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Fondaparinux Sodium

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Contents

Abstract

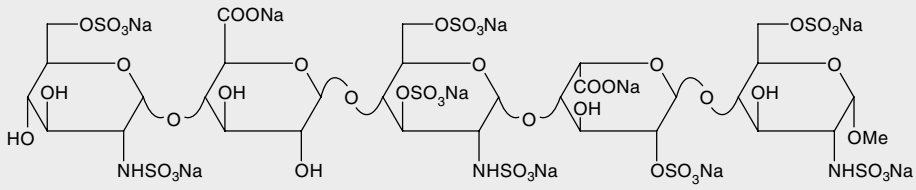
▲ Fondaparinux sodium, a selective factor Xa inhibitor, is the first in a new class of antithrombotics. It binds selectively with high affinity to antithrombin III and specifically catalyses the inactivation of factor Xa. The elimination half-life of fondaparinux sodium permits once daily treatment.

▲ A randomised, double-blind, parallel-group, dose-ranging, multicentre phase IIb study in 933 eligible patients established that a subcutaneous dose of between 1.5 and 3mg of fondaparinux sodium has the optimum efficacy and safety profile for prophylaxis of venous thromboembolism in patients undergoing major orthopaedic surgery.

▲ Fondaparinux sodium, given to more than 3600 patients undergoing major orthopaedic surgery who participated in prospective, randomised, double-blind, multicentre phase III clinical trials, significantly reduced the incidence of venous thromboembolism, with an overall risk reduction of 55.2% compared with enoxaparin.

▲ Fondaparinux sodium was well tolerated by patients undergoing major orthopaedic surgery, and at the recommended clinical dose of 2.5mg has a similar tolerability profile, including bleeding events, to standard enoxaparin regimens. Fondaparinux sodium has not been reported to cause antibody-induced thrombocytopenia.

Features and properties of fondaparinux sodium (SR 90107A/Org 31540)	
Indications	
Anticoagulant for prophylaxis of venous thromboembolism (VTE) following major orthopaedic surgery	
Mechanism of action	
Selective antithrombin III (AT III)-mediated factor Xa inhibitor	
Dosage and administration (recommended dosage)	
Prevention of VTE	
Initial dose	2.5mg at least 6 hours after surgery
Maintenance dose	2.5mg once daily
Route of administration	Subcutaneous
Pharmacokinetic profile (in healthy, young, male volunteers)	
Peak plasma concentration for 2.5mg dose	0.34 mg/L
Time to peak plasma concentration	1.7h
Mean elimination half-life (range)	17.2h (13 to 21h)
Main route of elimination	Renal
Adverse events	
Most frequent at therapeutic dosage	Minor bleeding



Chemical structure of Fondaparinux sodium

One of the most significant postoperative complications in major orthopaedic surgery to the lower limbs is the risk of venous thromboembolism (VTE).[1,2] Orthopaedic surgery itself has a strong thrombogenic effect.[3] Despite effective prophylaxis with low molecular weight heparins (LMWHs), 30.6% of patients undergoing knee replacement, 16.1% of those undergoing elective hip replacement and 27% of patients with hip fracture will develop deep vein thrombosis (DVT) after surgery.[2] The risk of subsequent pulmonary embolism (PE) is high in patients with symptomatic or asymptomatic DVT.[1,3] Between 4 and 10% of patients undergoing major orthopaedic surgery develop clinical PE; the majority of these are fatal.[4-6] VTE is also associated with a longer period of inpatient care, and associated higher costs.[7] Prophylaxis with anticoagulants including unfractionated heparin, LMWHs, and warfarin has reduced the risk of VTE significantly,[3] but this has been associated with some unwanted effects such as heparin-induced thrombocytopenia (HIT) and heparin-associated osteopenia (unfractionated heparin, LMWHs),[8,9] bleeding complications and a need to monitor anticoagulation closely (unfractionated heparin, warfarin).[8-10]

LMWHs are currently the treatment of choice for preventing VTE in major orthopaedic surgery.[11-13] LMWHs inhibit factor Xa and to a lesser extent thrombin (factor IIa) by binding to antithrombin III (AT III), and thus enhancing the activity of AT III.[12] LMWHs have less interaction with platelets and platelet factor 4 (PF4) than unfractionated heparin and are less likely to induce thrombocytopenia.[8,14] Their predictable anticoagulant response means that coagulation monitoring is unnecessary.[8] LMWH's need to be administered perioperatively for maximum benefit; because of the risk of epidural haematoma, this limits their use in prophylaxis where patients undergo surgery using regional anaesthesia.[15]

Increasing focus on agents that specifically prevent undesirable coagulation without affecting primary haemostasis[16] has led to the discovery of the synthetic pentasaccharides, substances that specifically inhibit factor Xa activity, producing an antithrombotic effect without factor IIa-inhibiting or antiplatelet activity.[17]

Fondaparinux sodium is a new pentasaccharide obtained by chemical synthesis.[18] It is sulphated, and is designed to bind specifically to AT III.[18] This article focuses on the use of fondaparinux sodium as prevention against VTE in patients undergoing major orthopaedic surgery.

