# Evolving Concepts in the Treatment of Venous Thromboembolism: The Role of Factor Xa Inhibitors

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Anticoagulation is an essential component of the care of patients with venous thromboembolism (VTE). Traditional anticoagulants for the treatment of VTE include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and the oral vitamin K antagonist, warfarin. A variety of anticoagulant agents with improved pharmacologic and clinical profiles are emerging and offer benefits over the traditional therapies. One of the most recent advances has been the development of new agents, such as oral direct thrombin inhibitors and factor Xa inhibitors, that have a more selective and targeted effect on the coagulation cascade. Recent clinical trials have evaluated fondaparinux, the first commercially available factor Xa inhibitor, in the treatment of patients with deep vein thrombosis and pulmonary embolism and indicate efficacy and safety as compared with traditional options such as UFH and LMWH. Fondaparinux is a welcomed addition to the available antithrombotic options.

**Key Words:** venous thromboembolism, factor Xa inhibitors, anticoagulants, heparin, warfarin, fondaparinux, treatment options.

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Venous thromboembolism (VTE) represents a major public health problem in the United States. An estimated 250,000–600,000 patients annually receive a diagnosis of and are hospitalized for VTE.[1, 2] Morbidity and mortality rates associated with VTE are high, and the costs of treatment are estimated at $1.5 billion/year.[3] Deep vein thrombosis (DVT) and pulmonary embolism are the presenting manifestations of VTE. The disease usually results as a consequence of various surgical procedures and medical conditions. Patients with VTE can have either symptomatic or asymptomatic disease. Manifestations of pulmonary embolism are often clinically silent; therefore, death can occur suddenly before effective treatment can be started. Death due to pulmonary embolism occurs in 1–2% of hospitalized patients, with the 3-month mortality rate reported at 10–17.5%.[4, 5] Also, VTE is associated with long-term morbidity, with 20–30% of patients developing postthrombotic syndrome within 7–13 years after an acute episode of DVT.[6]

Anticoagulation is an essential component of the care of patients with DVT and pulmonary embolism. Inadequate treatment has been associated with a 47% symptomatic recurrence of the disease within 3 months. In contrast, less than 5% of patients who receive adequate treat-ment will develop a recurrent event.[7] Various conventional anticoagulants have been evaluated and have proved effective in the treatment of VTE, including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin; however, these agents are not without limitations. A variety of anticoagulant agents with improved pharmacologic and clinical profiles in the treatment of VTE are emerging and offer benefits over traditional therapies.

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## Treatment of Venous Thromboembolism

The goal of treatment in patients with VTE is to prevent thrombus extension, embolization to

the lungs, death due to pulmonary embolism, and the development of complications such as recurrent thromboembolic events and the postthrombotic syndrome. An additional goal of treatment is to achieve these objectives with therapies that minimize adverse effects and patient inconvenience. Anticoagulation is the key therapeutic component in treating patients with VTE. Pulmonary embolism and DVT are treated by using similar anticoagulant drugs and physical methods. Anticoagulation treatment for VTE can be divided into an initial phase (≥ 5 days) followed by a period of long-term anticoagulation (≥ 3 mo). Traditional anticoagulants for the initial and long-term treatment phases include UFH, LMWH, and warfarin.[8] The standard initial treatment for DVT is UFH or LMWH. For patients with pulmonary embolism, continuous, dose-adjusted, intravenous UFH still is considered the preferred treatment in many countries. Less frequently used options include thrombolytics and various physical methods. Emerging treatment options for VTE include the synthetic factor Xa inhibitors and the oral direct thrombin inhibitors.

**Traditional Anticoagulants**

Heparins: UFH and LMWH

Heparin has been the mainstay anticoagulant for initial treatment of VTE for several decades. Discovered in the early 20th century, UFH is a heterogeneous mixture of glycoaminoglycans commercially isolated from porcine or bovine mucosa.[9] It exerts its anticoagulant effect through a plasma cofactor, antithrombin. Unfractionated heparin binds to antithrombin by a distinct five-saccharide sequence, causing a conformational change in antithrombin. Antithrombin, in turn, inhibits thrombin (factor IIa) and factor Xa. Only larger saccharide chains (> 18 units) are able to catalyze thrombin inhibition. The smaller heparin molecules (< 18 units) containing the "high-affinity" pentasaccharide sequence accelerate inactivation of factor Xa but are unable to inactivate thrombin. Unfractionated heparin is a heterogeneous mixture of chains with molecular weights of 3000–30,000 daltons, with only one third of molecules exhibiting anticoagulant activity. Heparin has a short half-life; therefore, it must be administered parenterally.[10] Various oral formulations of heparin have been investigated; however, all have limitations and none are commercially available. Heparin's nonspecific binding to a number of plasma and cellular proteins results in decreased bioavailability and substantial interpatient variability in anticoagulant response. Therefore, when given in therapeutic doses, UFH requires frequent laboratory monitoring to assess the level of anticoagulation, as measured by activated partial thromboplastin time (aPTT).[10]

