereby obviating the need for routine coagulation monitoring.<sup>33</sup>

### Ximelagatran

The first oral, direct thrombin inhibitor, ximelagatran is a prodrug of melagatran (Figure 3), a 429-dalton dipeptide that fits within the active-site cleft of thrombin and blocks the enzyme's interactions with its substrates.<sup>34</sup> Thus, melagatran is a stoichiometric inhibitor of thrombin that forms a reversible 1:1 complex with the enzyme. Melagatran exhibits poor bioavailability after oral administration. Ximelagatran, which has a molecular mass of 474, was developed to overcome this problem. With the addition of an ester and a hydroxyl group to the carboxyl and amidine groups of melagatran, respectively, ximelagatran is more lipophilic than melagatran. Consequently, ximelagatran is readily absorbed in the small intestine.<sup>34</sup> Plasma levels of ximelagatran peak in the blood 30 minutes after drug ingestion (Figure 4). Although ximelagatran has no intrinsic anticoagulant activity, it is rapidly converted to melagatran via 2 intermediates. The bioavailability of melagatran after administration of oral ximelagatran is  $\approx 20\%$ . Plasma levels of melagatran peak 2 hours after

ximelagatran ingestion; melagatran circulates with a half-life of 3 hours in healthy volunteers and 4 to 5 hours in patients. Because melagatran has a relatively short half-life, ximelagatran is administered orally twice daily.<sup>34</sup>

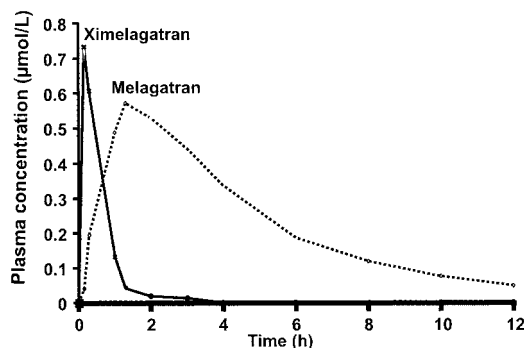
Ximelagatran produces a predictable anticoagulant response after fixed oral dosing. The half-life of melagatran does not vary among ethnic groups<sup>35</sup> and is not influenced by obesity<sup>36</sup> or mild to moderate hepatic insufficiency.<sup>37</sup> Ximelagatran does not interact with drugs that are metabolized by cytochrome P450 isozymes CYP2C19, CYP2C9, or CYP3A4.<sup>34</sup>

At least 80% of systemic melagatran is eliminated unchanged via the kidneys. The half-life of melagatran is slightly prolonged in the elderly, likely reflecting their reduced creatinine clearance.<sup>38</sup>

Coagulation monitoring is unnecessary for ximelagatran because it produces a predictable anticoagulant response.<sup>34</sup> Like all direct thrombin inhibitors, ximelagatran prolongs the activated partial thromboplastin time and international normalized ratio (INR). However, its effect on these tests is not dose-dependent and the extent of prolongation depends on the reagent used for testing. If monitoring is required, the ecarin clotting time, a test that has yet to be standardized, provides the best estimate of drug concentration.

### Potential Advantages of New Anticoagulants

Fondaparinux was developed to replace heparin or LMWH for initial treatment of VTE, whereas idraparinux and ximelagatran were designed to compete with vitamin K antagonists. Because of their rapid onset of action, however, idraparinux and ximelagatran also may be useful for initial treatment of VTE, as well as for extended therapy.



**Figure 4.** Plasma levels of ximelagatran and melagatran after administration of oral ximelagatran to healthy volunteers. Ximelagatran levels in the blood peak 30 minutes after drug administration, whereas the levels of melagatran peak at 2 hours. Melagatran has a half-life of 3 hours in young healthy volunteers

**TABLE 1. Comparison of Fondaparinux and Idraparinux with LMWH**

Feature	Fondaparinux	Idraparinux	LMWH
Target	Factor Xa	Factor Xa	Factor Xa and thrombin
Route of administration	SC	SC	SC
Half-life (h)	17	80	4
Endothelial cell binding	None	None	Some
Protein binding	None	None	Some
Clearance	Renal	Renal	Renal
HIT	No	No	Rare
Antidote	None	None	Partial neutralization with protamine sulfate

LMWH indicates low-molecular-weight heparin; SC, subcutaneous; HIT,

**TABLE 2. Comparison of Ximelagatran with Vitamin K Antagonists**

Feature	Ximelagatran	Vitamin K Antagonists
Target	Thrombin	Vitamin K-dependent clotting factors (factor VII, IX, X, and prothrombin)
Route of administration	Oral	Oral
Onset of action (h)	2	72 to 96
Food interactions	None	Affected by vitamin K content of diet
Drug interactions	None	Multiple drugs affect pharmacokinetics or pharmacodynamics
Therapeutic window	Wide	Narrow
Coagulation monitoring required	No	Yes
Liver function monitoring required	Yes	No
Antidote	None	Vitamin K produces slow reversal

