Emerging Options for Thromboprophylaxis After Orthopedic Surgery: A Review of Clinical Data

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In four randomized, controlled studies of patients undergoing orthopedic surgery, the antithrombotic efficacy and safety of subcutaneous fondaparinux 2.5 mg once/day were compared with those of subcutaneous enoxaparin regimens that were approved by the United States Food and Drug Administration. In patients undergoing elective hip replacement surgery, fondaparinux significantly reduced the frequency of venous thromboembolism (VTE). However, in a second trial that compared fondaparinux with enoxaparin 30 mg twice/day beginning 12–24 hours after surgery, a 26% risk reduction in favor of fondaparinux was not statistically significant. In patients undergoing elective knee replacement surgery, fondaparinux significantly reduced the risk of VTE compared with enoxaparin without increasing the risk of clinically relevant bleeding, although the risk of major bleeding defined by the bleeding index was significantly higher with fondaparinux. Fondaparinux was superior to enoxaparin 40 mg once/day in the setting of hip fracture surgery, with no increased risk of major bleeding. Meta-analysis of the four studies confirms the superior antithrombotic efficacy of fondaparinux over enoxaparin in orthopedic surgery and suggests that the risk of major bleeding is similar to that of enoxaparin when the first dose of fondaparinux is given at least 6 hours after surgery.

Key Words: thromboprophylaxis, orthopedic surgery, fondaparinux, enoxaparin, efficacy, safety.

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The efficacy and safety of thromboprophylaxis with fondaparinux were established in an international phase III clinical trial program consisting of four randomized, parallel-group, double-blind studies.[1–4] Since many experts considered low-molecular-weight heparin (LMWH) to be the most effective option for prophylaxis against venous thromboembolism (VTE) in patients undergoing orthopedic surgery,[5] all four studies compared fondaparinux head-to-head with enoxaparin. Patients in these studies received either subcutaneous fondaparinux 2.5 mg/day or subcutaneous enoxaparin in a regimen that was approved by the United States Food and Drug Administration (FDA), that is, either 40 mg/day or 30 mg twice/day.[6] (These enoxaparin regimens are approved for hip or knee replacement surgeries. Enoxaparin is not approved for hip fracture surgery.)

All four studies in the clinical trial program[1–4] used identical outcome measures for thromboprophylactic efficacy and safety (Table 1) to facilitate combined analysis. The primary efficacy outcome of adjudicated VTE was defined as a composite of both symptomatic and asymptomatic deep vein thrombosis (DVT) and symptomatic pulmonary embolism. Efficacy outcomes were confirmed through the use of routine ascending bilateral contrast venography of the legs between days 5 and 11, or earlier if thrombosis was suspected by the investigator. Any suspected pulmonary embolism was

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Table 1. Outcome Measures for Efficacy and for Safety and Exclusion Criteria in the Four Phase III Trials of Fondaparinux[1–4]

Efficacy Measures	Safety Measures	Exclusion Criteria
Primary outcome	Primary outcome	Pregnancy
Adjudicated VTE to day 11 (DVT, pulmonary embolism, or both)	Major bleeding	Active bleeding
	Fatal bleeding	Acute bacterial endocarditis
	Bleeding into critical organ	Congenital or acquired bleeding disorder
Secondary outcomes	Bleed leading to repeat surgery	Hemorrhagic stroke in previous 3 mo
Any DVT	Bleed with bleeding index ≥ 2	Ulcerative or angiodysplastic gastrointestinal disease
Proximal DVT	Secondary outcomes	Brain, spinal, or ophthalmologic surgery in previous 3 mo
Distal DVT	Minor bleeding	Planned indwelling intrathecal or epidural catheter for > 6 hrs after surgery
Symptomatic VTE to day 11	Transfusions	Patients who required or received anticoagulation within 2 days of study
Symptomatic VTE to day 49	Units transfused (replacing volume)	Hypersensitivity to heparin, LMWH, pork, or iodinated contrast media
	Death (any cause)	Serum creatinine level > 2 mg/dl despite hydration
		Platelet count < 100 x 10^3/mm^3
		Contraindication to anticoagulation
		Concurrent addictive disease

VTE = venous thromboembolism; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin.

confirmed by high-probability lung scanning, pulmonary angiography, spiral computed tomography, or autopsy. The primary safety outcome of major bleeding was defined as a composite of fatal bleeding, bleeding into a critical organ (retroperitoneal, intracranial, intraspinal, or into other critical organs), bleed leading to repeat surgery, and overt bleeding with a bleeding index of 2 or higher. The bleeding index was defined as the number of whole blood or packed red blood cell units transfused plus the difference between the prebleeding and postbleeding hemoglobin values in grams/deciliter. Results of the clinical trial program of fondaparinux for thromboprophylaxis in orthopedic surgery are summarized below.