1. Pharmacodynamic Profile

Mechanism of Action

• Fondaparinux sodium prevents thrombus formation by selectively binding to AT III, thus catalysing the specific inactivation of factor Xa, interrupting the coagulation cascade at the point where the intrinsic and extrinsic coagulation paths merge.[18] Inhibition of factor Xa prevents the for-

mation of thrombin, and subsequently the formation of fibrin and the activation of factors V, VIII and XIII and protein C; this activity of fondaparinux sodium eventually leads to the inhibition of thrombus formation and thrombus growth.[18]

AT III Mediated Factor Xa Activity

• Fondaparinux sodium has a high affinity for the pentasaccharide binding site on AT III with an *in vitro* dissociation constant (K_d) of 41[18,19] to 58 nmol/L.[20,21] Catalytic activation by fondaparinux sodium causes an irreversible conformational change in AT III that results in a considerable increase in the rate of factor Xa inactivation when compared with the rate seen with free or uncomplexed AT III.[18]

• The fondaparinux sodium-AT III complex inhibits prothrombinase formation rather than prothrombinase activity.[20] In an *in vitro* study designed to differentiate between prothrombinase activity and prothrombinase formation, fondaparinux sodium demonstrated greater inhibition of prothrombinase formation, with an IC_{50} (concentration inhibiting 50% of activity) of 0.27 μg/ml when compared to prothrombinase activity at an IC_{50} of 4.5 μg/ml.[22]

• Fondaparinux sodium impairs thrombin generation as a result of its AT III-mediated inhibition of factor Xa.[17] The IC_{50} for thrombin generation was 0.13 μmol/L for fondaparinux sodium *in vitro*.[20]

• Fondaparinux sodium does not display significant effects in overall coagulation tests such as activated partial thromboplastin time and prothrombin time (PT).[18,23] It has a pure antifactor Xa effect and has no antifactor IIa activity at therapeutic plasma concentrations.[24]

• Studies in healthy volunteers[23] showed that fondaparinux sodium has no significant effect on bleeding time[23] and plasma AT III levels,[23] indicating that it has no antifactor IIa activity.[18] In these studies low (2.8mg) and high (28.6mg) doses of subcutaneous fondaparinux sodium were administered to healthy volunteers.[23]

• Repeated injections of fondaparinux sodium had no significant effect on plasma AT III levels (data not reported).[23]

Effects on Platelets

• Fondaparinux sodium does not cause spontaneous platelet aggregation (data not reported),[17,25,26] nor does it appear to form reactive complexes with PF4 or cause antibody-related platelet activation.[26,27] Two *in vitro* studies[26,27] investigated the effect of increasing doses of fondaparinux sodium (1 to 150 mg/L) on plasma from patients (n = 79) with type II HIT. Results showed that HIT antibody binding to PF4 was not enhanced;[26,27] conversely, fondaparinux sodium inhibited HIT antibody-induced platelet activation in a dose-related manner.[26]

Effects on Other Coagulation Factors

• The effect of fondaparinux sodium on factor IXa has been examined in several *in vitro* studies and in animal models. In animal studies there appears to be no effect,[28] however, *in vitro* studies using plasma from human volunteers indicated that fondaparinux sodium inactivated factor IXa with an apparent pseudo-first order rate constant of 0.76/min/μg pentasaccharide/ml.[29] This inhibitory effect of fondaparinux sodium is three orders of magnitude lower than that observed for factor Xa inhibition and is consequently assumed to have no pharmacological relevance. No activity against factor XIa appeared to occur *in vitro*.[29]

• Fondaparinux sodium has demonstrated an AT III-dependent inhibiting effect on tissue factor (TF) bound factor VIIa.[30] *In vitro*, the fondaparinux sodium-AT III complex produced a time- and dose-dependent inhibition of TF bound factor VIIa in two different assay methods (clotting and amidolytic).[30] The failure of fondaparinux sodium alone to inactivate TF-bound factor VIIa con-

firmed that the effect was AT III dependent.[30] A further *in vitro* study using plasma from human volunteers demonstrated that fondaparinux sodium 0.5 μg/ml inhibited factor VIIa generation and/or activation, after coagulation was triggered by the extrinsic and intrinsic clotting pathways [76% (extrinsic pathway) and 90% (intrinsic pathway) inhibition].[31] It is unclear whether fondaparinux sodium inhibits factor VIIa as a result of its inhibitory effect on factor Xa.[32]

Efficacy in Animal Models of Venous Thrombosis

• In various animal models, the antithrombotic effect (size of clot, reduction in mean thrombus weight) of fondaparinux sodium given intravenously in doses ranging from 12.5 to 200 μg/kg[33,34] and 7 to 145 μg/kg (5 to 100 U/kg)[24] was observed. Inhibition of thrombus formation by fondaparinux sodium occurred in a dose-dependent manner, with the highest dose (200 μg/kg) totally inhibiting clot formation.[24,33] The efficacy of fondaparinux sodium when compared with heparin was dependent on the thrombogenic challenge used (tissue thromboplastin, Feiba, human serum).[33] In addition, fondaparinux sodium demonstrated strong antifactor Xa activity, but no antifactor IIa activity.[20,24,33,34]