Unfractionated heparin dosed to achieve aPTT greater than 1.5 is effective in the initial treatment of VTE. Attaining an adequate level of anticoagulation quickly after starting heparin therapy is crucial, as the risk of VTE recurrence is significantly higher in patients with an aPTT ratio less than 1.5 during the first few days of therapy. Therefore, an adequate bolus dose of UFH should be given, and frequent aPTT monitoring, every 6 hours, is indicated during the first 24 hours of infusion. The initial phase of heparin therapy needs to be followed by long-term anticoagulation with warfarin. Warfarin can be started on the first day of UFH therapy and should be continued for at least 3–6 months, or longer if indicated. Heparin therapy must be continued for at least 4–5 days and until concurrent use with warfarin has achieved an international normalized ratio (INR) of 2–3 for at least 48 hours. In patients with more complicated DVT or major pulmonary embolism, UFH can be continued for approximately 10 days.[11]

The LMWHs are derived by chemical or enzymatic depolymerization of UFH, resulting in shorter heparin chains of 3800–5000 daltons. The LMWHs inactivate thrombin to a lesser extent than does UFH because the smaller molecular fragments cannot bind both thrombin and antithrombin simultaneously. The LMWHs have an enhanced affinity for inhibiting factor Xa, compared with their activity against thrombin. Factor Xa:IIa ratios for LMWHs are agent specific and range from 4:1–2:1.[10] The LMWHs have substantially improved pharmacodynamic and pharmacokinetic properties compared with those of UFH. The LMWHs display a lesser extent of binding to plasma and cellular proteins than does UFH, resulting in a more predictable anticoagulant response. Consequently, routine monitoring of the intensity of anticoagulation and dosage adjustments are not required.[10] In addition, LMWHs have longer plasma half-lives, allowing once- or twice-daily administration, improved subcutaneous bioavailability, and dose-independent clearance.[12] Thrombotic complications, including the risk of heparin-induced thrombocytopenia (HIT), occur to a much lesser extent with LMWH than with UFH. However, LMWH

cross-reacts with UFH and should not be given as an alternative anticoagulant in patients with HIT.[10, 13]

The use of LMWHs in the treatment of VTE has been well established. Several clinical trials have confirmed their efficacy, safety, and cost-effectiveness over those of UFH.[13–16] Meta-analyses of LMWHs in the treatment of VTE also have shown that LMWHs are at least as effective as UFH in preventing recurrent thromboembolic events.[17, 18]

Despite the advances offered by the LMWHs, these agents have limitations. Due to their relatively short half-life, twice-daily rather than once-daily dosing often is required. In addition, the potential for treatment failure is increased due to the lack of dosing guidelines, resulting in underdosing these agents in obese patients.

### Oral Anticoagulants: Warfarin

The initial treatment phase of VTE with UFH or LMWH is continued by treatment with oral anticoagulants. These agents interfere with the metabolism of vitamin K, inhibiting the synthesis of biologically active coagulation factors II, VII, IX, and X. Warfarin, discovered in the early 1940s, is the most widely used oral anticoagulant in North America. Warfarin's efficacy is influenced by significant interindividual variations such as dietary fluctuations in vitamin K, drug interactions, and genetic factors. Warfarin has a narrow therapeutic index, indicating a relatively small margin between safety and toxicity. Frequent laboratory monitoring of warfarin's anticoagulant effect by means of the INR is required to allow for dosage adjustments that aid in attaining efficacy without compromising safety.

