Fondaparinux vs Enoxaparin for the Prevention of Venous Thromboembolism in Major Orthopedic Surgery

A Meta-analysis of 4 Randomized Double-blind Studies

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Background: Orthopedic surgery remains a condition at high risk of venous thromboembolism (VTE). Fondaparinux, the first of a new class of synthetic selective factor Xa inhibitors, may further reduce this risk compared with currently available thromboprophylactic treatments.

Methods: A meta-analysis of 4 multicenter, randomized, double-blind trials in patients undergoing elective hip replacement, elective major knee surgery, and surgery for hip fracture (N=7344) was performed to determine whether a subcutaneous 2.5-mg, once-daily regimen of fondaparinux sodium starting 6 hours after surgery was more effective and as safe as approved enoxaparin regimens in preventing VTE. The primary efficacy outcome was VTE up to day 11, defined as deep vein thrombosis detected by mandatory bilateral venography or documented symptomatic deep vein thrombosis or pulmonary embolism. The primary safety outcome was major bleeding.

Results: Fondaparinux significantly reduced the incidence of VTE by day 11 (182 [6.8%] of 2682 patients) compared with enoxaparin (371 [13.7%] of 2703 patients), with a common odds reduction of 55.2% (95% confidence interval, 45.8% to 63.1%; $P<.001$); this beneficial effect was consistent across all types of surgery and all subgroups. Although major bleeding occurred more frequently in the fondaparinux-treated group ($P=.008$), the incidence of clinically relevant bleeding (leading to death or reoperation or occurring in a critical organ) did not differ between groups.

Conclusion: In patients undergoing orthopedic surgery, 2.5 mg of fondaparinux sodium once daily, starting 6 hours postoperatively, showed a major benefit over enoxaparin, achieving an overall risk reduction of VTE greater than 50% without increasing the risk of clinically relevant bleeding.

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DESPITE THE USE of currently available thromboprophylactic treatments, venous thromboembolism (VTE) is still frequent, and it remains a life-threatening complication in patients undergoing major orthopedic surgery.[1,2] Thus, there is still a need for improved thromboprophylactic treatment in these patients. The pentasaccharide fondaparinux is the first of a new class of synthetic antithrombotic agents that acts through specific inhibition of factor Xa, devoid of direct activity against thrombin (factor IIa).[3-5] This inactivation of factor Xa via antithrombin results in effective inhibition of thrombin generation.[6,7] Fondaparinux sodium is 100% bioavailable when administered subcutaneously and does not undergo metabolism. In healthy volunteers, fondaparinux exhibits a linear pharmacokinetic profile with little variability between subjects.[8] The half maximum plasma concentration is reached within 25 minutes, and the dose-independent elimina-

tion half-life is 15 hours, allowing once-daily administration.

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The fondaparinux clinical program was designed to compare the efficacy and safety of fondaparinux with low-molecular-weight heparin for the prevention of VTE in patients undergoing major orthopedic surgery of the lower limbs. Low-molecular-weight heparin was chosen as the comparator because it has been reported to be more effective than warfarin in hip and knee replacement surgery.[1] More than 8000 patients (age, 18-101 years; body weight, 30-226 kg) have been studied in phase 2 and 3 clinical trials. In all these trials, the primary assessment for efficacy was based on bilateral venography, the standard recommended method for the evaluation of new antithrombotic drugs in patients undergoing major orthopedic procedures.[9,10] A postoperative start of fondaparinux was cho-

sen to maximize convenience and safety. In a dose-ranging study of 0.75 to 8.0 mg of fondaparinux sodium once daily, starting 6 hours postoperatively, in patients undergoing hip replacement surgery, a statistically significant dose response for the prevention of VTE was demonstrated.[11] Moreover, the results of this study suggested that fondaparinux had the potential to improve significantly the risk-benefit ratio for VTE prophylaxis compared with low-molecular-weight heparin.[11] Based on these results, a 2.5-mg, once-daily dosage of fondaparinux sodium, starting postoperatively, was selected for the 4 phase 3 studies.

