Venous thromboembolism (VTE) is a common but preventable disease. The last decade has witnessed major advances in VTE treatment and prophylaxis. Low molecular weight heparins (LMWH) became the agents of choice in the treatment of deep venous thrombosis (DVT) and are increasingly used in the treatment of stable pulmonary embolism (PE). Increasing focus on simplicity and efficacy has led to the discovery of the synthetic pentasaccharides, substances that specifically inhibit factor Xa activity, producing an antithrombotic effect without affecting other coagulation factors or platelets. Fondaparinux, the first pentasaccharide introduced into the market, was first tried as a prophylactic agent against VTE in patients undergoing major orthopedic procedures, such as hip fracture, total hip and knee replacements, such approach appeared to be more effective than LMWH. Fondaparinux was also used, with promising results, in prophylaxis in patients undergoing major abdominal surgery and high risk medical patients. Pentasaccharides were recently tried in the treatment of both DVT and PE. The largest clinical investigation program ever undertaken in this therapeutic area, has shown that pentasaccharides are as safe and as effective as either unfractionated heparin (UFH) or LMWH, with the added convenience of once daily injection, no need for monitoring the anticoagulant effect and no major side effects such as thrombocytopenia. Therefore, the efficacy, the safety profile and the added convenience for both patients and physicians alike, will probably keep pentasaccharides as the front runner among new anticoagulants of the future. This article focuses on the use of fondaparinux as a prophylactic agent against VTE in patients undergoing major orthopedic and abdominal surgery along with high risk medical patients; it will also discuss the recent promising data on its use to treat active DVT and PE.


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Pentasaccharides. A new class of anticoagulants ... Abdel-Razeq

Pentasaccharides. The new class of anticoagulants. Fondaparinux (Arixtra®, Sanofi-Synthelabo, France) is the first agent of a new class of selective factor Xa inhibitors (pentasaccharides). Figure 1 shows the chemical structure of fondaparinux. This new synthetic compound, with no animal-source components, has been designed to bind selectively to a single target in the plasma, antithrombin, which inactivates factor Xa, thus resulting in strong inhibition of thrombin generation and clot formation.26,27 Fondaparinux is devoid of direct activity against factor II (thrombin). As a result of this specific interaction, fondaparinux enhances, by a factor of approximately 300, the AT-mediated inactivation of factor Xa. Figure 2 shows the detailed mechanism of action of fondaparinux. Each molecule of this compound binds to one molecule of AT at a specific site and with a very high affinity. This binding induces a critical conformational change in AT, exposing a loop containing an Arginine residue that binds factor Xa. Exposure of the Arginine-containing loop greatly increases the affinity of AT for factor Xa, enhancing the natural inhibitory effect of AT against factor Xa.28 Once AT binds to factor Xa, further conformational change releases the fondaparinux unchanged from its binding site and would allow fondaparinux to go and to interact with another molecule of AT. In summary, each molecule of fondaparinux can bind to several molecules of AT consecutively, and thus allowing AT to act as a buffer for the excess of fondaparinux; therefore, in case of overdose, although there is an excess of fondaparinux, there is no free to AT which it can bind and thus, the antithrombotic effect plateaus.29 It has been estimated that the inhibition of one factor Xa molecule prevents the generation of approximately 50 molecules of prothrombin, thus contributing to the high level of antithrombotic potency of fondaparinux even at a low dose.26 Thus, inhibition of factor Xa interrupts the coagulation cascade at its core step and prevents the formation and development of thrombi. This allows the fondaparinux to prevent clot formation, whether