The new anticoagulants have potential advantages over existing agents. Focusing first on the parenteral agents, both fondaparinux and idraparinux have properties that distinguish them from LMWH (Table 1), the anticoagulant that is rapidly replacing heparin for initial VTE treatment. Whereas the bioavailability of LMWH after SC injection is 80% to 90%,<sup>6</sup> fondaparinux and idraparinux exhibit almost complete bioavailability.<sup>28,29,33</sup> In addition, there is less between-patient variability in the anticoagulant response with fondaparinux and idraparinux than with LMWH. These differences reflect the fact that fondaparinux and idraparinux are homogeneous preparations of synthetic pentasaccharide units that bind only to antithrombin.<sup>39</sup> In contrast, LMWH preparations are composed of heparin fragments that range in molecular weight from 1000 to 10 000 daltons. Only 15% to 20% of these fragments possess a pentasaccharide sequence.<sup>6</sup> Longer chains can bind nonspecifically to endothelial cells and various plasma proteins.<sup>40,41</sup> Pentasaccharide-independent binding of heparin chains to endothelial cells reduces bioavailability because these cellular binding sites must be saturated before the LMWH chains can enter the circulation and interact with antithrombin. Binding to plasma proteins, the levels of which differ between patients, explains the between-patient variability in the anticoagulant response to LMWH. Although fondaparinux and idraparinux have greater bioavailability than LMWH and produce a more predictable anticoagulant response, it is unclear whether these properties endow the new anticoagulants with clinical advantages over LMWH.

Fondaparinux and idraparinux have half-lives of 17 and 80 hours, respectively. In contrast, LMWH has a half-life of only 4 to 5 hours. Despite its relatively short half-life, LMWH is effective when given once daily for VTE treatment, although uncertainty remains as to whether once-daily LMWH is as effective as twice-daily dosing.<sup>42</sup> A potential explanation for the extended antithrombotic activity of LMWH is its capacity to induce the release of tissue factor pathway inhibitor (TFPI) from the vasculature.<sup>43,44</sup> An endogenous anticoagulant, TFPI limits the initiation of coagulation by inhibiting tissue factor-bound factor VIIa in a factor Xa-dependent fashion.<sup>45</sup> In contrast to LMWH, neither fondaparinux nor idraparinux

fondaparinux and idraparinux may preclude the need for this additional anticoagulant mechanism.

Although LMWH can induce HIT, the risk of HIT is lower with LMWH than with heparin.<sup>46</sup> In contrast, fondaparinux and idraparinux do not cause HIT because they do not bind to platelets or platelet factor 4 (PF4). Thus, HIT is triggered by antibodies directed against the heparin/PF4 complex.<sup>47</sup> Fondaparinux and idraparinux do not bind to platelets. Therefore, they do not cause platelet activation and subsequent PF4 release. Likewise, because these agents do not bind to PF4, they do not induce the conformational changes in PF4 that render it antigenic. These properties endow fondaparinux and idraparinux with a safety advantage over heparin and LMWH and may render these new agents useful for HIT treatment, a possibility that requires evaluation in clinical trials.

Osteoporosis can occur after long-term treatment with heparin or LMWH.<sup>48,49</sup> The risk of this complication should be lower with fondaparinux and idraparinux because shorter heparin chains cause less bone loss than longer chains in cell culture systems and in laboratory animal models.<sup>50,51</sup> For extended treatment, therefore, fondaparinux and idraparinux may be safer than heparin or LMWH.

As an orally active anticoagulant, ximelagatran has potential advantages over vitamin K antagonists (Table 2). Vitamin K antagonists have a delayed onset of action. Thus, these agents act as anticoagulants by interfering with vitamin K-dependent, post-translational modification of the vitamin K-dependent clotting factors, an essential step in the synthesis of functional coagulation proteins.<sup>25</sup> The antithrombotic effect of vitamin K antagonists most probably reflects reductions in the functional levels of prothrombin and factor X, a process that requires 4 to 5 days of treatment. Because of their slow onset of action, initial therapy with vitamin K antagonists is usually supported by overlapping treatment with a parenteral anticoagulant in patients with established thrombosis, or in those at high risk for thrombosis.<sup>2</sup> In contrast, ximelagatran has a rapid onset of action, thereby obviating the need for concomitant administration of a parenteral anticoagulant when starting treatment.

As mentioned earlier, vitamin K antagonists have a narrow therapeutic window. Furthermore, genetic differences in me-

anticoagulant response to vitamin K antagonists.<sup>35</sup> These factors contribute to the need for routine coagulation monitoring, which is inconvenient for patients and physicians. In contrast, ximelagatran, with a wider therapeutic window than vitamin K antagonists and no food or drug interactions, can be given without coagulation monitoring.<sup>34</sup> Building on their unique properties, fondaparinux, idraparinix, and ximelagatran have been compared with conventional anticoagulant regimens in VTE patients.

### Clinical Trials With New Anticoagulants

Fondaparinux and ximelagatran have completed phase III clinical trials for treatment of VTE. Idraparinix has completed phase II evaluation, and phase III clinical trials are underway. The results of these trials are discussed.