Two phase 3 studies were conducted in elective hip replacement surgery, the European Pentasaccharide Hip Elective Surgery Study (EPHESUS) (N=2309)[12] and the Pentasaccharide in Total Hip Replacement Surgery Study (PENTATHLON) 2000 (N=2275),[13] 1 in elective major knee surgery (the Pentasaccharide in Major Knee Surgery Study [PENTAMAKS]; N=1049),[14] and 1 in hip fracture surgery (the Pentasaccharide in Hip Fracture Surgery Study [PENTHIFRA]; N=1711).[15] The efficacy and safety of this fondaparinux dosage was compared with the 2 subcutaneous dosages of enoxaparin recommended for use in orthopedic surgery by health authorities and the manufacturer, that is, 40 mg once daily, starting 12 hours preoperatively,[12,15] and 30 mg twice daily, starting 12 to 24 hours after surgery.[13,14] These 4 studies were planned with the same comparative drug, end points, and adjudication committee, with the purpose of subsequently performing a meta-analysis of their data. We report herein the results of this meta-analysis.

PATIENTS AND METHODS

STUDY DESIGN

The 4 multicenter studies were conducted as randomized, parallel-group, double-blind clinical trials. In all 4 studies, the day of surgery was defined as day 1. Treatment was scheduled to last up to days 5 to 9 after surgery. Patients were then followed up in person, by mail, or telephone between days 35 and 49 after surgery. These studies were conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and Good Clinical Practice guidelines and local regulations. The protocol was approved by independent ethics committees or institutional review boards, where applicable, and written informed consent was obtained from all patients before randomization.

PATIENT POPULATION

Patients aged at least 18 years were considered for inclusion if they were scheduled for primary elective total hip replacement surgery or revision of at least 1 component of a previously implanted total hip prosthesis,[12,13] elective major knee surgery (ie, surgery requiring resection of the distal end of the femur or proximal end of the tibia or revision of at least 1 component of a previously implanted total knee prosthesis),[14] or standard surgery for fracture of the upper third of the femur, including femoral head and neck (if surgery was planned within 48 hours after admission).[15]

In PENTHIFRA,[15] patients were excluded if they presented multiple trauma affecting more than 1 organ system or if more than 24 hours had elapsed between the causative trauma

and hospital admission. In the 3 other studies, patients were excluded if bilateral joint surgery was planned during the same procedure or within 2 weeks after inclusion.[12-14] As usual in thromboprophylaxis studies, other main reasons for exclusion, common to the 4 studies, were as follows: active bleeding; acute bacterial endocarditis; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; planned indwelling intrathecal or epidural catheter during the study treatment period; unusual difficulty in achieving epidural or spinal anesthesia (eg, more than 2 attempts); hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contrast medium; contraindication to anticoagulant therapy; current addictive disorders; serum creatinine concentration above 2.04 mg/dL (180 µmol/L) in a well-hydrated patient; and platelet count below 100×10^9/L. Patients who required anticoagulant therapy for chronic comorbid conditions were also excluded. The use of any type of anticoagulant, antiplatelet, fibrinolytic agent, or dextran within a few days prior to randomization was discouraged. However, the use of aspirin prior to enrollment was not an exclusion criterion.

RANDOMIZATION OF THE PATIENTS, MEDICATIONS, AND DOSING SCHEDULE

In all studies, patients were randomly assigned to receive subcutaneously either fondaparinux sodium (Arixtra; Sanofi-Synthelabo, Paris, France, and NV Organon, Oss, the Netherlands) or enoxaparin sodium (Clexane, Klexane, or Lovenox; Aventis Pharma, Bridgewater, NJ) in a double-blind manner. In the 2 studies (PENTAMAKS and PENTATHLON 2000) comparing 2.5 mg of fondaparinux sodium once daily, starting 6 hours after surgery, with the 30-mg twice-daily regimen of enoxaparin (the regimen recommended for use by North American health authorities and the manufacturer) starting 12 to 24 hours after surgery, randomization took place immediately after surgery.[13,14] In the 2 studies (PENTHIFRA and EPHESUS) comparing 2.5 mg of fondaparinux sodium once daily, starting 6 hours after surgery, with the 40-mg once-daily regimen of enoxaparin sodium (the regimen recommended for use by health authorities and the manufacturer) starting 12 hours before surgery and followed by a second injection 12 to 24 hours after surgery, randomization took place before surgery.[12,15] In all 4 studies, the protocol required that the first injection of fondaparinux be administered 6±2 hours after surgery and the second injection at least 12 hours after the first one but no more than 24 hours after surgical closure. However, in the PENTHIFRA study, fondaparinux was started 12±2 hours before surgery if surgery was delayed 24 to 48 hours after admission.[15]

The following recommendations were given to the investigators of the 4 studies: throughout the treatment period, intermittent pneumatic compression, dextran, and thrombolytic or anticoagulant agents were prohibited; centers were instructed to avoid the use of aspirin or nonsteroidal anti-inflammatory drugs whenever possible; other antiplatelet agents were prohibited; the use of graduated compression stockings was allowed and that of physiotherapy was recommended; investigators could extend prophylaxis during follow-up with any currently available therapy, but only after venography had been performed; and in the event that VTE occurred during the study, treatment was left to the investigator's discretion.