surgery, especially those with malignancy. Medical patients with acute cardiac, respiratory, infectious and inflammatory diseases are also considered to be at high risk for VTE.15,16 The last decade has witnessed major advances in the treatment of VTE. Weight-adjusted LMWH became the standard initial therapy for patients with established DVT, given subcutaneously, once or twice a day, for approximately one week.27 For patients with PE, the initial treatment remains intravenous dose-adjusted unfractionated heparin (UFH) for the same period, however, low molecular weight heparins (LMWH) are increasingly used in patients with stable PE. Various antithrombotic agents have been proposed for the prevention and treatment of VTE, but they all suffer from some limitations.18-20 The main issues in any antithrombotic agent are efficacy, major side effects and convenience. Despite the use of various antithrombotic agents, including LMWH, the incidence of venographically proven that DVT is still high in major orthopedic surgery, ranging from 14-50% after hip replacement, and from 30-50% after knee replacement surgery.23 Heparin induced thrombocytopenia (HIT) is an important and potentially life-threatening side effect of heparin therapy, and is still an issue to be considered even with LMWH.22

The convenience of the dosing schedule and the need for close monitoring of the current anticoagulants are other issues to be considered. Unfractionated heparin is still widely used to treat PE and some complicated DVT. Few patients achieve a therapeutic range within the first 24 hours, a critical period in VTE therapy. All LMWH are of porcine origin, a fact that had resulted in delayed application of these products in our daily practice. Despite multiple randomized studies in major orthopedic procedures showing superior efficacy, compared to UFH, some local physicians are still reluctant to prescribe them.23

Factor Xa and antithrombin (the central role). The coagulation process is a series of enzymatic reactions, involving the sequential activation of numerous plasma components, the coagulation factors. Each reaction leads to the activation of a coagulation factor. In vivo coagulation is triggered by the expression of a “tissue factor” (TF) that immediately binds to activated factor VIIa circulating in the plasma.24 Once formed, the TF/VIIa complex (the extrinsic pathway of the coagulation cascade) activates factor X to factor Xa and traces of factor IX to factor IXa. Activated factor IX then induces activation of the intrinsic pathway, which leads to efficient generation of more factor Xa. The intrinsic pathway is also activated by contact factors: high molecular weight kininogen (HMWK), prekallikrein and factor XII. In summary, coagulation is triggered by the extrinsic pathway and amplified by the intrinsic pathway, with both pathways converging at the level of factor Xa production. Thus, factor Xa plays a central role in the coagulation process. Together with factor Va, calcium and phospholipids, it forms the prothrombinase complex, which activates the conversion of prothrombin (factor II), into thrombin (factor IIa). This cascade leads to the conversion of fibrinogen into fibrin and clot formation. Coagulation is controlled by physiological mechanisms that maintain a balance between coagulation factors and endogenous inhibitors. Antithrombin (AT) is one of the main endogenous inhibitors of blood coagulation. When activated, AT neutralizes factor Xa and thereby powerfully inhibits thrombin generation.25
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Figure 1 - The chemical structure of fondaparinux.

Figure 2 - Mechanism of action of fondaparinux: fondaparinux [1] binds with high affinity to its binding site on antithrombin (AT), resulting in [2] irreversible conformational changes which [3] enables it to bind and inhibits activated factor X (Xa) which is needed to activate factor II (prothrombin) to thrombin.

triggered by the extrinsic or intrinsic pathways, since it works at the level of the common pathway steps.30

1. Clinical studies on prophylaxis. 1. Orthopedic surgery. Fondaparinux was first tried for VTE prophylaxis in patients undergoing major orthopedic procedures. Four large multicenter, randomized, double-blind clinical trials were performed in patients undergoing major orthopedic surgery.31–34 In all 4 trials, fondaparinux was given at a dose of 2.5 mg subcutaneously once a day. The first dose was started 6 hours (4-8 hours) postoperatively; the second dose was given at least 12 hours after the first one, but not more than 24 hours after the surgical procedure. In all 4 studies, the primary assessment for efficacy was based on a mandatory bilateral venography of the legs between day 5 and 11, or earlier, if thrombosis was clinically suspected. In patients undergoing hip fracture surgery or elective total hip replacement, the Pentasaccharide in Hip-Fracture Surgery (PENTHIFRA)31 and European Pentasaccharide Hip Elective Surgery Study (EPHESUS),32 fondaparinux at the above dose and schedule was compared to 40 mg of enoxaparin once daily, started 12 hours preoperatively; a regimen widely used in Europe. Whereas in the Pentasaccharide in Major Knee Surgery Study (PENTAMAKS)33 (major knee surgery) and PENTATHALON 200034 (elective THR) studies, fondaparinux was compared to enoxaparin given at 30 mg twice daily, started 12 hours postoperatively; a regimen commonly used in North America. Fondaparinux was significantly superior to LMWH in all 4 studies. The results of these studies are shown in Figure 3a, 3b, 3c and 3d.