Owing to the slow onset of the effect of warfarin, a stable anticoagulant response may not be achieved until 5 or more days after the start of treatment or any change in dosage. Patient response to warfarin is highly variable. Although the average daily dose to maintain patients within the appropriate therapeutic range is 4–5 mg, dosage requirements range from less than 1 mg/day to more than 20 mg/day to reach a similar end point.[19] Adjusted-dose warfarin at an INR goal of 2.5 (range 2.0–3.0) is the standard for the treatment of VTE. Higher INR levels tend to increase the occurrence of bleeding without additional benefit in reducing VTE. Warfarin should be started in conjunction with UFH or LMWH once the diagnosis of VTE is confirmed. Heparin or LMWH should be continued concomitantly with warfarin for a minimum of 5 days and until the INR is greater than 2.0 for 48 hours. Warfarin then should be continued for at least 3–6 months. Patients at high risk, such as those with recurrent VTE, hypercoagulable states, or cancer, should receive long-term anticoagulation therapy.[8] Warfarin is contraindicated during pregnancy (especially during wks 6–12) as it crosses the placenta and can cause fetal malformations and spontaneous abortion. The long-term therapy of choice in pregnant patients with VTE is subcutaneous LMWH or UFH given at treatment dosages.[8]

## Emerging Anticoagulants

### Oral Direct Thrombin Inhibitors

The direct thrombin inhibitors bind with thrombin to prevent an interaction between the enzyme and substrates. Advantages of direct thrombin inhibitors include a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of plasma protein and platelet interactions that can lead to complications such as HIT. Unlike heparin, direct thrombin inhibitors do not require antithrombin as a cofactor and do not bind to plasma proteins. Therefore, they produce a more predictable anticoagulant effect, and variability of patient response is relatively low compared with that of other drug classes.[12]

Direct thrombin inhibitors include recombinant hirudin (lepirudin) and smaller synthetic derivatives such as hirulog or bivalirudin. Argatroban belongs to a family of small direct thrombin inhibitors that bind noncovalently to the enzyme's active site.[20] Similar agents include napsagatran, melagatran, and melagatran's parent molecule, ximelagatran. Ximelagatran is a novel oral direct thrombin inhibitor that is under development. Clinical evidence suggests that ximelagatran has a wider therapeutic index than that of warfarin, displays a low interindividual variability, and has a linear pharmacokinetic and pharmacodynamic profile; therefore, it may not require monitoring of its anticoagulant effect.[20] Ximelagatran is in advanced phases of clinical development and is being evaluated for the treatment of VTE.[21]

### Selective Factor Xa Inhibitors

Factor Xa inhibitors have a selective and targeted effect on clotting factors within the

coagulation cascade. Similar to thrombin, factor Xa can be inhibited directly or indirectly. The direct inhibitors bind to factor Xa without a cofactor, thus blocking its activity. Direct factor Xa inhibitors in development include tick anticoagulant peptide, YM-60828, and the orally active agent, DX-9065A.[22–24] Indirect factor Xa inhibitors, such as fondaparinux, have a higher affinity for antithrombin than do the naturally occurring pentasaccharides, with a greater inhibitory activity against factor Xa than that of heparin or LMWH. Fondaparinux is a synthetic version for the pentasaccharide sequence of heparin that leads to antithrombin-mediated factor Xa inactivation.[24] Fondaparinux leads to the inhibition of thrombin generation, without a direct effect on thrombin itself. In addition, a minimal amount of thrombin is retained, which may have clinical advantages in wound healing.[25]

As a synthetic entity, fondaparinux offers the advantages of no risk of animal pathogen transmission, batch-to-batch consistency, and unlimited sourcing.[24] Unlike the heparins, fondaparinux does not affect platelet function and does not react with heparin–platelet factor 4 antibodies, thus lessening the risk of HIT.[26, 27] Fondaparinux was approved by the United States Food and Drug Administration in December 2001 for the prophylaxis of DVT in patients undergoing hip fracture, hip replacement, and knee replacement surgeries. Fondaparinux is administered by subcutaneous injection, and owing to its predictable pharmacokinetic profile and no variations in dose response, it does not require monitoring of its anticoagulant effect. Fondaparinux has a half-life of 17–21 hours, allowing the convenience of once-daily administration.[28]

In the treatment of VTE, fondaparinux compared favorably with dalteparin in a phase II study.[29] This study was a double-blind, randomized, parallel-group, dose-finding trial that compared fondaparinux with dalteparin in 456 patients. Patients were treated with subcutaneous fondaparinux 5.0, 7.5, or 10.0 mg once/day or with subcutaneous dalteparin 100 IU/kg twice/day for 5–10 days. The primary efficacy outcome was the change in thrombus mass as determined by compression ultrasonography in combination with perfusion lung scintigraphy performed at baseline and repeated on day 7 ± 1. Overall, 45.2% of fondaparinux-treated patients and 48.7% of dalteparin-treated patients had a positive outcome (absolute difference 3.5%, 95% confidence interval [CI] -7.2–15%).