OUTCOME MEASURES

The primary outcome with respect to efficacy was VTE (defined as deep vein thrombosis [DVT], pulmonary embolism [PE], or both) up to day 11. Secondary efficacy outcomes included

total, proximal, and distal-only DVT and symptomatic VTE up to day 11 and PE (fatal and nonfatal) up to day 49. Patients were systematically examined for DVT by mandatory ascending bilateral contrast venography of the legs[16] between days 5 and 11, but no more than 2 days after the last study drug injection, or earlier if thrombosis was clinically suspected. Symptomatic PE was confirmed by high-probability lung scanning, pulmonary angiography,[17] helical computed tomography, or, in the event of death, at autopsy.

The primary safety outcome was major bleeding, which included the 4 following categories: fatal bleeding; bleeding that was retroperitoneal, intracranial, intraspinal, or involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more. The bleeding index was calculated as the number of units of packed red blood cells or whole blood transfused plus prebleeding minus postbleeding hemoglobin values in grams per deciliter. Secondary safety outcomes were death, other bleeding, transfusion requirements, thrombocytopenia, and any other adverse events.

During the treatment period, the investigator performed daily assessments for signs and symptoms of VTE. During follow-up, patients were instructed to report any symptoms or signs of VTE or bleeding and any other clinical event occurring since treatment completion. Efficacy outcomes, including review of all venograms, bleeding, and death, were adjudicated by a central independent committee, the members of which were unaware of the patients' treatment assignment.

STATISTICAL ANALYSIS AND APPROPRIATENESS OF POOLING

All 4 studies were superiority studies designed to demonstrate a risk reduction for VTE of 30% in 2 studies[14,15] and 45% in the 2 others.[12,13] The primary efficacy outcome analysis included data on all patients who had received at least 1 dose of study medication, undergone the appropriate surgery, and had an adequate VTE assessment by day 11. Safety analysis included data on patients who had received at least 1 dose of study medication.

Odds reductions with 95% confidence intervals (CIs) for each study and each type of surgery were calculated and presented graphically for the primary efficacy end point. Before pooling all the efficacy data, the homogeneity among the 4 studies, between the 2 hip replacement studies, and among the 3 types of surgery were tested using the Zelen exact test. The common odds reduction was estimated with 2-sided 95% CIs using a stratified exact approach. In addition, odds reductions with 95% CIs not adjusted by study were calculated according to predefined covariates. An odds reduction equal to 1 indicates no difference between the treatments; less than 1, fondaparinux is better; and more than 1, enoxaparin is better. Safety parameters were analyzed by summing the numbers of events observed in each study. To explore whether a relationship exists between main efficacy or safety outcomes and timing of the first injection of fondaparinux, we performed a post hoc analysis using a logistic regression model.

RESULTS

STUDY POPULATIONS AND PATIENT CHARACTERISTICS

Between November 1998 and January 2000, 7344 patients were randomized in 375 centers worldwide (Argentina, Australia, Canada, 18 European countries, New Zealand, South Africa, and the United States). One hundred seven patients did not receive any study drug, leaving 7237 (98.5%) available for the analysis of safety (**Table 1**); 26 patients did not undergo appropriate surgery. Venography could not be performed or could not be evaluated in 1826 of the patients who did not develop a symptomatic objectively documented venous thromboembolic event by day 11. Thus, 5385 patients (73.3%) were included in the analysis of primary efficacy, a percentage similar to that usually reported in large multicenter studies using bilateral venography in orthopedic surgery.[18-22]

Baseline characteristics did not differ significantly between the 2 groups in patients analyzed for safety (**Table 2**) or for primary efficacy (data not shown). Similarly, for each type of operation, specific surgical characteristics were comparable between the 2 groups (**Table 3**). In 45.8% of patients in the fondaparinux-treated group and in 44.3% in the enoxaparin-treated group, anesthesia was regional only. The median time between surgery and primary efficacy assessment was 7 days in the fondaparinux group and 8 days in the enoxaparin group, with most patients being assessed between days 5 and 11 as planned. The 2 groups did not differ in regard to the last day of active treatment or use of concomitant treatments up to day 11 (**Table 4**).