Elective Hip Replacement Surgery

Venous thromboembolism is a common complication after total hip replacement surgery. Despite prophylaxis with recommended measures such as LMWH, warfarin, or intermittent pneumatic compression, approximately 16–22% of patients undergoing elective hip replacement surgery will experience a venographically proved DVT.[5] Moreover, symptomatic DVT or pulmonary embolism occurs before hospital discharge in approximately 1% of patients in United States hospitals who undergo total hip replacement.[7] Patients who experience VTE after orthopedic surgery have increased morbidity and mortality, have a longer length of stay, and incur significantly greater costs than those who do not experience this complication.[7] More effective thromboprophylaxis would be expected to reduce the frequency of these complications and thus improve the quality of care of patients undergoing elective hip replacement surgery.

The European Pentasaccharide Hip Elective Surgery Study (EPHESUS)[1] and the Pentasaccharide in Total Hip Replacement Surgery Study (PENTATHLON 2000)[2] compared the efficacy and safety of fondaparinux with two FDA-approved enoxaparin regimens in the prevention of VTE in patients undergoing elective hip replacement surgery. Patients were eligible if they were aged 18 years or older and were scheduled for primary elective total hip replacement surgery or revision of at least one component of a previously implanted total hip prosthesis. Exclusion criteria for these phase III clinical trials are listed in Table 1.

In EPHESUS, the first dose of fondaparinux 2.5 mg was given 6 hours (range 4–8 hrs) after surgery, with the second dose given no sooner than 12 hours after the first dose. Fondaparinux then was administered once/day for 5–9 days after surgery. The patients who were randomly assigned to the enoxaparin arm received 40 mg once/day in accordance with FDA-approved labeling. In 78% of these patients, the first dose

Table 2. Efficacy Outcomes to Day 11: EPHESUS[1]

Event	Fondaparinux[a]	Enoxaparin[a]	p Value
Adjudicated VTE	37/908 (4)	85/919 (9)	<0.0001
Any DVT	36/908 (4)	83/918 (9)	<0.0001
Proximal DVT	6/922 (1)	23/927 (2)	<0.0021
Distal DVT	30/909 (3)	67/917 (7)	<0.0001
Symptomatic VTE	5/1129 (0.4)	3/1123 (0.3)	0.73

EPHESUS = European Pentasaccharide Hip Elective Surgery Study; VTE = venous thromboembolism; DVT = deep vein thrombosis.
[a]Data are no. of patients with event/no. of evaluable patients (%).

was administered 12 hours before surgery, with the second injection given 12–24 hours after surgery; subsequent dosing was once/day. In the other 22% of patients, the first dose of enoxaparin was administered after rather than before surgery mainly because of the use of regional anesthesia during surgery. Like fondaparinux, enoxaparin was continued for 5–9 days after surgery.

The proportion of patients who developed VTE in EPHESUS was significantly lower in the fondaparinux arm than in the enoxaparin arm (Table 2). The relative risk reduction in the primary end point (adjudicated VTE) was 55.9% with fondaparinux compared with enoxaparin. Significant risk reductions in some secondary end points (any DVT, proximal DVT, and distal DVT) were also seen. Treatment of VTE was left up to the discretion of the investigator, and many patients with DVT detected with venography received treatment. Significantly fewer patients in the fondaparinux group than in the enoxaparin group were treated for VTE by day 11 (4% vs 9%, p<0.001). No significant difference in symptomatic VTE was observed. The low rate of symptomatic VTE by day 49 (1% in both groups) may reflect the early diagnosis and treatment of venographically detected asymptomatic DVT and the relatively large number of patients (52% in both groups) who received extended prophylaxis after day 11. No significant differences were noted in any of the safety outcomes during the study or up to day 49. The number of patients who experienced major or minor bleeding was low in both groups (Table 3).

