Patients undergoing major orthopaedic surgical procedures, including total hip arthroplasty (THA), total knee arthroplasty (TKA), and surgery for hip fracture, have a high rate of postoperative venous thromboembolism (VTE). Without thromboprophylaxis, the lowest reported incidence of fatal pulmonary embolism (PE) following hip fracture is 3% to 4%; the corresponding risk of fatal PE in THA and TKA is 0.3% to 0.4%. In addition, VTE causes increased morbidity and is a significant burden on both patients and the health care system.1

Dose-adjusted warfarin, low-molecular-weight heparin (LMWH), and, to a lesser extent, unfractionated heparin (UFH) all have been used as thromboprophylactic agents to reduce the high incidence of VTE associated with major orthopaedic surgery. In this setting, each of these agents has been shown to decrease the risk of VTE compared with no prophylaxis. However, it is important to continue to seek methods to reduce even further the absolute residual rate of deep vein thrombosis (DVT) in this population. Selective factor Xa inhibitors represent a new class of agents. Fondaparinux, a synthetic, selective, factor Xa inhibitor, has been approved for VTE prevention in patients undergoing THA, TKA, and hip fracture surgery based on its efficacy and comparable safety in clinical trials against the LMWH enoxaparin. Fondaparinux also received regulatory approval for extended (4-week) prophylaxis based on findings of a 96% risk reduction in venographically detected DVT and an 88% risk reduction in symptomatic VTE events in patients receiving 4-week versus 1-week treatment after hip fracture surgery.2

Structure and Mechanism of Action

Fondaparinux is a sulfated pentasaccharide manufactured by total chemical synthesis3 (Fig. 1). Because it is produced synthetically, there is no batch-to-batch structural variation or risk of transmissible disease resulting from pathogen contamination, as theoretically exists for therapeutic animal-source heparins (UFH and LMWH). The structure of fondaparinux is based on the sequence in heparin molecules that binds to antithrombin, the primary endogenous inhibitor of coagulation. This binding promotes a conformational change in antithrombin that leads to marked enhancement in its basal rates of factor Xa and thrombin (factor IIa) inactivation. By design, the sulfation pattern in fondaparinux differs from that of the native pentasaccharide sequence in heparin, resulting in a much higher binding affinity to antithrombin and, therefore, more efficient anticoagulation. Although the pentasaccharide structure of fondaparinux is sufficient for binding to antithrombin and for enhancement of antithrombin-mediated factor Xa inactivation, it lacks the additional residues present in heparin that are required for catalyzing antithrombin-mediated thrombin inactivation. Thus, fondaparinux exerts its anticoagulant effect in an antithrombin-dependent mechanism of action in which selective enhancement of factor Xa inactivation, without any effect on thrombin activity, leads to the inhibition of thrombin generation and consequently inhibition of fibrin formation. This is in contrast to the heparins, which catalyze the inactivation of both factor Xa and thrombin. For heparins, the degree of thrombin inhibition varies by

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type of heparin (UFH or LMWH) and by the particular LMWH preparation.

**Pharmacokinetics**

Following subcutaneous administration of a single 2.5-mg dose (the prophylactic dose), fondaparinux is rapidly absorbed and exhibits 100% bioavailability, reaching its half-maximal and maximal plasma concentrations within 25 ± 5 minutes and 1.7 ± 0.4 hours, respectively. The drug’s half-life is approximately 17 hours, and it is cleared by the kidneys. Fondaparinux exhibits a favorable and predictable pharmacokinetic profile, with linear dose-dependent factor Xa inhibition observed within the drug’s therapeutic range of plasma concentration (<2 mg/L). Unlike the heparins, particularly UFH, its binding properties are functionally specific. The major proportion of the drug binds to antithrombin, and there is minimal nonspecific binding to other plasma proteins or cellular components. As a result, there is a predictable dose response with little individual variability. No dose adjustments for age or sex are recommended. Collectively, these features allow for subcutaneous, once-daily, fixed fondaparinux dosing without any requirement for monitoring the drug’s anticoagulant effect. Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance, <30 mL/min), and it should be used with caution in patients with moderate renal impairment (creatinine clearance, 30 to 50 mL/min). With the heparins, the risk of osteopenic complications and heparin-induced thrombocytopenia due to a high degree of nonspecific cellular binding is of considerable concern. Because fondaparinux does not suppress osteoblast formation, does not activate osteoclasts, and does not activate platelets, the risk of these serious complications with fondaparinux use is highly unlikely.