Table 1. Patients Included in the Analyses and Reasons for Exclusion*

	Fondaparinux Group	Enoxaparin Group
Randomized	3668 (100)	3676 (100)
Not treated	52 (1.4)	55 (1.5)
Inclusion/exclusion criteria not met	23 (0.6)	26 (0.7)
Informed consent withdrawn	12 (0.3)	17 (0.5)
Adverse event	5 (0.1)	3 (0.1)
Death	2 (0.1)	1 (0.0)
Other	10 (0.3)	8 (0.2)
Treated with at least 1 dose of study drug (evaluable for safety)	3616 (98.6)	3621 (98.5)
Not evaluable for primary efficacy	934 (25.5)	918 (25.0)
No surgery or inappropriate surgery	13 (0.4)	13 (0.4)
Venography not done or inadequate	921 (25.1)	905 (24.6)
Venography not done	535 (14.6)	509 (13.8)
Inadequate venography	386 (10.5)	396 (10.8)
Evaluable for primary efficacy	2682 (73.1)	2703 (73.5)

*Data are number (percentage) of patients.

Table 2. Characteristics of Treated Patients at Baseline

Characteristic	Fondaparinux Group (n = 3616)	Enoxaparin Group (n = 3621)
Mean ± SD age, y	68.0 ± 12.9	68.2 ± 12.9
Male/female sex, No.	1440/2176	1442/2179
Mean ± SD weight, kg	77.3 ± 18.5	76.8 ± 18.6
Mean ± SD body mass index, kg/m²*	27.4 ± 5.6	27.3 ± 5.7
Body mass index ≥30 kg/m², No. (%)*	907 (25.7)	970 (27.6)
Previous venous thromboembolism, No. (%)*	149 (4.1)	179 (4.9)
Orthopedic surgery within the previous 12 mo, No. (%)*	367 (10.1)	332 (9.2)

*In both treatment groups, data were missing for some patients.

Table 3. Surgical Characteristics by Treatment Group (Treated and Operated-On Patients)*

Characteristic	Fondaparinux Group	Enoxaparin Group
Elective Hip Replacement		
Type of surgery		
Primary	1950/2257 (86.4)	1956/2253 (86.8)
Revision	307/2257 (13.6)	297/2253 (13.2)
Use of cement	1251/2255 (55.5)	1271/2249 (56.5)
Mean ± SD duration of surgery, h:min	2:25 ± 0:53	2:26 ± 0:55
Hip Fracture		
Type of fracture		
Cervical only	400/831 (48.1)	388/839 (46.3)
Trochanteric†	373/831 (44.9)	368/839 (43.9)
Subtrochanteric	58/831 (7.0)	82/839 (9.8)
Type of surgery		
Total prosthesis	56/831 (6.7)	58/841 (6.9)
Half prosthesis	193/831 (23.2)	183/841 (21.8)
Osteosynthesis‡	582/831 (70.0)	600/841 (71.3)
Use of cement	176/831 (21.2)	183/841 (21.8)
Mean ± SD duration of surgery, h:min	1:41 ± 0:39	1:44 ± 0:44
Elective Major Knee Replacement		
Type of surgery		
Primary	478/517 (92.5)	479/517 (92.6)
Revision	39/517 (7.5)	38/517 (7.4)
Use of cement	482/517 (93.2)	484/517 (93.6)
Mean ± SD duration of surgery, h:min	2:07 ± 0:39	2:08 ± 0:42

*Data are number of surgical procedures number of patients (percentage) unless otherwise specified.
†Not associated with any subtrochanteric fracture.
‡This category included nailing, screwing, plate, and any type of combined surgery.

Table 4. Treatments Received During the Study Treatment Period by Patients Assessed for Primary Efficacy*

Treatment	Fondaparinux Group (n = 2682)	Enoxaparin Group (n = 2703)
Study treatment		
Last day of active treatment†		
Before day 5	35 (1.3)	45 (1.7)
Day 5 to day 9	2593 (96.7)	2607 (96.4)
After day 9	54 (2.0)	51 (1.9)
Concomitant treatments		
Prohibited therapy‡	69 (2.6)	73 (2.7)
Discouraged therapy§	775 (28.9)	787 (29.1)
Graduated compression stockings	1933 (72.1)	1919 (71.0)

*Data are number (percentage) of patients.
†Day 1 was the day of surgery.
‡Dextran, anticoagulant, or antiplatelet agents other than aspirin or thrombolytic therapy.
§Nonsteroidal anti-inflammatory agents or aspirin.