#### Fondaparinux

Fondaparinux has been evaluated for treatment of VTE in 2 phase III clinical trials. In the MATISSE-DVT study, 2205 patients with DVT were randomized, in a double-blind fashion, to receive either fondaparinux (in dosages of 5, 7.5, or 10 mg SC once daily depending on body weight) or enoxaparin (1 mg/kg SC twice daily) for at least 5 days, followed by a minimum of a 3-month course of treatment with a vitamin K antagonist.<sup>52</sup> At 3 months, rates of recurrent symptomatic VTE with fondaparinux or enoxaparin were 3.9% and 4.1%, respectively, whereas rates of major bleeding were 1.1% and 1.2%, respectively.

In the open-label MATISSE PE trial, 2213 patients with PE were randomized to receive either fondaparinux (in dosages of 5, 7.5, or 10 mg SC once daily depending on body weight) or heparin (by continuous IV infusion) for 5 days, followed by a minimum of a 3-month course of therapy with a vitamin K antagonist.<sup>53</sup> At 3 months, rates of recurrent symptomatic VTE with fondaparinux or heparin were 3.8% and 5.0%, respectively, whereas rates of major bleeding were 1.3% and 1.1%, respectively. The results of the MATISSE studies suggest that fondaparinux is as effective as LMWH or unfractionated heparin for initial VTE treatment. Furthermore, fondaparinux is easier to administer than unfractionated heparin.

#### Idraparinix

In a phase II, dose-finding trial, idraparinix was compared with warfarin for treatment of patients with proximal DVT.<sup>54</sup> In this trial, 659 patients were treated for 5 to 7 days with enoxaparin and then randomized to receive once-weekly SC idraparinix (2.5, 5.0, 7.5, or 10 mg) or warfarin for 12 weeks. The primary efficacy end point, changes in compression ultrasound and perfusion lung scan findings, was similar in all idraparinix groups and did not differ from that in the warfarin group. There was a clear dose response for major bleeding in patients given idraparinix with an unacceptably high rate of major bleeding in those given the 10-mg dose. Two patients, both of whom were in the 5-mg idraparinix group, experienced fatal bleeds. Patients given the lowest dose of idraparinix had less bleeding than those randomized to warfarin ( $P=0.029$ ). Based on these data, ongoing phase III trials are

SC once weekly) with 5 to 7 days of enoxaparin, followed by at least 3 months of warfarin therapy for treatment of patients with DVT or PE.

#### Ximelagatran

The double-blind, phase III THRIVE treatment study randomized 2491 patients with acute DVT to receive either oral ximelagatran (36 mg twice daily) alone for 6 months or enoxaparin (1 mg/kg SC twice daily for a minimum of 5 days), followed by warfarin (target INR of 2.0 to 3.0) for 6 months.<sup>55</sup> The primary end point, objectively documented recurrent VTE, occurred in 2.1% and 2.0% of patients given ximelagatran and enoxaparin/warfarin, respectively. Rates of major bleeding were similar in the ximelagatran and enoxaparin/warfarin groups (1.3% and 2.2%, respectively), as were the all-cause mortality rates (2.3% and 3.4%, respectively;  $P=NS$ ). These results suggest that oral ximelagatran is as effective as conventional anticoagulant treatment with enoxaparin followed by warfarin in preventing recurrent VTE in patients with acute DVT. However, unlike enoxaparin or dalteparin, ximelagatran can be given orally, and in contrast to warfarin, ximelagatran does not require coagulation monitoring or dose adjustment. Consequently, ximelagatran has the potential to streamline treatment.

Ximelagatran also has been evaluated for the long-term secondary prevention of recurrent thrombosis in patients with VTE. An open-label, phase III study (THRIVE III) randomized 1233 patients who had completed a 6-month course of anticoagulant therapy for treatment of VTE to oral ximelagatran (24 mg twice daily) or placebo for an additional 18 months.<sup>56</sup> The primary end point, objectively documented recurrent VTE, occurred in 2.8% of patients given ximelagatran and in 12.6% of those randomized to placebo (hazard ratio 0.16;  $P<0.001$ ). Major bleeding rates were similar between the ximelagatran and placebo groups (1.1% versus 1.3%, respectively; hazard ratio 1.16), and there were no fatal or intracranial bleeds. Hence, data from this study indicate that lower-dosage ximelagatran (24 mg twice daily) can effectively prevent recurrent VTE.

### Potential Role of New Anticoagulants in VTE Treatment

The introduction of LMWH provided a major advance in initial VTE treatment. With once- or twice-daily SC administration and no need for coagulation monitoring, LMWH paved the way for out-of-hospital treatment. New anticoagulants have the potential to further streamline VTE treatment and to offer potential safety advantages over existing agents. Based on the results of the MATISSE-DVT and MATISSE-PE trials,<sup>52,53</sup> fondaparinux can be used in place of LMWH or heparin for initial treatment of VTE. Although more convenient to administer than heparin, like LMWH, fondaparinux must be given daily by SC injection. However, fondaparinux may be safer than heparin or LMWH because it does not cause HIT.

Idraparinix and ximelagatran have the potential to be used as sole therapy for VTE treatment. In the case of idraparinix, a single SC injection at the time of VTE diagnosis circum-

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