**Indications for Use**

Fondaparinux is approved in both North America and Europe for standard, short-term thromboprophylaxis after THA, TKA, and hip fracture surgery. It is currently the only agent approved in the United States for short-term and extended prophylaxis in the hip fracture setting. These indications were based on the findings of four phase III clinical trials of short-term fondaparinux prophylaxis in THA, TKA, and hip fracture surgery and one phase III clinical trial of extended fondaparinux prophylaxis in hip fracture surgery (Table 1).

The fondaparinux phase III clinical program in major orthopaedic surgery included four multicenter, international, randomized, controlled, double-blind trials—two in THA and one each in TKA and hip fracture surgery—all with the same central independent adjudication committee. Based on phase II dose-finding studies of VTE prophylaxis in THA, fondaparinux 2.5 mg as a single daily dose was determined to be the most appropriate dose for subsequent phase III studies. The phase III trials compared the efficacy and safety of fondaparinux (2.5 mg daily subcutaneously injected, starting 6 ± 2 hours postoperatively) with one of two approved enoxaparin regimens (40 mg daily subcutaneously, starting 12 ± 2 hours preoperatively, or 30 mg twice daily subcutaneously, starting 12 to 24 hours postoperatively) (Table 1). Prophylaxis was continued for 7 ± 2 days. The primary efficacy end point was the incidence of VTE up to postoperative day 11, defined as DVT detected by mandatory bilateral venography or confirmed symptomatic DVT or PE. The primary safety end point was the incidence of major bleeding, defined as fatal bleeding, major organ bleeding, bleeding leading to reoperation, or overt bleeding with a bleeding index ≥2. (The bleeding index was calculated as the number of units of packed red cells or whole blood transfused plus the hemoglobin values before the bleeding episode minus the hemoglobin values after the episode [g/dL]). In each of the four trials, fondaparinux was associated with a lower incidence of VTE at 11 days compared with standard enoxaparin regimens, with three of the four trials demonstrating a significant (P < 0.001) reduction in favor of fondaparinux and one THA study showing no difference between the groups (Table 1).

As defined by the design of the phase III clinical trial program, this efficacy benefit of fondaparinux was reflected in greater reductions in venographically confirmed DVT rates. As revealed in a meta-analysis of the four phase III trials in THA, TKA, and hip fracture surgery, fondaparinux led to a >50% overall reduction in VTE risk (55.2% common odds reduction; P < 0.001) relative to standard enoxaparin regimens. This efficacy benefit was achieved with no increase in clinically relevant bleeding and no influence of age, gender, body mass index, type and length of surgery, or anesthesia specifics (Table 1).

Overall differences in the rate of major bleeding between the fondaparinux and enoxaparin groups were restricted to an increased incidence of an overt bleeding
event with a bleeding index ≥2 in those receiving fondaparinux (84/3,616 [2.3%] versus 53/3,621 [1.5%]).9 The rate of bleeding was significantly greater in TKA compared with THA and hip fracture surgery. The clinical relevance of this bleeding parameter, however, remains unclear. Importantly, as demonstrated in a recent post hoc analysis of patients who received their first dose of fondaparinux between 3 and 9 hours postoperatively, the timing of administration of the initial dose seems to play a role in its safety with respect to bleeding. In patients, including frail subpopulations (age ≥75 years, weight ≤110 lb [50 kg], or with moderate renal impairment [30 to 50 mL/min]), who received injections of active fondaparinux at least 6 hours after skin closure, the incidence of major bleeding episodes was 1.8%, similar to the overall 1.7% incidence observed for approved enoxaparin regimens in the original phase III findings.9,11 The recommendation is that, when fondaparinux is used for VTE prophylaxis in major orthopaedic surgery, the first dose should be administered at least 6 to 8 hours postoperatively to avoid increased bleeding risk.