Table 3. Safety Outcomes to Day 11: EPHESUS[1]

Outcome	Fondaparinux[a] (n=1140)	Enoxaparin[a] (n=1133)
Primary		
Fatal bleeding	0 (0)	0 (0)
Bleeding into critical organ	0 (0)	0 (0)
Repeat surgery due to bleed	5 (< 1)	3 (< 1)
Bleeding index ≥ 2	42 (4)	29 (3)
Secondary		
Minor bleeding	44 (4)	38 (3)
Transfusions after surgery	714 (63)	690 (61)
Units transfused	2	2
Death	0 (0)	2 (0.2)

EPHESUS = European Pentasaccharide Hip Elective Surgery Study.
[a]Data are no. (%) of patients for all outcomes except units transfused, which are the mean no. of units/patient.

In the PENTATHLON 2000 trial,[2] patients assigned to the enoxaparin arm received 30 mg twice/day beginning 12–24 hours after surgery, in accordance with FDA-approved labeling. The efficacy outcomes of PENTATHLON 2000 are displayed in Table 4. A trend to superiority of fondaparinux over enoxaparin was observed in the primary end point of adjudicated VTE; however, unlike in EPHESUS, this difference did not reach statistical significance. Significant differences favoring fondaparinux were observed in rates of some secondary outcome measures (such as any DVT and distal DVT), and a nonsignificantly larger number of patients in the enoxaparin arm than in the fondaparinux arm were treated for VTE (7% vs 5%, p=0.086).

A curious finding in PENTATHLON 2000 was the difference in symptomatic VTE favoring enoxaparin over fondaparinux (1% vs 0.1% at day 11, p=0.006; 3% vs 1% at day 49, p=0.01). The reason for the observed difference in symptomatic VTE at 49 days is unclear but could reflect the higher rate of extended prophylaxis (for patients who were not treated for a thrombotic event) that occurred in the enoxaparin arm compared with the fondaparinux arm (28% vs 25%, p=0.186). It has been established that extended prophylaxis reduces the risk of late-occurring symptomatic VTE, so the difference in late-occurring symptomatic VTE should be interpreted with caution.[8] Furthermore, since DVT was detected at venography more frequently in patients assigned to enoxaparin than to fondaparinux, more patients in the enoxaparin

Table 4. Efficacy Outcomes: PENTATHLON 2000[2]

Event	Fondaparinux[a]	Enoxaparin[a]	p Value
Adjudicated VTE	48/787 (6)	66/797 (8)	0.099
Any DVT	44/784 (6)	65/796 (8)	0.047
Proximal DVT	14/816 (2)	10/830 (1)	0.42
Distal DVT	34/796 (4)	54/800 (7)	0.037
Symptomatic VTE	10/1126 (1)	1/1128 (0.1)	0.0062

PENTATHLON = Pentasaccharide in Total Hip Replacement Surgery Study; VTE = venous thromboembolism; DVT = deep vein thrombosis.
[a]Data are no. of patients with event/no. of evaluable patients (%).

arm received anticoagulation after surgery. This too would be expected to reduce the rate of late-occurring symptomatic VTE complications. Thus, the finding of decreased symptomatic events up to day 49 in the enoxaparin arm of PENTATHLON 2000 is unlikely to represent a clinically meaningful advantage of enoxaparin over fondaparinux in practice. The more frequent use of extended prophylaxis and therapeutic anticoagulation in the enoxaparin arm likely changed the natural history of the disease and probably accounts for the difference in symptomatic events seen up to day 49. No significant differences in any of the primary or secondary safety outcomes were observed in PENTATHLON 2000 (Table 5).

Table 5. Safety Outcomes to Day 11: PENTATHLON 2000[2]

Outcome	Fondaparinux[a] (n=1128)	Enoxaparin[a] (n=1129)
Primary		
Fatal bleeding	0 (0)	0 (0)
Bleeding into critical organ	0 (0)	1 (0.1)
Repeat surgery due to bleed	2 (0.2)	2 (0.2)
Bleeding index ≥ 2	18 (2)	8 (0.7)
Secondary		
Minor bleeding	17 (2)	24 (2)
Transfusions after surgery	593 (53)	555 (49)
Units transfused	2	2
Death	3 (0.3)	1 (0.1)

PENTATHLON = Pentasaccharide in Total Hip Replacement Surgery Study.
[a]Data are no. (%) of patients for all outcomes except units transfused, which are the mean no. of units/patient.

Elective Major Knee Surgery

Failure to provide thromboprophylaxis in patients undergoing total knee replacement surgery is associated with a prevalence of venographically proved VTE of 40–84%.[5] Commonly recommended antithrombotic measures, such as LMWH, warfarin, and intermittent pneumatic compression, reduce this rate to 28–47%.[5] In fact, approximately 1% of patients in the United States experience symptomatic VTE during hospitalization for their orthopedic procedure.[7] These complications are associated with increased morbidity and mortality, a longer length of stay, and significantly greater costs than when VTE does not occur.[7] Thus, more effective thromboprophylaxis should improve the quality of care of patients who undergo elective major knee surgery.