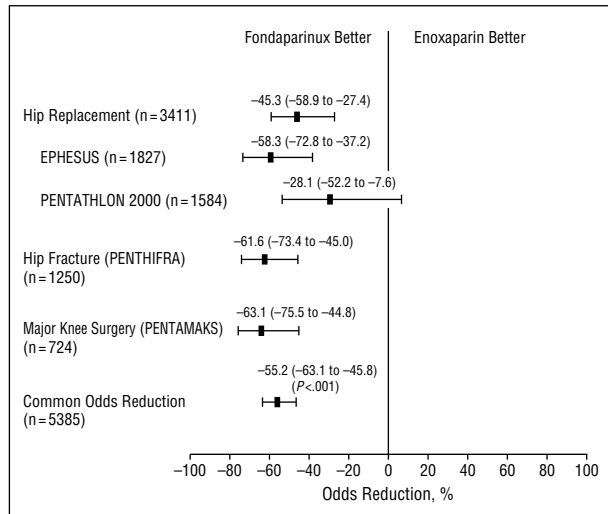**Table 5. Incidence of Venous Thromboembolic Events up to Day 11 (Primary Efficacy Outcome)***

Event	Fondaparinux Group	Enoxaparin Group
Venous thromboembolism (primary outcome)	182/2682 (6.8)	371/2703 (13.7)
Any deep vein thrombosis†	174/2677 (6.5)	363/2698 (13.5)
Any proximal deep vein thrombosis‡	35/2756 (1.3)	81/2775 (2.9)
Distal deep vein thrombosis only‡	141/2704 (5.2)	293/2709 (10.8)

*Data are number of patients with events/number of patients assessed (percentage).
†Venography was not evaluable in 10 patients with pulmonary embolism, 5 in each group. Patients were considered as evaluable when proximal and distal deep veins in both legs were visualized. However, if deep vein thrombosis was seen in any one of the veins visualized, the patient was considered to have reached the end point even if the venous system was not visualized entirely.
‡The number of patients with available data for this parameter was higher than 5385, since visualization of proximal and distal deep veins in both legs was no longer a prerequisite. For instance, a patient was considered evaluable for proximal deep vein thrombosis provided that the proximal deep veins in both legs were visualized, irrespective of whether the distal veins were entirely visualized.

All but 36 patients in the fondaparinux group and 34 patients in the enoxaparin group were followed up to day 49. Follow-up duration was comparable between the 2 groups. Of the 6687 patients who did not receive treatment for an acute thromboembolic event in hospital, 1396 (40.9%) in the fondaparinux group and 1340 (41.0%) in the enoxaparin group received prolonged thromboprophylaxis, on the investigator's initiative, primarily with heparins or vitamin K antagonists.

INCIDENCE OF VTE

The overall incidence of VTE up to day 11 was lower in the fondaparinux group than in the enoxaparin group (182 [6.8%] of 2682 patients compared with 371 [13.7%] of 2703) (**Table 5**). The common odds reduction of 55.2% in favor of fondaparinux was highly significant ($P<.001$; 95% CI, 45.8%-63.1%) (**Figure 1**). In total hip replacement, hip fracture and major knee replacement surgery patients, the odds reductions for VTE up to day 11 were 45.3%, 61.6%, and 63.1% in favor of fondaparinux, respectively (Figure 1). Similarly, the incidence of total, distal, and proximal DVT up to day 11 was lower in the fondaparinux group than in the enoxaparin group (Table 5). The common odds reduction in favor of fondaparinux for proximal DVT up to day 11 was 57.4% (95% CI, 35.6%-72.3%). The incidence of symptomatic VTE by day