A second post hoc analysis based on the phase III clinical trial program examined the relationship between the duration of VTE prophylaxis (up to 11 days) and efficacy.12 Efficacy increased significantly (P < 0.001) the longer the duration of postoperative prophylaxis for both fondaparinux and enoxaparin (fondaparinux VTE incidence: ≤5 days, 8.7%; 6 to 8 days, 6.7%; 9 to 11 days, 5.2%; enoxaparin VTE incidence: ≤5 days, 17.0%; 6 to 8 days, 13.4%; 9 to 11 days, 11.7%). However, the superior efficacy of fondaparinux relative to enoxaparin was demonstrated independent of prophylaxis duration.12 Thus, placing in context the collective findings from the timing and duration post hoc analyses, the best benefit-to-risk profile occurs when fondaparinux is given for at least 9 to 11 days postoperatively, with the first dose administered 6 to 8 hours after surgery.

The results of the duration post hoc analysis—for the major orthopaedic setting overall—anticipated to some extent the findings of the PENTHIFRA Plus trial, which evaluated the use of extended duration (4-week) fondaparinux thromboprophylaxis.2 In this double-blind multicenter trial, 656 patients were randomized to either fondaparinux 2.5 mg subcutaneously once daily or placebo for 19 to 23 days, following a prerandomization course of standard, short-term (6 to 8 days) fondaparinux

### Table 1

| Indication (No. of patients enrolled) | Dose | Enoxaparin n/N (%) | Fondaparinux n/N (%) | RRR (95% CI) | P value | Bleeding index ≥2 |
|--------------------------------------|------|--------------------|----------------------|--------------|---------|------------------|
| Elective hip replacement surgery (2,309)* | 2.5 mg (Fon) qd vs 40 mg (Eno) qd starting preoperatively for 5 to 9 days* | 85/919 (9.2) | 37/908 (4.1) | −55.9 (−72.8 to −33.1) | <0.001 | 4.0% vs 3.0% |
| Elective hip replacement surgery (2,275)† | 2.5 mg (Fon) qd vs 30 mg (Eno) bid starting postoperatively for 5 to 9 days† | 66/797 (8.3) | 48/787 (6.1) | −26.4 (−25.8 to 10.8) | 0.099 | 2.0% vs 0.7% |
| Hip fracture surgery (1,711)§ | 2.5 mg (Fon) qd vs 40 mg (Eno) qd starting preoperatively for 5 to 9 days* | 119/624 (19.1) | 52/626 (8.3) | −56.4 (−70.3 to −39.0) | <0.001 | 1.8% vs 1.9% |
| Elective knee replacement surgery (1,049)¶ | 2.5 mg (Fon) qd vs 30 mg (Eno) bid starting postoperatively for 5 to 9 days‡ | 101/363 (27.8) | 45/361 (12.5) | −55.2 (−70.2 to −36.2) | <0.001 | 1.7% vs 0.0% |
| Major orthopaedic surgery (7,344)‖ | 2.5 mg (Fon) qd vs 30 mg (Eno) bid or 40 mg (Eno) qd for 5 to 9 days | 371/2,703 (13.7) | 182/2,682 (6.8) | −50.6 (−59.1 to −40.9) | <0.001 | 2.3% vs 1.5% |
| Hip fracture surgery (737)‖ | Postoperatively 2.5 mg (Fon) qd for 25 to 31 days vs postoperatively 2.5 mg (Fon) qd for 7 ± 1 days, then placebo for 21 ± 2 days | 77/220 (35.0) | 3/208 (1.4) | −95.9 (−99.7 to −87.2) | <0.001 | 1.8% vs 0.0% |