2. Pharmacokinetic Profile

Absorption and Distribution

• The absorption of a subcutaneous dose of fondaparinux sodium 2.5mg (the recommended daily dose; section 5) given to healthy young male volunteers (n = 16) was rapid and complete. A mean maximum plasma concentration (C_{max}) of 0.34 mg/L was achieved in a mean time (t_{max}) of 1.7 hours.[35] The mean half-maximum plasma concentration ($C_{max}/2$) was reached after 25 minutes. Absolute bioavailability after a subcutaneous 2.5mg dose was 100%,[35,36] with a volume of distribution (corrected for the subcutaneous route) of 8.2L.[36] Mean plasma concentrations were >$C_{max}/2$ values for up to 11 hours after subcutaneous administration of a single dose of fondaparinux 2.5mg.[35,36]

• Age appeared to have a minimal effect on the pharmacokinetics of fondaparinux sodium. Healthy, elderly, male and female volunteers aged between 60 and 85 years (n = 25) were given single subcutaneous doses of fondaparinux sodium ranging from 2 to 8mg.[36] C_{max} values ranging from 0.28 to 0.91 mg/L were achieved in approximately 2.5 hours; although the area under the plasma concentration-time curve (AUC) increased in proportion to the dose given (values ranged from 5.63 to 19.24 mg • h/L), the volume of distribution (corrected for the subcutaneous route) was constant (10 to 10.8L).[36]

• The pharmacokinetics of fondaparinux sodium are essentially linear.[36] In a dose-ranging study, healthy elderly male and female volunteers aged between 60 and 85 years (n = 41) were given doses of fondaparinux sodium ranging from 2 to 20mg as a single intravenous injection.[36] C_{max} ranged from 0.6 mg/L following a 2mg dose to 3.84 mg/L after a 20mg dose; C_{max} and AUC values (which ranged from 6 to 38.84 mg • h/L according to the dose administered) generally increased in proportion to the dose given. Volume of distribution ranged from 7.4 to 10.9L over this dose range.[36]

• In healthy, young, male volunteers (n = 71) given once-daily subcutaneous injections of fondaparinux sodium 4 (12 volunteers) or 10mg (59 volunteers) over consecutive days, steady-state plasma concentrations were reached after the third or fourth dose. t_{max} was achieved between 1.5 and 2.3 hours at steady state; C_{max} and AUC values at steady state were 1.3 times higher than after a single dose.[36]

• At concentrations ≤2 mg/L (the therapeutic range), fondaparinux sodium was highly and specifically bound *in vitro* to antithrombin III (>94%),

but did not appear to bind to other plasma proteins (albumin, glycoprotein).[37]

Metabolism and Elimination

• Fondaparinux sodium is excreted unchanged mainly through the kidney.[35] The terminal elimination half-life ($t_{1/2}$) of a single subcutaneous dose of fondaparinux sodium 2.5mg given to healthy young volunteers ranged from 13 to 21 hours (mean 17.2h). Plasma clearance (CL_P) was 0.306 to 0.474 L/h and renal clearance (CL_R) ranged from 0.27 to 0.474 L/h.[35] Mean residence time was almost 24 hours.[35]

• When healthy, elderly, male and female volunteers aged between 60 and 85 years (n = 25) were given single subcutaneous doses of fondaparinux sodium ranging from 2 to 8mg,[36] $t_{1/2}$ (18.8 to 20.7h), CL_P (approximately 0.37 L/h), the percentage of fondaparinux sodium recovered in urine up to 72 hours postdose (about 65%) and CL_R (approximately 0.26 L/h) were independent of dose.[36]

• The pharmacokinetic parameters of fondaparinux sodium after intravenous administration were similar to those observed after subcutaneous administration. In healthy, elderly male and female volunteers who were given single intravenous doses of fondaparinux sodium 2 to 20 mg in a dose-ranging study, $t_{1/2}$ was 16.4 to 18.4 hours and CL_P ranged from 0.32 to 0.47 L/h, generally increasing in a dose-related manner.[36] The percentage of fondaparinux sodium recovered in urine up to 72 hours postdose ranged from 69 to 77%, and CL_R ranged from 0.27 to 0.47 L/h, generally increasing with dose.[36]

• Excretion and elimination of subcutaneous fondaparinux sodium at steady state after repeated dosages (fondaparinux sodium 4 or 10mg once daily; n = 71) in healthy, young, male volunteers were similar to data observed after a single dose (CL_P 0.47 to 0.51 L/h; $t_{1/2}$ 13 to 14h; percentage of fondaparinux sodium recovered in urine up to 72 hours postdose = 61%; CL_R 0.32 L/h).[36]

Drug Interaction Potential

• Fondaparinux sodium has been shown to have no pharmacokinetic interaction with warfarin in young healthy volunteers (n = 12).[38] In a randomised, double-blind, placebo-controlled study, coadministration of a loading dose of oral warfarin 15 and 10mg on the fourth and fifth days with once-daily subcutaneous fondaparinux sodium 4mg had no effect on the AUC, $t_{1/2}$, C_{max} or t_{max} of fondaparinux sodium when compared with fondaparinux sodium alone. The effect of warfarin on PT was unchanged in the presence of fondaparinux sodium.[38]