11 was low and did not differ between the 2 groups— 0.6% in the fondaparinux group (22 of 3603 patients) and 0.4% in the enoxaparin group (15 of 3608 patients) ($P=.25$). Fatal PE occurred in 2 (0.1%) and 3 (0.1%) patients in the fondaparinux and enoxaparin groups, respectively. Corresponding figures with respect to nonfatal PE were 9 (0.2%) and 7 (0.2%) patients. Overall, the superiority of fondaparinux over enoxaparin regarding primary efficacy was consistent according to age, sex, obesity (body mass index [calculated as weight in kilograms divided by the square of height in meters] ≥30), type of anesthesia (general or regional only), use of cement, and duration of surgery (**Figure 2**). The number of patients treated for a venous thromboembolic event by day 11, based on the local site assessment of primary efficacy, was significantly lower in the fondaparinux group (199 [5.5%] of 3616 patients) than in the enoxaparin group (351 [9.7%] of 3621 patients) ($P<.001$).
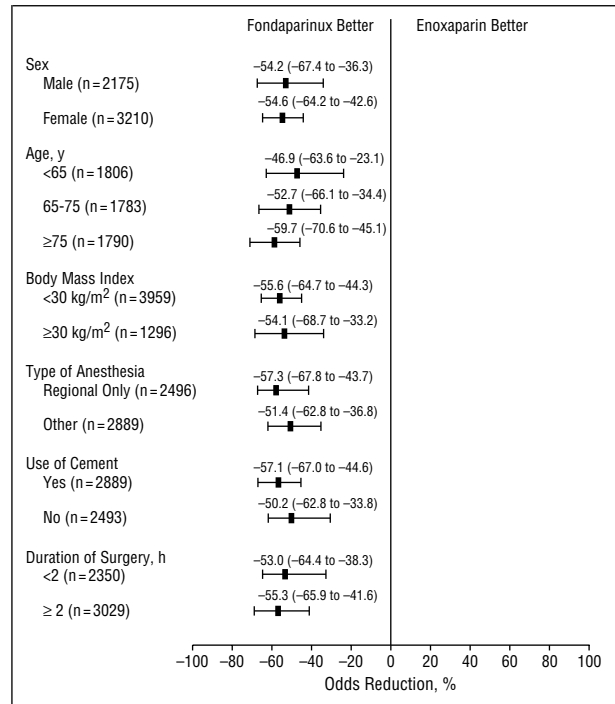
Figure 1. Incidence of venous thromboembolism up to day 11 (primary efficacy). Odds reduction per type of surgery and per study and estimated common odds reduction (exact 95% confidence interval) with fondaparinux relative to enoxaparin. Homogeneity test: *P*=.06 for all studies; *P*=.07 for elective hip replacement studies; *P*=.16 for the 3 types of surgery. Common odds ratio test: *P*<.001. Corresponding relative risks with exact 95% confidence intervals were −55.9% (−72.8% to −33.1%) for the European Pentasaccharide Hip Elective Surgery Study (EPHESUS), −26.3% (−52.8% to 10.8%) for the Pentasaccharide in Total Hip Replacement Surgery Study (PENTATHLON) 2000, −55.2% (−70.2% to −36.2%) for the Pentasaccharide in Major Knee Surgery Study (PENTAMAKS), −56.4% (−70.3% to −39.0%) for the Pentasaccharide in Hip Fracture Surgery Study (PENTHIFRA), −43.0% (−57.9% to −24.6%) for hip replacement (*P*<.001), and −50.6% (−59.1% to −40.9%) for the common reduction in risk.

Between days 1 and 49, the incidence of fatal PE was 0.3% (11 of 3603 patients) and 0.3% (10 of 3608 patients), and for nonfatal PE, 0.5% (19 of 3603 patients) and 0.4% (13 of 3608 patients) in the fondaparinux and enoxaparin groups, respectively.

BLEEDING EPISODES AND DEATH

Overall, there were 96 adjudicated major bleeding events (2.7%) among the 3616 fondaparinux-treated patients compared with 63 (1.7%) among the 3621 enoxaparin-treated patients (*P*=.008, Fisher exact test) up to day 11. There were 2 bleeding events in a critical organ in the enoxaparin group (of which 1 was fatal) compared with none in the fondaparinux group (**Table 6**). Twelve bleeding episodes leading to another operation were reported in the fondaparinux group compared with 8 in the enoxaparin group. Of the 3616 fondaparinux-treated patients, 84 (2.3%) experienced overt bleeding associated with a bleeding index of 2 or more compared with 53 (1.5%) of the 3621 enoxaparin-treated patients. Thus, the difference in major bleeding was mainly accounted for by an excess of bleeding with a bleeding index of 2 or more.