The Pentasaccharide in Major Knee Surgery Study (PENTAMAKS)[3] compared the efficacy and safety of fondaparinux 2.5 mg/day beginning 6 hours (range 4–8 hrs) after surgery with enoxaparin 30 mg twice/day beginning 12–24 hours after surgery, in accordance with FDA-approved labeling. The design of PENTAMAKS was similar to that of the other phase III studies in the clinical trial program. Efficacy and safety outcomes, as well as exclusion criteria, were identical for all of the trials (Table 1).

The efficacy outcomes for PENTAMAKS are presented in Table 6. Compared with enoxaparin, fondaparinux reduced the relative risk of adjudicated VTE by 55.2%. Fondaparinux also significantly reduced the relative risk of the secondary end points of any DVT (by 54.1%) and distal DVT (by 55.9%) compared with enoxaparin. There was a trend toward reduced proximal DVT with fondaparinux compared with enoxaparin (relative risk reduction 54.5%, p=0.06). As was seen in EPHESUS, significantly more patients were treated for VTE in the enoxaparin group (25.1%) than in the fondaparinux group (15.1%, p<0.001). In addition, 19% of patients assigned to fondaparinux and 20% of those assigned to enoxaparin received extended prophylaxis. It is likely that the frequent use of extended prophylaxis and the early detection and treatment of DVT account for the lack of a significant difference in the rate of symptomatic VTE seen

Table 6. Efficacy Outcomes to Day 11: PENTAMAKS[3]

Event	Fondaparinux[a]	Enoxaparin[a]	p Value
Adjudicated VTE	45/361 (12.5)	101/363 (27.8)	<0.001
Any DVT	45/361 (12.5)	98/361 (27.1)	<0.001
Proximal DVT	9/368 (2.4)	20/372 (5.4)	0.06
Distal DVT	35/372 (9.4)	78/366 (21.3)	<0.001
Symptomatic VTE	3/517 (0.6)	7/517 (1.4)	0.34

PENTAMAKS = Pentasaccharide in Major Knee Surgery Study; VTE = venous thromboembolism; DVT = deep vein thrombosis.
[a]Data are no. of patients with event/no. of evaluable patients (%).

by day 49 (1.0% vs 1.9%, p=0.3).

A significant difference in major bleeding between fondaparinux and enoxaparin was observed in the PENTAMAKS trial. Overall, major bleeding occurred in 11 patients assigned to fondaparinux and 1 patient assigned to enoxaparin (p=0.006). This difference can be attributed to nine cases of major bleeding associated only with a bleeding index of 2 or more in patients receiving fondaparinux (Table 7). In these cases, bleeding was at the surgical site in seven patients, and the study drug was discontinued in three of the nine patients. Since the drug was continued in most of the patients with a bleeding index of 2 or more, the clinical relevance of this finding is open to question. The rates of minor bleeding, need for transfusion, and other adverse events did not differ significantly between the two groups.

Table 7. Safety Outcomes to Day 11: PENTAMAKS[3]

Outcome	Fondaparinux[a] (n=517)	Enoxaparin[a] (n=517)
Primary		
Fatal bleeding	0 (0)	0 (0)
Bleeding into critical organ	0 (0)	0 (0)
Repeat surgery due to bleed	2 (0.4)	1 (0.2)
Bleeding index ≥ 2	9 (1.7)	0 (0)
Secondary		
Minor bleeding	14 (2.7)	19 (3.7)
Transfusions after surgery	222 (42.9)	197 (38.1)
Units transfused	1.9	1.8
Death	2 (0.4)	3 (0.6)

PENTAMAKS = Pentasaccharide in Major Knee Surgery Study.
[a]Data are no. (%) of patients for all outcomes except units transfused, which are the mean no. of units/patient.

Hip Fracture Surgery

The rate of venographically proved DVT is 24–27% in patients undergoing hip fracture surgery, despite recommended thromboprophylactic options. Fatal pulmonary embolism occurs in 4–13% of patients undergoing surgery for hip fracture repair who do not receive any thromboprophylaxis. Symptomatic VTE occurs in approximately 1.3% of patients in the United States who are hospitalized for hip fracture surgery.[7] These events are associated with increased morbidity and mortality, a longer length of stay, and significantly greater costs of treating the patient who is hospitalized with hip fracture.[7] More effective thromboprophylaxis would be expected to improve outcomes in patients who undergo hip fracture surgery.