• Fondaparinux sodium appears to have no phamacokinetic interaction with aspirin (acetylsalicylic acid) in healthy, young volunteers (n = 16).[39] A randomised, double-blind, placebo-controlled study demonstrated that coadministration of a single oral dose of aspirin 975mg on the fourth day with once-daily subcutaneous fondaparinux sodium 10mg had no effect on the AUC, $t_{1/2}$, C_{max} or t_{max} of fondaparinux sodium when compared with fondaparinux sodium alone. The effect of aspirin on platelet aggregation was unchanged when coadministered with fondaparinux sodium.[39]

• Coadministration of fondaparinux sodium with piroxicam had no effect on pharmacokinetic parameters compared with fondaparinux sodium alone in healthy, young volunteers (n = 12).[40] In a randomised, double-blind, placebo-controlled study, coadministration of once-daily subcutaneous fondaparinux sodium 10mg on the seventh to tenth days with once-daily oral piroxicam 20 mg had no effect on the $t_{1/2}$ or the CL_R of fondaparinux sodium when compared with fondaparinux sodium alone. The effect of piroxicam on platelet aggregation or gastrointestinal blood loss was unchanged in the presence of fondaparinux sodium.[40]

3. Therapeutic Trials

Fondaparinux sodium has been evaluated in a fully published phase IIb randomised, double-blind, parallel-group, dose-ranging, multicentre study[1] and in four fully published phase III prospective, randomised, double-blind, multicentre clinical trials.[41-44] Results of the four phase III trials [the North American Pentasaccharide in Total Hip Replacement Surgery 2000 (PENTATHLON 2000),[41] Pentasaccharide in Major Knee Surgery (PENTAMAKS),[43] European Pentasaccharide Hip Elective Surgery (EPHESUS),[44] and Pentasaccharide in Hip-Fracture (PENTHIFRA)[42] studies] were part of a worldwide VTE prevention programme involving over 7000 patients undergoing major orthopaedic surgery. In all four studies patients were randomised to either subcutaneous fondaparinux sodium 2.5mg once daily (starting between 4 and 8 hours postoperatively, with the second dose ≥12 hours after the first dose) or to the standard enoxaparin regimen (30mg twice daily in North America, starting between 12 and 24 hours postoperatively, and 40mg once daily in Europe, starting 10 to 14 hours preoperatively, with the second dose 12 to 24 hours postoperatively). Patients were treated for 9 days or until the predischarge venogram, no earlier than the fifth day. The prespecified primary analysis was the comparison of VTE incidence up to day 11. Secondary efficacy outcomes included total, proximal or distal DVT or symptomatic VTE up to day 11 and symptomatic VTE up to day 49.[41-44]

Phase II Study

- In the phase IIb study, 933 patients received subcutaneous fondaparinux sodium 0.75, 1.5, 3, 6 or 8mg or subcutaneous enoxaparin 30mg, for the prevention of DVT and PE after total hip replacement.[1] Subcutaneous fondaparinux sodium was administered within 6 ± 2 hours after surgery and then once daily at 8 am. Subcutaneous enoxaparin was administered initially within 12 to 24 hours after surgery, and subsequently every 12 hours at 8 am and 8 pm in accordance with the approved regimen of enoxaparin. The study continued for 10 days, or until the predischarge venogram that was no earlier than 5 days after surgery. Assignment to the fondaparinux sodium 8mg and 6mg groups was stopped early in the trial because of the incidence of major bleeding events, according to strict predefined safety rules. Of the original 933 patients, 593 were included in the intent-to-treat efficacy analysis.[1]

- All doses of fondaparinux sodium reduced the risk of DVT/PE substantially. A clear dose-response effect was shown, with the incidence of thromboembolism decreasing proportionally as the dose increased ($p = 0.002$).[1] The fondaparinux sodium 3mg group had a lower rate of thromboembolism (1.7%) than both the 0.75mg (11.8%, $p = 0.003$) and 1.5mg (6.7%, p value not reported) groups and the enoxaparin 30mg recipients (9.4%, $p = 0.01$).[1] The relative risk reduction (RRR) for fondaparinux sodium 3mg versus enoxaparin 30mg was 82%. Two patients in the fondaparinux sodium 0.75mg group developed PE during the treatment period and one patient treated with enoxaparin died of PE during follow-up.[1]

Phase III Studies

- In a European hip replacement or revision study, the EPHESUS study,[44] 1827 of 2309 patients were evaluable for efficacy analysis. Compared to enoxaparin, fondaparinux sodium treatment significantly reduced the incidence of VTE in patients undergoing hip replacement or revision at day 11 (4 *vs* 9%; $p < 0.0001$) [figure 1a]; patients treated with fondaparinux sodium had a 55.9% RRR of VTE ($p < 0.0001$) when compared with the enoxaparin group.[44]

- In the PENTAMAKS study,[43] 724 of 1049 patients who underwent elective major knee surgery in 64 centres in North America were eligible for evaluation. By day 11, significantly fewer patients