A meta-analysis of the 4 studies was performed,35 a total of 7344 patients were randomized in more than 300 centers worldwide. The superior efficacy of fondaparinux over enoxaparin was demonstrated in all types of surgeries with a relative VTE risk reduction of 61.6%, 63.1% and 45.3% in hip fracture, major knee, and hip replacement surgery. The superior efficacy of fondaparinux over enoxaparin was achieved without significant increase in the risk of bleeding.36

Duration of prophylaxis in orthopedic patients. In a retrospective cohort study of 19,586 California Medicare patients undergoing THR and 24,059 patients undergoing TKR, the diagnosis of VTE was made after discharge in 76% of THR and 47% of TKR cases. The median time to diagnosis was 17 days for THR and 7 days for TKR.37 This study illustrates that limiting prophylaxis for the in-patient duration is clearly not enough, especially with the recent advances in medical care, which resulted in shorter hospital stay. Several studies have addressed the issue of extended out of hospital prophylaxis for patients undergoing major orthopedic procedures. In most of these studies, the incidence of venography-proven DVT was reduced by 50%.38–42 In a recent meta-analysis of randomized clinical trials, Cohen et al43 have also shown that the incidence of symptomatic VTE was decreased by 50% following extended out-of-hospital prophylaxis. These results opened the door for another study to compare the efficacy and safety of the pentasaccharide, fondaparinux, in extended out-of-hospital prophylaxis for patients undergoing major orthopedic procedures. In most of these studies, the incidence of venography-proven DVT was reduced by 50%.38–42 In a recent meta-analysis of randomized clinical trials, Cohen et al43 have also shown that the incidence of symptomatic VTE was decreased by 50% following extended out-of-hospital prophylaxis. These results opened the door for another study to compare the efficacy and safety of the pentasaccharide, fondaparinux, in extended out-of-hospital prophylaxis (the PENTATHALON 2000 plus study). In this double-blind multicenter trial, 656 patients undergoing hip fracture surgery were enrolled. All patients received fondaparinux at a dose of 2.5 mg once daily, given as a subcutaneous injection for 6-8 days; patients were then randomized to continue on fondaparinux, at the same dose and schedule, or placebo for a total of 19-23 days. Using venography as an end point, only
3 (1.4%) of the 208 fondaparinux-treated patients had VTE, compared to 77 (35%) of 220 patients on the placebo arm. Extended use of fondaparinux resulted in a relative VTE risk reduction of 95.9% (95% confidence interval [CI] 87.2-99.7%, p<0.001). Similarly, the incidence of symptomatic VTE was significantly lower with fondaparinux (0.3%) than with placebo (2.7%). There was no difference between the 2 groups in the incidence of clinically relevant bleeding.44