In the post hoc analysis, we examined the relationship between bleeding and the timing of the first fondaparinux injection using a logistic regression model to analyze data from 3422 (95%) of the 3616 patients receiving fondaparinux. This analysis showed that there was a statistically significant relationship between the incidence of major bleeding and the timing (between 3 and 9 hours after surgery) of the first fondaparinux injection (*P*=.008), whereas efficacy was not affected by this

Figure 2. Incidence of venous thromboembolism up to day 11 (primary efficacy). Estimated common odds reduction (95% confidence interval) with fondaparinux relative to enoxaparin according to baseline categorical covariates.

Table 6. Safety Outcomes*

Outcome	Fondaparinux Group (n = 3616)	Enoxaparin Group (n = 3621)
Treatment period (up to day 11)		
Fatal bleeding	0	1 (0.0)
Bleeding in critical organ	0	1 (0.0)
Bleeding leading to another operation	12 (0.3)	8 (0.2)
Bleeding with a bleeding index ≥2†	84 (2.3)	53 (1.5)
Any transfusions‡	1950 (53.9)	1864 (51.5)§
Wound infection	37 (1.0)	29 (0.8)
Complications at surgical site leading to prolonged hospitalization or rehospitalization	52 (1.4)	52 (1.4)
Death from any cause	15 (0.4)	21 (0.6)
Study period (up to day 49)		
Death from any cause	48 (1.3)	52 (1.4)

*Data are number (percentage) of patients.
†The bleeding index was calculated as the number of units of packed red blood cells or whole blood transfused plus prebleeding minus postbleeding hemoglobin (g/dL) values.
‡After the start of study treatment.
§*P* = .04.

timing (*P*=.67). Similarly, there was a statistically significant relationship between the incidence of overt bleeding associated with a bleeding index of 2 or more and the timing of the first fondaparinux injection (*P*=.008) (**Figure 3**).

The incidence of major bleeding did not differ according to whether cement was used (92 [2.4%] of 3847 patients) or not (67 [2.0%] of 3363 patients). The incidence of fatal bleeding, critical organ bleeding, and bleed-
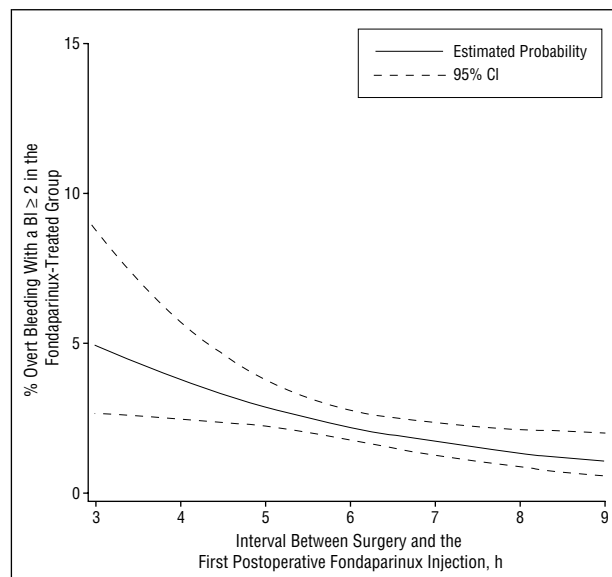
Figure 3. Incidence of overt bleeding associated with a bleeding index (BI) of 2 or more according to the timing of the first postoperative injection of fondaparinux (delay between skin closure and injection, in hours) in fondaparinux-treated patients. Regression logistic model; *P*=.008. CI indicates confidence interval.

ing events leading to reoperation did not differ between the 2 groups, either overall or according to age, sex, obesity, or duration of surgery (data not shown). Other (minor) bleeding events occurred in 3.0% of patients (109 of 3616 patients) in the fondaparinux group and in 2.7% (99 of 3621 patients) in the enoxaparin group. By day 49, 48 (1.3%) and 52 (1.4%) patients in the fondaparinux and enoxaparin groups, respectively, had died.

OTHER ADVERSE EVENTS

No episode of decreased platelet count was reported as a serious adverse event in either group. The 2 groups did not differ with respect to the occurrence of any other adverse events during the treatment or follow-up period. The incidence of wound infection by day 11 was low and did not differ between the 2 groups: 1.0% (37 of 3616 patients) in the fondaparinux group and 0.8% (29 of 3621 patients) in the enoxaparin group. Similarly, the incidence of complications at the surgical site leading to prolonged hospitalization or rehospitalization did not differ between the 2 groups (Table 6).