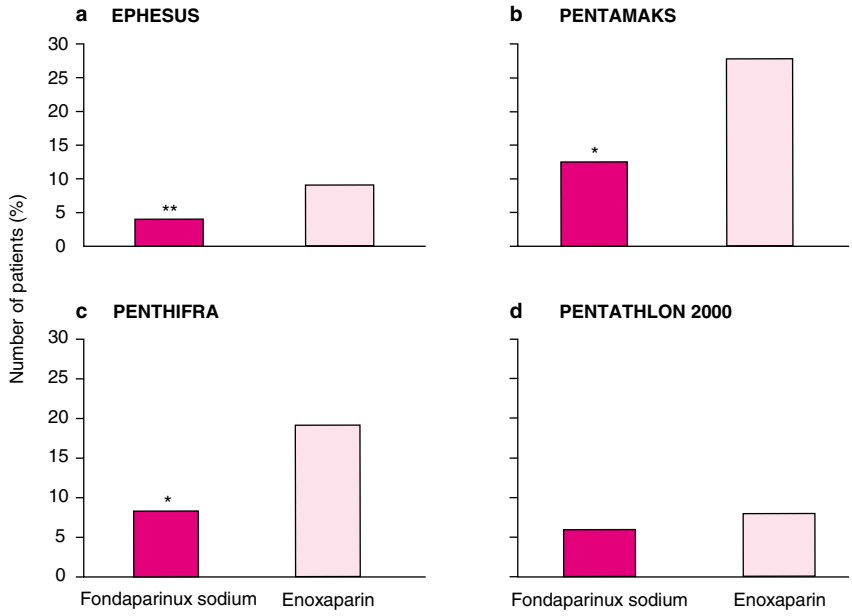


Fig. 1. Efficacy of fondaparinux sodium versus enoxaparin. Incidence of venous thromboembolism (VTE) by the 11th day after major orthopaedic surgery in patients treated with once-daily subcutaneous fondaparinux sodium (F) compared with treatment using the standard enoxaparin (E) regimen. Four randomised, prospective, double-blind, multicentre, phase III trials were part of a worldwide VTE prevention programme involving over 7000 patients undergoing major orthopaedic surgery. Evaluable patients in **(a)** the European Pentasaccharide Hip Elective Surgery (EPHESUS) study[44] were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 908) or E 40mg once daily starting preoperatively (n = 919);[44] **(b)** the Pentasaccharide in Major Knee Surgery (PENTAMAKS) study[43] were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 361) or E 30mg twice daily starting postoperatively (n = 363);[43] **(c)** the (Pentasaccharide in Hip-Fracture) PENTHIFRA study[42] were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 626) or E 40mg once daily starting preoperatively (n = 624)[42] and **(d)** the North American Pentasaccharide in Total Hip Replacement Surgery 2000 (PENTATHLON 2000) study[41] were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 787) or E 30mg twice daily starting postoperatively (n = 797).[41] Patients were treated for 9 days or until the predischarge venogram, no earlier than day 5. The prespecified primary analysis was the comparison of VTE incidence up to day 11. * $p < 0.001$, ** $p < 0.0001$ *vs* E.

treated with fondaparinux sodium had evidence of VTE than patients treated with enoxaparin (12.5% *vs* 27.8%, $p < 0.001$) [figure 1b]; the RRR of VTE in favour of fondaparinux sodium versus enoxaparin was 55.2% ($p < 0.001$).[43]

• The PENTHIFRA study[42] evaluated 1250 of 1711 patients undergoing surgery for fracture of the upper third of the femur in 99 multinational centres. By the primary endpoint (day 11 of the study) there was a significant reduction in the incidence of DVT (evidenced by venography) in patients treated with fondaparinux sodium than in enoxaparin recipients (8.3 *vs* 19.1%; $p < 0.001$) [figure 1c]. Efficacy analysis showed a RRR of VTE of 56.4% ($p < 0.001$) in favour of fondaparinux sodium.[42]

• PENTATHLON 2000[41] studied 2275 patients undergoing hip replacement or revision in centres in Australia and North America. Analysis of the 1584 evaluable patients showed that at day 11, fewer patients treated with fondaparinux sodium than with enoxaparin had evidence of VTE (6 *vs* 8%); however, this reduction was not statistically significant [figure 1d]. The RRR of VTE (26.3%) was clinically relevant and favoured fondaparinux sodium over enoxaparin.[41]

Meta-Analysis of the Four Trials

• Results of this global VTE prevention programme comparing fondaparinux sodium treatment with enoxaparin demonstrated that fondaparinux sodium had a major clinical benefit in the prevention of VTE following major orthopaedic surgery, with a lower overall incidence of VTE (6.8 *vs* 13.7%) and an overall risk reduction (RR) of 55.2% favouring fondaparinux sodium over enoxaparin.[45] Furthermore, the RR values for total hip replacement (45.3%),[46] hip fracture (61.6%)[45] and major knee (63.1%)[45] surgery were similar. The incidence of proximal (1.3 *vs* 2.9%) or distal (5.2 *vs* 10.8%) DVT up to day 11 also favoured prophylaxis with fondaparinux sodium over enoxaparin (no p-values reported) and the RR for proximal DVT was 57.4%.[45]