The Pentasaccharide in Hip-Fracture Surgery Study (PENTHIFRA)[4] compared fondaparinux 2.5 mg/day with enoxaparin 40 mg/day. In the enoxaparin group, the first dose was given 12 hours before surgery and the second 12–24 hours after surgery, whereas the first fondaparinux dose was administered 6 hours (range 4–8 hrs) after surgery. However, if surgery was to be delayed 24–48 hours after admission, fondaparinux was administered 12 hours before surgery. In addition, if spinal or epidural anesthesia was planned, preoperative injections were omitted. Fondaparinux was given preoperatively to 11% of patients, whereas enoxaparin was given preoperatively to approximately 25% of patients. Study design, exclusion criteria, and efficacy and safety measures were identical to those of the previously mentioned trials (Table 1). However, patients in PENTHIFRA were excluded if they presented with trauma affecting more than one organ system, if more than 24 hours had elapsed between trauma and hospitalization, or if surgery would be performed more than 48 hours after admission.

The risk of the primary end point of adjudicated VTE was reduced by 56.4% with fondaparinux compared with enoxaparin (Table 8). The risks of the secondary end points of any DVT, proximal DVT, and distal DVT were reduced by 58.2%, 78.7%, and 55.4%, respectively, with fondaparinux compared with enoxaparin

Table 8. Efficacy Outcomes to Day 11: PENTHIFRA[4]

Event	Fondaparinux[a]	Enoxaparin[a]	p Value
Adjudicated VTE	52/626 (8.3)	119/624 (19.1)	<0.001
Any DVT	49/624 (7.9)	117/623 (18.8)	<0.001
Proximal DVT	6/650 (0.9)	28/646 (4.3)	<0.001
Distal DVT	42/627 (6.7)	94/626 (15.0)	<0.001
Symptomatic VTE	4/831 (0.5)	4/840 (0.5)	<1.00

PENTHIFRA = Pentasaccharide in Hip-Fracture Surgery Study; VTE = venous thromboembolism; DVT = deep vein thrombosis.
[a]Data are no. of patients with event/no. of evaluable patients (%).

(p<0.001 for all). Significantly more patients in the enoxaparin arm than in the fondaparinux arm were treated for VTE (11.7% vs 6.1%, p<0.001). Furthermore, of the patients who were not treated for a VTE, 58.5% of patients in the fondaparinux group and 55.8% of patients treated with enoxaparin received prolonged thromboprophylaxis. This very high rate of extended prophylaxis combined with early detection and treatment of VTE probably accounts for the very low frequency and similar symptomatic event rates by day 49 in the two groups. No significant difference in the rates of major bleeding was seen in PENTHIFRA (Table 9). However, minor bleeding occurred more commonly in the fondaparinux arm (4.1% vs 2.1%, p=0.02). The PENTHIFRA trial established fondaparinux as a safe and efficacious agent for VTE prophylaxis after hip fracture surgery. It is currently the only product approved by the FDA for this indication.

Table 9. Safety Outcomes to Day 11: PENTHIFRA[4]

Outcome	Fondaparinux[a] (n=831)	Enoxaparin[a] (n=842)
Primary		
Fatal bleeding	0 (0)	1 (0.1)
Bleeding into critical organ	0 (0)	0 (0)
Repeat surgery due to bleed	3 (0.4)	2 (0.2)
Bleeding index ≥ 2	15 (1.8)	16 (1.9)
Secondary		
Minor bleeding	34 (4.1)	18 (2.1)
Transfusions after surgery	421 (50.7)	422 (50.1)
Units transfused	2.7	2.8
Death	11 (1.3)	16 (1.9)

PENTHIFRA = Pentasaccharide in Hip-Fracture Surgery Study.
[a]Data are no. (%) of patients for all outcomes except units transfused, which are mean no. of units/patient.

Meta-analysis of the Phase III Studies

The very similar or identical designs and outcome measures in the four phase III studies facilitated meta-analysis of the efficacy and safety data.[9] Of the 7344 patients who were randomized into these trials, approximately 25% of patients in both groups could not be included in the efficacy analysis, primarily because venography could not be performed or the images could not be evaluated. There were 7237 patients who received at least one dose of study drug, and their data were therefore available for the analysis of safety. All but 36 patients in the fondaparinux group and 34 patients in the enoxaparin group were followed up until day 49.