* = Regimen approved worldwide.
† = North American–approved regimen.
CI = confidence interval, Eno = enoxaparin, Fon = fondaparinux, n = number of patients experiencing the event, N = total number of patients assessed for this event, RRR = relative reduction in risk.
The primary efficacy outcome was VTE incidence over the double-blind phase of the study, defined as DVT detected by bilateral venography or symptomatic DVT or PE. The primary safety outcome was major bleeding, defined as described for the fondaparinux phase III clinical trials. Extended fondaparinux prophylaxis reduced the incidence of all VTE to 1.4% versus 35.0% with placebo—a 95.9% reduction in risk in favor of fondaparinux ($P < 0.001$). There was a parallel significant ($P = 0.02$) 88.8% reduction in the risk of symptomatic VTE compared with placebo, reflecting a decrease from a 2.7% incidence of symptomatic events with placebo to 0.3% with extended-duration fondaparinux.2 The efficacy benefit of 4-week fondaparinux thromboprophylaxis was achieved without any statistically significant increase in major bleeding (2.4% versus 0.6% with placebo; $P = 0.06$).2 Similar low rates of VTE were observed even in patients considered to be at particularly high risk of VTE because of female sex, increased age, or impaired renal function.13Taken together, the evidence from the fondaparinux clinical trial program appears to show that the duration of thromboprophylaxis has a dramatic impact on reducing the incidence of VTE and that extended prophylaxis offers the promise of even further reductions in the risk of VTE, including symptomatic VTE.

### Drug Interactions and Adverse Effects

Studies14 in healthy volunteers showed no significant adverse events as well as no pharmacokinetic or pharmacodynamic interactions between fondaparinux and several drugs likely to be coadministered in patients undergoing major orthopaedic surgery, including aspirin, piroxicam, digoxin, and warfarin. As with all approved anticoagulants, the use of fondaparinux in conjunction with neuraxial anesthesia or epidural analgesia raises the issue of the potential for increased risk of spinal hematoma. In the fondaparinux phase III trials in major orthopaedic surgery, among patients with assessable venograms, 2,496 received neuraxial anesthesia, with or without general anesthesia, and indwelling catheters were not allowed.9 There were no case reports of epidural hematoma in any of the four studies. In addition, the superior efficacy of fondaparinux relative to enoxaparin was maintained, independent of the type of anesthesia received (57.3% and 51.4% risk reductions relative to enoxaparin with, respectively, regional-only and other forms of anesthesia).10 Because the risk of major bleeding increases with age, caution is advised when using fondaparinux in the elderly. Fondaparinux is contraindicated in patients weighing <110 lb (50 kg) or in those with severe renal impairment.

### Dosage and Cost

Prophylaxis with UFH or warfarin substantially reduces the risk of VTE after orthopaedic surgery, and either one is thus more cost effective than no prophylaxis. LMWHs are sufficiently superior to UFH and, although more expensive, are considered cost effective. Fondaparinux is considered to be a cost-effective alternative to LMWHs.15 Fondaparinux is dosed at 2.5 mg/day, compared with enoxaprin at 30 mg bid (United States) or 40 mg/day (Europe). Wholesale prices to hospitals in the United States for these medications are approximately $30 a day for fondaparinux, $24 a day for two injections of enoxaparin 30 mg, and $16 a day for enoxaparin 40 mg.16 Retail prices for these medications are somewhat higher (Table 2) and are much higher than for UFH or warfarin. However, cost-effectiveness analyses indicate that fondaparinux provides a cost savings over enoxaparin in the United States17 and is the recommended strategy in the United Kingdom.18

### Summary

It is inappropriate to wait for symptoms of VTE in patients with silent DVT before initiating treatment to prevent both fatal and nonfatal PE.1 The high risk of DVT
and PE associated with major orthopaedic surgery suggests the need to reduce the incidence of asymptomatic DVT with effective thromboprophylaxis and, by extension, indicates the importance of venographic end points as efficacy outcome measures in thromboprophylaxis trials. The strength of the fondaparinux clinical trial program in THA, TKA, and hip fracture surgery is that its findings demonstrate that the agent is safe and leads to an overall >50% reduction in VTE risk (based on a significant decrease in venographic DVT events) relative to approved enoxaparin regimens. Similarly, there is compelling evidence to support the use of fondaparinux for extended thromboprophylaxis, based on a 96% reduction in all VTE and an 88% reduction in symptomatic VTE in hip fracture patients, a population at especially high risk of developing VTE. Given this evidence, fondaparinux is approved for these prophylaxis indications in both the United States and Europe. The recently published Seventh American College of Chest Physicians (ACCP) Guidelines for the prevention of VTE strongly support the use of fondaparinux in patients undergoing elective THA and TKA and hip fracture surgery, with fondaparinux the only agent to receive grade 1A recommendations in all major orthopaedic surgery settings.

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