• The majority of patients in both treatment arms (>90%) in all four phase III studies were followed up to day 49.[41-44] Between the first and 49th day after surgery, few patients receiving fondaparinux sodium or enoxaparin had died following a PE in the EPHESUS,[44] PENTAMAKS,[43] PENTHIFRA,[42] and PENTATHLON 2000[41] studies. In addition, few patients in either treatment group had developed nonfatal PEs by day 49 in these studies.[41-44] The incidence of fatal or nonfatal pulmonary embolism after treatment with fondaparinux sodium or enoxaparin by days 11 and 49 was low (<1%) and did not differ between the treatment groups.[45]

4. Tolerability

Phase II Study

• The phase IIb study[1] indicated that the proportion of patients with a major bleeding event was not significantly different from that of enoxaparin 30mg in the fondaparinux sodium 3mg group (3.5 *vs* 4.5%), and less than that in the fondaparinux sodium 1.5mg group (3.5 *vs* 0.5%, p = 0.05). This study established accurate dose-response curves for safety and efficacy and identified the optimal dose range for future clinical trials.[1]

• The incidence of minor bleeding events with fondaparinux sodium 0.75mg reported in the phase IIb study was lower (0.5%) than with enoxaparin (3.1%), and was similar to that with enoxaparin at doses of fondaparinux sodium 1.5, 3, 6 and 8mg (2.7, 3.4, 2.8 and 3.8% respectively).[1]

Phase III Studies

• The primary tolerability outcome in all phase III studies[41-44] was the incidence of major bleeding [including fatal bleeding, bleeding involving a critical organ or requiring reoperation, and overt bleeding with a bleeding index ≥2 (calculated as [number of units transfused] + [prebleeding Hb values – postbleeding Hb values])]. Secondary outcomes included death, minor bleeding, a need for transfusion, thrombocytopenia and any other adverse event. All patients receiving the study drug were included in the tolerability analysis. A meta-analysis[45] of the four phase III studies[41-44] reported that fondaparinux sodium 2.5mg had a similar tolerability profile, including clinically relevant bleeding events, to that of the standard enoxaparin regimen (figure 2).

• Patients treated with either fondaparinux sodium (n = 1140) or enoxaparin (n = 1133) in the EPHESUS study had a similar low incidence of major bleeding events by day 11, with a bleeding index ≥2 observed in 4% of fondaparinux recipients and 3% of those treated with enoxaparin; very few patients (<0.5%) in either treatment group experienced bleeding requiring reoperation (5 *vs* 3 patients) [figure 3a]. Secondary adverse events were infrequent and their incidence in both treatment groups was similar.[44]

• Patients in the PENTATHLON 2000 study who received either fondaparinux sodium (n = 1128) or enoxaparin (n = 1129) experienced very few bleeding events (figure 3b). Although more patients receiving fondaparinux sodium had a bleeding index

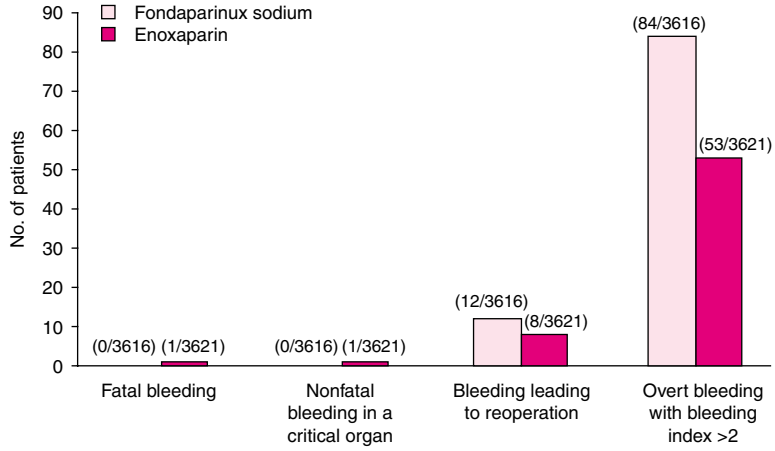


Fig. 2. Incidence of clinically important bleeding events following once-daily subcutaneous fondaparinux sodium (F) or the standard subcutaneous enoxaparin regimen (E). Meta-analysis of data[45] from 3616 patients receiving fondaparinux sodium 2.5mg once daily starting postoperatively and 3621 patients receiving the standard enoxaparin regimen (30mg twice daily in North America, starting between 12 and 24 hours postoperatively, and 40mg once daily in Europe, starting 10 to 14 hours preoperatively, with the second dose 12 to 24 hours postoperatively). Four randomised, prospective, double-blind, multicentre, phase III trials [the European Pentasaccharide Hip Elective Surgery (EPHESUS),[44] North American Pentasaccharide in Total Hip Replacement Surgery 2000 (PENTATHLON 2000),[41] Pentasaccharide in Hip-Fracture (PENTHIFRA),[42] and Pentasaccharide in Major Knee Surgery (PENTAMAKS)[43] studies] were part of a worldwide venous thromboembolism prevention programme in patients undergoing major orthopaedic surgery. The incidence of major bleeding events in all four studies was pooled.[45] Patients were treated for 9 days or until the predischarge venogram, no earlier than the fifth day. The prespecified primary analysis was incidence of a major bleeding event (fatal bleeding, bleeding in critical organ, bleeding leading to reoperation, or bleeding index ≥2). Two major bleeding events (one incident of fatal bleeding and another of nonfatal bleeding in a critical organ) occurred in the enoxaparin treated group; no patients treated with fondaparinux sodium experienced either of these events.[45]