2. **Prophylaxis in surgical patients.** Fondaparinux was also tried for prophylaxis in surgical patients. In a multicenter, randomized, double-blind trial (the Pegasus study), more than 2000 patients undergoing high-risk abdominal surgery expected to last more than 45 minutes under general anesthesia were eligible if they were >60 years, or >40 years with one or more other risk-factors including cancer surgery, obesity, history of VTE, heart failure, chronic obstructive pulmonary disease or inflammatory bowel disease. Patients were randomized to receive fondaparinux at a dose of 2.5 mg starting 6 hours after surgery or dalteparin 5000 IU; both were given subcutaneously once daily, (dalteparin was also given 2 hours preoperatively at 2500 units subcutaneously). Both agents were given for 7 ± 2 days, and patients were followed up for 30 ± 2 days. The results of this study were presented during the 29th meeting of the International Society of Thrombosis and Hemostasis (ISTH) in July 2003.45 Based on screening venography that was carried out between day 5 and 10 postoperatively, 47 of 1027 (4.1%) patients who had received fondaparinux had VTE, compared to 62 of 1021 (6.1%) in the dalteparin group. There was no significant difference in major or minor bleeding in both groups.45 In subgroup analysis, the incidence of VTE was significantly lower in 696 cancer patients who underwent abdominal surgery who had received fondaparinux had VTE, compared to 62 of 1021 (6.1%) in the dalteparin group. There was no significant difference in major or minor bleeding in both groups.45 In subgroup analysis, the incidence of VTE was significantly lower in 696 cancer patients who underwent abdominal surgery who had received fondaparinux had VTE, compared to 62 of 1021 (6.1%) in the dalteparin group. There was no significant difference in major or minor bleeding in both groups.45

3. **Prophylaxis in medical patients.** The use and...
assessment of VTE prophylaxis is less well studied in non-surgical hospitalized patients. Very few trials have used routine venography to assess thrombosis risk and the effectiveness of preventive measures in medical patients. In one recent study (the ARTEMIS trial), which was also presented in the 29th meeting of the ISTH, July 2003, more than 800 patients hospitalized for acute cardiac, respiratory, infectious or inflammatory diseases, and considered to be at moderate risk of VTE were enrolled. These patients were randomized to receive either 2.5 mg fondaparinux once-daily subcutaneously or placebo, starting within 48 hours of admission and continued for 6-14 days. A bilateral venogram was performed on day 6-15. The incidence of all VTE was 10.5% in the fondaparinux group, compared to 15.6% in the placebo group. There was no difference in major or minor bleeding in both groups. This study illustrated the real need for prophylaxis in high-risk medical patients, and it also showed that fondaparinux is effective and safe for this indication, too. However, one can argue that a lower incidence of VTE could have been achieved with the much cheaper UFH. This study would have been of more value if it compared fondaparinux with the current standard agent for such indication namely UFH.

II. The use of pentasaccharides for venous thromboembolism treatment. The encouraging results discussed above in prophylaxis, encouraged investigators to try fondaparinux in the treatment of established DVT and PE. Two trials have used fondaparinux to treat DVT (MATISSE-DVT) and PE (MATISSE-PE). These studies, the largest clinical investigation programs ever undertaken in this therapeutic area, were presented at the 44th annual meeting of the American Society of Hematology (ASH) in December 2002 and updated during the 29th meeting of ISTH in July 2003. Both trials were similarly designed to demonstrate that fondaparinux was at least as effective as the current initial standard treatments of PE and DVT. The MATISSE-DVT trial was a multicenter, randomized, double-blind, in patients with confirmed acute symptomatic DVT, comparing the efficacy and safety of fondaparinux with enoxaparin. More than 2000 patients were randomized to receive either a fixed once-daily dose of 7.5 mg fondaparinux subcutaneously (5.0 mg in patients ≤50 kg, and 10.0 mg in patients >100 kg) or twice-daily, body-weight adjusted enoxaparin subcutaneously (1 mg/ kg) for at least 5 days and until anticoagulation with vitamin K antagonists was therapeutic (INR 2-3). The primary efficacy outcome was recurrent VTE during 3 months of follow-up. The main safety outcomes were major bleeding and death. In an intention-to-treat analysis, 43 (3.9%) of the 1098 fondaparinux-treated patients had symptomatic recurrent thromboembolic events, as compared with 45 (4.1%) of the 1107 enoxaparin-treated patients (absolute difference 0.2% in favor of fondaparinux; 95% CI of -1.8 to 1.5%). Major bleeding during the initial treatment period occurred in 1.1% of fondaparinux patients and 1.2% of enoxaparin patients. Mortality rates at 3 months were comparable. This study demonstrated that once daily, fixed-dose fondaparinux was at least as effective and equally safe as twice-daily body-weight-adjusted enoxaparin in the initial treatment of patients with symptomatic DVT. This would further simplify the treatment of DVT since no body weight adjustment is necessary and only one subcutaneous injection per day is required. One third of the patients were treated on an outpatient basis.