The overall frequency of VTE in the fondaparinux-treated patients was 6.8%, compared with 13.7% in those assigned to enoxaparin. The common odds reduction in overall VTE of 55.2% in favor of fondaparinux was significant (p<0.001, 95% confidence interval 45.8–63.1%). Moreover, the common odds reduction in favor of fondaparinux for proximal DVT was 57.4% (95% confidence interval 35.6–72.3%). Superiority of fondaparinux in the common odds reduction for VTE was seen across the three study populations; specifically, 45.3% in total hip replacement, 61.6% in hip fracture surgery, and 63.1% in major knee surgery (p<0.001 for all 3 groups). The number of patients who were treated for VTE was significantly lower in the fondaparinux group (5.5%) than in the enoxaparin group (9.7%, p<0.001). Approximately 41% of both the fondaparinux- and the enoxaparin-treated patients received extended thromboprophylaxis. This, combined with early detection and treatment of VTE, probably accounts for the low rate of symptomatic VTE in the fondaparinux (0.6%) and enoxaparin (0.4%) groups (p=0.25).

The rates of fatal bleeding, bleeding into a critical organ, bleed leading to repeat surgery, and minor bleeding did not differ between the two groups. However, major bleeding events were more common in fondaparinux-treated patients

(2.7%) than in patients treated with enoxaparin (1.7%, p= 0.008). This finding can be attributed largely to increased bleeding events associated only with a bleeding index of 2 or more (in 2.3% of fondaparinux-treated patients vs only 1.5% of enoxaparin-treated patients). Many patients in the phase III trials received fondaparinux sooner than 6 hours after surgery, since the recommended dosing window was 4–8 hours after surgery. A logistic regression model was performed and demonstrated a significant relationship between the frequency of major bleeding and the timing (3–9 hrs after surgery) of the first fondaparinux dose (p=0.008). This model demonstrated that when the first dose of fondaparinux was administered 6 or more hours after surgery, superior efficacy of fondaparinux was maintained, yet the rate of major bleeding became similar to the rate seen in the enoxaparin arm. This finding underscores the importance of waiting 6–8 hours after surgery before administration of the first dose of fondaparinux.

The phase III clinical trial results indicate that fondaparinux is more effective than enoxaparin, with similar major bleeding risks, when dosed according to the recommended labeling. Further study on the efficacy of fondaparinux when dosed the morning after surgery is under way. A study is currently under way to examine the efficacy of fondaparinux when dosed either 6–8 hours after surgery or on the morning of the day after surgery. In the meantime, fondaparinux should not be administered sooner than 6 hours after surgery (to minimize the risk of bleeding) and not later than 8 hours after surgery (to provide optimal antithrombotic efficacy).

Conclusion

The risk of VTE after orthopedic surgery remains high in United States hospitals, with approximately 1% of patients developing VTE during their hospital stay. Efforts directed at improving the quality of care in this patient population must include optimization of thromboprophylaxis regimens. The evidence suggests that fondaparinux reduces the risk of VTE after orthopedic surgery more effectively than enoxaparin, with a similar safety profile.

References

1. **Lassen MR, Bauer KA, Eriksson BI, Turpie AGG, for the European Pentasaccharide Elective Surgery Study (EPHESUS) Steering Committee.** Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002;359:1715–20.
2. **Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the PENTATHLON 2000 Study Steering Committee.** Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002;359:1721–6. (Erratum in Lancet 2002;360:1102.)
3. **Bauer KA, Eriksson BI, Lassen MR, Turpie AGG, for the Steering Committee of the Pentasaccharide in Major Knee Surgery Study.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345:1305–10.
4. **Eriksson BI, Bauer KA, Lassen MR, Turpie AGG, for the Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001;345:1298–304.
5. **Geerts WH, Heit JA, Clagett GP, et al.** Prevention of venous thromboembolism. Chest 2001;119(suppl 1):S132–75.
6. **Aventis Pharmaceuticals Inc.** Lovenox (enoxaparin sodium injection) package insert. Bridgewater, NJ; 2003.
7. **Ollendorf DA, Vera-Llonch M, Oster G.** Cost of venous thromboembolism following major orthopedic surgery in hospitalized patients. Am J Health-Syst Pharm 2002;59:1750–4.
8. **Eikelboom JW, Quinlan DJ, Douketis JD.** Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. Lancet 2001;358:9–15.
9. **Turpie AGG, Bauer KA, Eriksson BI, Lassen MR.** Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833–40.