≥2 than enoxaparin recipients (2 *vs* 0.7%), this difference was not statistically significant; treatment was discontinued in 39% (7 of 18 patients with a bleeding index ≥2) of fondaparinux sodium recipients and 63% (5 of 8) of the enoxaparin group. Few patients (0.2%) in each treatment group had bleeding leading to reoperation and one patient in the enoxaparin group had bleeding into a critical organ. The incidence of secondary outcomes with fondaparinux sodium or enoxaparin treatment was similar.[41]

• Patients in the PENTHIFRA study[42] showed a similar tolerability profile to patients in the other phase III studies (figure 3c). By day 11, the most frequent major bleeding event that occurred in >1% of patients in either the fondaparinux sodium (n = 831) or enoxaparin (n = 842) treatment groups was a bleeding index ≥2 (1.8 *vs* 1.9%). One patient treated with enoxaparin died from fatal bleeding; few patients in either group required reoperation because of major bleeding (0.4 *vs* 0.2%).[42] Overall, there was no significant difference in the number of major bleeding events in either treatment group (18 *vs* 19 patients) by day 11. There was little difference between patients treated with fondaparinux sodium and those treated with enoxaparin for secondary adverse events apart from minor bleeding, where significantly more patients treated with fondaparinux sodium experienced minor bleeding (4.1 *vs* 2.1%; p = 0.02).[42]

• In the PENTAMAKS study[43] the most frequent major bleeding event that occurred by day 11 in >1% of patients treated with either fondaparinux sodium (n = 517) or enoxaparin (n = 517) was a bleeding index ≥2 (1.7 *vs* 0%) [figure 3d]; the only other major bleeding event was bleed-