The secondary efficacy outcome included the rate of DVT, pulmonary embolism, and other VTE events up to day 97 in patients with symptomatic extension or recurrent VTE. Recurrent VTE occurred in 2.4% of the fondaparinux-treated patients and 5% of dalteparin-treated patients (95% CI -2.1–10.1%). The rate of major bleeding did not differ significantly between the treatment groups. This trial demonstrated that fondaparinux appears to be a safe and effective agent in the treatment of patients with DVT and that it was effective across a wide dose range.

After the experience in the phase II study, two recent, large, randomized, phase III trials were conducted to assess the efficacy of fondaparinux in the treatment of DVT (MATISSE-DVT)[30] and pulmonary embolism (MATISSE-PE).[31] The DVT study (2212 patients) was a double-blind design and the pulmonary embolism study (2213 patients) was an open-label design to allow patients in the fondaparinux arm to be discharged early if considered medically appropriate.

In the DVT study, the comparator was the LMWH enoxaparin 1 mg/kg given subcutaneously twice/day, and in the pulmonary embolism study the comparator was continuous intravenous infusion UFH.[30] Fondaparinux 7.5 mg was administered subcutaneously once/day for patients weighing 50–100 kg, and for patients weighing less than 50 kg or more than 100 kg, 5- and 10-mg doses were given, respectively. In both studies, the initial treatment was given for at least 5 days and until an INR of 2–3 was reached with the vitamin K antagonists. The primary efficacy outcome was recurrent VTE during 3 months of follow-up, and the main safety outcomes were major bleeding and death.

In the pulmonary embolism trial, the intent-to-treat analysis showed that 42 (3.8%) of the 1103 fondaparinux-treated patients had recurrent VTE, compared with 56 (5%) of the 1110 UFH-treated patients, for an absolute difference of -1.2% in favor of fondaparinux (95% CI -3.0–0.5%).[31] This corresponded to a relative risk reduction of 25%. Major bleeding during the initial treatment phase was not different between the two groups: 1.3% and 1.1% in the fondaparinux and UFH groups, respectively. Mortality rates at 3 months were also comparable in the two groups. An additional interesting observation was reported in a subgroup analysis of patients with active cancer. Recurrent VTE occurred in 10 (8.9%) of 112 patients in the fondaparinux group and in 22 (17.2%) of 128 patients in the UFH group. In

addition, approximately 15% of the patients received fondaparinux in part on an outpatient basis, offering a more convenient and more economic option to in-hospital administered UFH.

Similar to the pulmonary embolism study, the DVT study, which was presented at the XIX Congress of the International Society of Thrombosis and Haemostasis, showed that fondaparinux was not inferior to the comparator enoxaparin, with no difference in bleeding complications.

Therefore, these trials demonstrate that once-daily, subcutaneous fondaparinux is at least as effective and as safe as UFH and LMWH in the treatment of patients with DVT and pulmonary embolism, respectively. The pulmonary embolism study has the largest randomized database that suggests that fondaparinux is a safe and effective alternative to UFH in the treatment of pulmonary embolism. As "direct" evidence from large randomized clinical trials on the efficacy of LMWH in the treatment of acute symptomatic pulmonary embolism is still limited, fondaparinux will be a welcomed addition to the available anticoagulants used for this indication, offering the advantage of a single drug regimen for symptomatic DVT or pulmonary embolism. In addition, fondaparinux offers the convenience of fixed, subcutaneous, once-daily dosing based on a predefined weight category for most patients. Finally, the ability to transition patients to the outpatient setting while receiving fondaparinux will reduce patient inconvenience and decrease the overall cost of treatment.

## Conclusion

Venous thromboembolism is a major but often overlooked health care problem that results in significant morbidity, mortality, and resource expenditures. The efficacy of anticoagulation therapy has been well documented in patients with VTE; however, traditional anticoagulants have limitations in practice. The emerging novel anticoagulants such as the oral direct thrombin inhibitors and the synthetic factor Xa inhibitors are promising and offer potential benefits over current therapies. In particular, the selective factor Xa inhibitor, fondaparinux, offers the advantage of a single, convenient drug regimen for treating symptomatic DVT or pulmonary embolism and thus is a welcomed addition to the available anticoagulant treatments.

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