COMMENT

The fondaparinux prophylaxis program in orthopedic surgery, involving 7344 patients, was specifically designed to allow an overview analysis to determine the efficacy and safety of the drug in all major orthopedic settings. The results show that 2.5 mg of fondaparinux sodium once daily, starting 6 hours after surgery, significantly reduced the rate of VTE by 55.2% compared with enoxaparin sodium. Prior meta-analyses of thromboprophylaxis in orthopedic surgery demonstrated that low-molecular-weight heparin consistently reduced the risk of DVT compared with placebo,[23,24] unfractionated heparin,[23-29]

and warfarin sodium,[27,29] and it is now considered a reference treatment in these patients.[1] The superior efficacy of fondaparinux over enoxaparin was demonstrated in all types of surgery, with a reduction in risk of 45.3%, 61.6%, and 63.1% in hip replacement, hip fracture, and major knee surgery, respectively. Moreover, it was demonstrated in all subgroups of patients irrespective of age, sex, obesity, type of anesthesia, use of cement, and duration of surgery. Similarly, compared with enoxaparin, fondaparinux reduced the incidence of proximal DVT, which is more prone to embolize,[30-32] with a reduction in risk of 57.4%. Publication bias is commonly acknowledged to be an important limitation of meta-analyses. However, the results of our meta-analysis do not represent an optimistic estimate of the treatment effect; they represent the total of phase 3 clinical experience with fondaparinux.

A number of factors could have contributed to the superior efficacy of fondaparinux over enoxaparin. These include (1) the different mechanisms of action of the 2 anticoagulants, fondaparinux being a pure factor Xa inhibitor while enoxaparin inhibits both factor Xa and thrombin; (2) the longer half-life of fondaparinux with an anticoagulant effect that lasts for 24 hours after a single injection; or (3) the regimen of fondaparinux, the first injection of which was 6±2 hours after surgery in all 4 studies, which was carefully selected based on the results of a large phase 2 dose-finding trial[12] in comparison with the recommended regimens of enoxaparin. Of note, in the fondaparinux-treated patient group, there was no significant relationship between the incidence of VTE and the timing of the first injection.

In our meta-analysis, the incidence of clinical PE was low (<1% during both the treatment and follow-up periods) and did not differ between the 2 groups. These rates are likely to be lower than would have been observed in clinical practice because most patients with positive venography at screening received anticoagulant therapy in therapeutic doses, and about 40% of the remaining patients who were free of VTE at day 11 received prolonged prophylaxis with heparins or warfarin after the study treatment period.

The use of pharmacological prophylaxis in patients undergoing major orthopedic surgery is of concern because of the potential increased risk of bleeding.[1] The incidence of major bleeding with low-molecular-weight heparin in this group has been reported to range from 0.9% to 11.7% in previous meta-analyses.[23,25,33,34] However, the definition of major bleeding was heterogeneous across studies. In the 4 fondaparinux prophylaxis studies, the incidence of bleeding events was low in both treatment groups. By day 11, no fatal bleeding or bleeding involving a critical organ occurred with fondaparinux compared with 2 occurrences with enoxaparin, and bleeding led to another operation in 0.3% of patients in the fondaparinux group compared with 0.2% in the enoxaparin group. Bleeding associated with a bleeding index of at least 2 was more frequent in patients receiving fondaparinux than in those receiving enoxaparin. However, the clinical relevance of a bleeding index of 2 or more is uncertain because it was not reflected as a difference in fatal bleeding, critical organ bleeding, bleeding lead-

ing to another operation, wound infection, or complications at the surgical site leading to prolonged hospitalization or rehospitalization between the 2 groups. Thus, we conclude that when compared with the 2 approved regimens of enoxaparin, the administration of fondaparinux starting 6 hours after surgery did not result in an increased risk of clinically relevant bleeding. In addition, there was an inverse relationship between the occurrence of bleeding with a bleeding index of 2 or more and the timing of the first injection of fondaparinux.

When this first injection was given 6 hours or more after skin closure, the occurrence of a positive bleeding index decreased and became similar to that found in the enoxaparin group.

In conclusion, this meta-analysis shows that 2.5 mg of fondaparinux once daily, starting 6 hours after surgery, was superior to the approved enoxaparin regimens in preventing VTE without increasing the risk of clinically relevant bleeding in patients undergoing major orthopedic surgery.

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