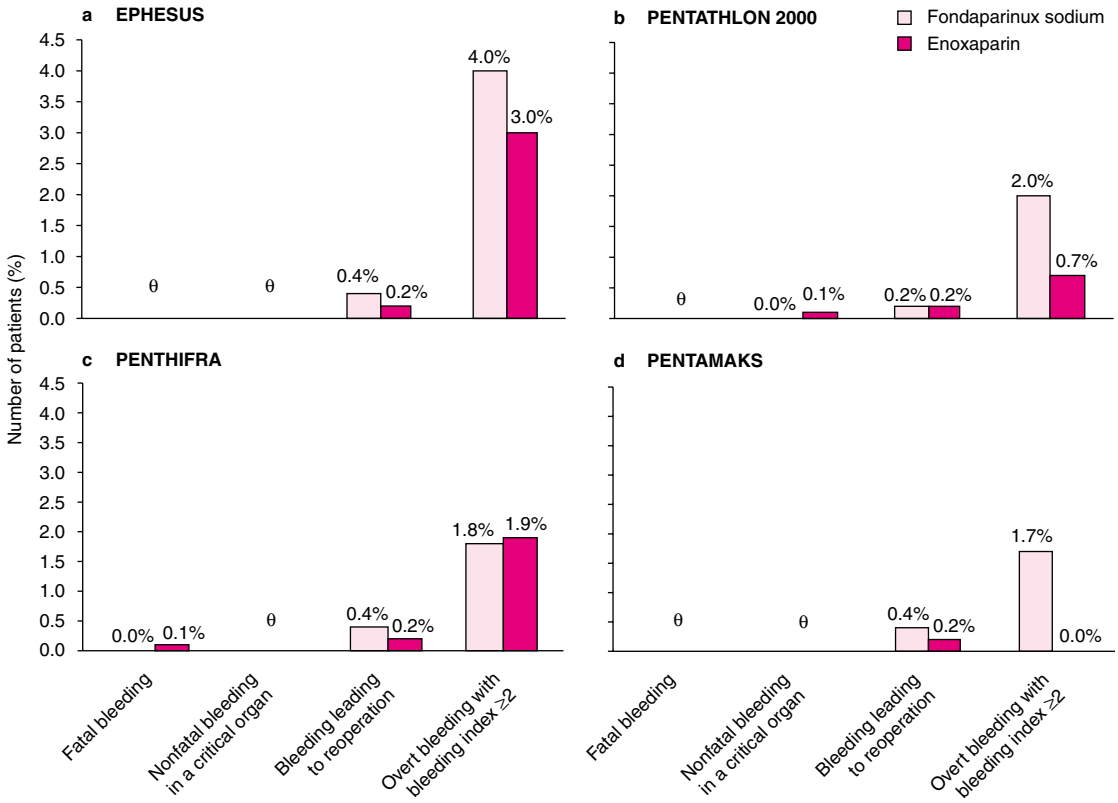


Fig. 3. Incidence of major bleeding events following once-daily subcutaneous fondaparinux sodium (F) or the standard subcutaneous enoxaparin regimen (E). Four randomised, prospective, double-blind, multicentre phase III trials were part of a worldwide venous thromboembolism prevention programme involving over 7000 patients undergoing major orthopaedic surgery. In **(a)** the European Pentasaccharide Hip Elective Surgery (EPHESUS) study,[44] patients were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 1140) or E 40mg once daily starting preoperatively (n = 1133);[44] **(b)** the North American Pentasaccharide in Total Hip Replacement Surgery 2000 (PENTATHLON 2000) study,[41] patients were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 1128) or E 30mg twice daily starting postoperatively (n = 1129);[41] **(c)** the Pentasaccharide in Hip-Fracture (PENTHIFRA) study,[42] patients were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 831) or E 40mg once daily starting preoperatively (n = 842);[42] and **(d)** the Pentasaccharide in Major Knee Surgery (PENTAMAKS) study,[43] patients were randomised to either subcutaneous F 2.5mg starting postoperatively (n = 517) or E 30mg twice daily starting postoperatively (n = 517).[43] Patients were treated for 9 days or until the predischarge venogram, no earlier than the fifth day. The prespecified primary analysis was incidence of a major bleeding event (fatal bleeding, bleeding in critical organ, bleeding leading to reoperation, or bleeding index ≥2). θ = no events in either treatment group.

ing leading to reoperation (0.4 *vs* 0.2%). Although significantly more major bleeding events occurred with fondaparinux sodium treatment than with enoxaparin (11 *vs* 1; p = 0.006), there was no significant difference in clinically important bleeding events (fatal bleeding, bleeding into a critical organ or bleeding requiring reoperation) observed between the two groups.[43] The incidence of secondary adverse outcomes between the two treatment groups did not differ.[43]

• A major complication of using prophylactic anticoagulation with epidural or spinal anaesthesia in orthopaedic surgery is the development of neuraxial haematomas.[3] Although a neuraxial haemotoma developed in one patient in the phase IIb study, this occurred after administration of a dose

of fondaparinux sodium 6mg (a dose considerably greater than the therapeutic dose of 2.5mg) and after several unsuccessful attempts at epidural catheterisation.[47] Regional anaesthesia was used in at least 60% of patients included in the safety analysis in the PENTHIFRA[42] and EPHESUS[44] studies, and in approximately 25% of those in the PENTATHLON 2000[41] and PENTAMAKS[43] studies. No major bleeding in a critical organ (including intraspinal bleeding) occurred with fondaparinux sodium 2.5mg treatment in these studies.[48]

• Fondaparinux sodium does not interact with platelets *in vitro* (see section 1), and has not been reported to cause thrombocytopenia in patients.[41-44]

• Major bleeding rarely occurs in patients undergoing orthopaedic surgery. Although no specific antidote is currently available for fondaparinux sodium,[49] several products are undergoing research and development[50,51] including recombinant activated factor VII.[52]

5. Dosage and Administration

Fondaparinux sodium is indicated for the prevention of VTE after major orthopaedic surgery of the lower limbs, including hip fracture and major knee or hip replacement surgery.[53,54] The recommended dose of fondaparinux sodium in the US and European Union (EU) is 2.5mg once daily as a subcutaneous injection, administered postoperatively.[53,54] The initial dose of fondaparinux sodium should be given at least 6 hours after surgical closure, provided haemostasis has been established. Post hoc analysis demonstrated that there was no relationship between the timing of the first administration of fondaparinux sodium and its efficacy.[48] When fondaparinux sodium is administered at least 6 hours (and up to 12 hours) after surgery, its superior efficacy over enoxaparin is maintained.[48] Conversely, there is a significant relationship between the timing of the first administration of fondaparinux sodium and its tolerability ($p < 0.05$ for the incidence of overt bleeding with a bleeding index ≥2).[48] When fondaparinux sodium is given at least 6 hours after surgical closure (in accordance with its labelling), the tolerability is optimum, with a rate of bleeding similar to that of enoxaparin.[41-44]

6. Fondaparinux Sodium: Current Status

Fondaparinux sodium has demonstrated greater efficacy than and equivalent tolerability to enoxaparin in fully published results of phase III trials and has been approved in the US for the prevention of thromboembolic events following hip fracture, hip replacement and knee replacement surgery.[53] In the EU, the Committee for Proprietary Medicinal Products has approved fondaparinux sodium for the same indications.[55] Ongoing research is investigating other possible applications for fondaparinux sodium: the Rembrandt investigators have evaluated fondaparinux sodium in the treatment of symptomatic DVT as an alternative to LMWH's in a phase II study.[56] A large phase III programme is underway in the treatment of DVT and PE.[57] Several thromboprophylaxis phase III studies in patients with a high risk of VTE are ongoing, including patients undergoing abdominal surgery (the PEGASUS and APOLLO studies)[58,59] and a study in medical patients with an increased risk of DVT (the ARTEMIS study).[60] In addition, preliminary studies have assessed the efficacy and tolerability of fondaparinux sodium for the treatment of acute myocardial infarction [the Pentasaccharide as an Adjunct to Fibrinolysis in ST-Elevation Acute Myocardial Infarction (PENTALYSE) study],[61] unstable angina [the Pentasaccharide in Unstable Angina (PENTUA) study][62,63] and in coronary angioplasty.[64]

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