In the MATISSE-PE trial, 2213 patients presenting with symptomatic PE were included in 214 centers in 20 countries worldwide. In this trial, patients were randomly assigned to receive either fondaparinux 7.5 mg subcutaneously, or a dose-adjusted continuous intravenous infusion of UFH for at least 5 days. In an intention-to-treat analysis, the incidence of symptomatic recurrent VTE over the 3-month follow-up period was 3.8% (42/1103 patients) in the fondaparinux group and 5% (56/1110 patients) in the UFH group (absolute difference 1.2%; 95% CI of -3% to 0.5%). The incidence of major bleeding was low and comparable in both groups (1.3% for fondaparinux versus 1.1% for UFH). There was no difference in mortality at 3 months.

The 2 MATISSE studies demonstrate that fondaparinux used at a fixed dose of 7.5mg once daily subcutaneously can effectively and safely treat the acute phases of both PE and DVT.

Thrombocytopenia is not an issue with pentasaccharides. Heparin induced thrombocytopenia (HIT) is an important and potentially life threatening side effect of heparin therapy. The clinical picture of HIT type II is characterized by significant thrombocytopenia alone or in combination with venous or arterial thromboembolic complication. It is believed to be an immunological reaction to the complex formed by Platelet Factor 4 (PF4) and unfractionated or low molecular weight heparin molecules. To identify whether fondaparinux could induce platelet aggregation in a HIT-positive test system, an aggregation assay was used in which platelet-rich plasma from normal donors was mixed with fondaparinux and the serum collected from clinically symptomatic HIT-positive individuals. In this model, fondaparinux at a final concentration of more than 20 times the therapeutic concentration, did not induce aggregation, whereas UFH produced a 40-80% aggregation response. None of the clinical studies discussed above that used fondaparinux at prophylactic doses in orthopedic,
general surgery or medical patients, or higher doses used to treat DVT or PE showed any significant thrombocytopenia. Having said this, there is no clinical experience in the use of the fondaparinux in patient with HIT and fondaparinux should not be used for this indication, yet.

**Reversal of the anticoagulant effect.** Prothrombin, a protein capable of binding strongly to heparin, is the antidote used in cases of heparin overdose. Although protamine is also proposed in these circumstances for LMWH, it does not fully neutralize their antithrombotic effect.\(^5\) In vitro studies performed on human plasma with protamine sulfate and fondaparinux revealed that at a concentration of protamine sulfate, 30-folds higher than that of fondaparinux, no neutralization of activity occurred as determined by coagulation tests or even anti-factor Xa assay. Clinical data as well do not appear to justify its use as a reversal agent.\(^56\)

Alternative antidotes were tried. In a recent randomized, placebo controlled three-parallel group trial in healthy male volunteers, the inhibition of thrombin generation induced by fondaparinux was rapidly and significantly reversed by the recombinant activated factor VIIa (rVIIa, NovoSeven).\(^57\) These results suggest that rVIIa may be an effective and safe reversal agent for fondaparinux.

**Future directions: The long acting pentasaccharides.** The increasing interest in this new class of anticoagulants has lead to the synthesis of a new pentasaccharide with the same mechanism of action like fondaparinux but with longer half-life, enabling once a week administration. The new compound is called Idraparinux. Preliminary data presented during the latest ISTH meeting\(^55\) have shown that Idraparinux administered once weekly is as effective and, as safe as, warfarin in treating proximal DVT. Additional benefits include the convenience of once weekly administration, no need for monitoring and the absence of food or drug interaction.

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**References**


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