

Evidence for Extended Prophylaxis in the Setting of Orthopedic Surgery

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Patients undergoing orthopedic surgery represent one of the highest risk groups for the development of venous thromboembolism (VTE). Evidence shows that this risk extends beyond the period in which the patient is hospitalized, especially for patients undergoing hip surgery. Clinical trials have shown that extended prophylaxis with the low-molecular-weight heparins is effective in reducing the rate of total VTE, and a meta-analysis demonstrated a reduction in symptomatic VTE with extended prophylaxis after total hip replacement surgery. Based on these results, the American College of Chest Physicians gives a grade 2A recommendation for the use of extended prophylaxis after orthopedic surgery. Until recently, data evaluating the role of prophylaxis in patients undergoing hip fracture surgery were limited. Subsequently, a novel anticoagulant, fondaparinux, demonstrated significant benefit in these patients and has become the first and only agent approved by the United States Food and Drug Administration (FDA) for use in patients undergoing hip fracture surgery. Despite the limitations of the older trials, their findings supported the need to evaluate extended prophylaxis in patients undergoing hip fracture surgery. In the first well-conducted trial of extended prophylaxis for hip fracture surgery, fondaparinux provided impressive results in reducing total and symptomatic VTE. The results of this trial have once again led to fondaparinux being the first and only agent to be granted FDA approval for the indication of extended prophylaxis in patients undergoing hip fracture surgery.

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Patients undergoing total knee replacement (TKR), total hip replacement (THR), or hip fracture surgery are generally thought to be at the highest risk for developing a deep vein thrombosis (DVT) and/or pulmonary embolism after surgery. Although the total and proximal DVT rates for hip fracture surgery are similar to those of THR and TKR, the rates of pulmonary embolism are much higher. Fatal pulmonary embolism has been reported to occur in 3.5–13%

of patients undergoing hip fracture surgery without prophylaxis compared with less than 1% for patients undergoing THR or TKR surgery.¹ Even with current prophylaxis methods, fatal pulmonary embolism will occur in 1–2% of patients.^{1,2}

Despite this high rate of serious venous thromboembolic events from hip fracture surgery, the American College of Chest Physicians (ACCP) concluded in its most recent guidelines (published in January 2001) that the existing evidence on prophylaxis against venous thromboembolism (VTE) in patients undergoing hip fracture surgery was insufficient to support any grade 1A recommendations.¹ The recent Pentasaccharide in Hip-Fracture Surgery Study

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(PENTHIFRA) showed that 11 days of fondaparinux 2.5 mg after surgery could provide more than a 50% reduction in venographic VTE compared with low-molecular-weight heparins (LMWHs) in patients undergoing hip fracture surgery.³ The results of PENTHIFRA led to fondaparinux being the first and only agent to receive approval by the United States Food and Drug Administration (FDA) for use in patients undergoing hip fracture surgery.

Notwithstanding this impressive improvement over current methods of prophylaxis, questions arose regarding the duration of prophylaxis in these patients. Current clinical trials have a number of limitations, with no comparisons between LMWHs and warfarin. Clinical trials evaluating prophylactic therapy in patients undergoing orthopedic surgery utilized an anticoagulant regimen used during the period of postsurgical hospitalization, which lasted 7–14 days.¹ However, the ACCP's most recent evidence-based guidelines on antithrombotic therapy note that the optimal duration of thromboprophylaxis after these surgical procedures is uncertain.¹ Evidence that the risk of VTE persists for a longer period is accumulating. At the same time, the length of hospital stay is decreasing, with many patients now being discharged 5 days or less after surgery, which would not provide an adequate duration of VTE prophylaxis.¹ The risk of VTE in THR and TKR surgery has been shown to extend into the outpatient period, especially after THR surgery. The median time to diagnosis of symptomatic DVT in patients who have undergone TKR surgery is 7 days, whereas it extends to 17 days for THR surgery.⁴ The diagnosis of DVT occurs after hospital discharge in 47% of patients who underwent TKR surgery and in 76% of patients who underwent THR surgery.⁴ This may be why extended prophylaxis after THR surgery seems to have better justification compared with that after TKR surgery.

The need for extended VTE prophylaxis after hip fracture surgery only recently has been evaluated. Similar to what has been demonstrated with THR surgery, the risk of clinical VTE events after hip fracture surgery increases after the in-hospital period. In PENTHIFRA, 73% of the clinical VTE events occurred during the follow-up period after the end of study treatment (days 11–49 after surgery).³ Eight symptomatic VTE events occurred within the 11 days after surgery, whereas an additional 22 events occurred between days 11 and 49. The same trend was

seen in fatal pulmonary embolism. Four fatal pulmonary embolism events occurred within the 11 days after surgery, whereas 11 fatal pulmonary embolism events occurred between days 11 and 49. This increase in clinical VTE events after the end of study treatment suggests a role for extended prophylaxis in patients undergoing hip fracture surgery.

Current Extended-Prophylaxis Recommendations

Hip Replacement Surgery

In-hospital prophylaxis of VTE for patients undergoing THR has received a grade 1A recommendation from the ACCP and is used in more than 90% of patients.¹ As discussed, patients undergoing THR are known to be at risk for developing VTE after hospital discharge despite appropriate in-hospital prophylaxis for 7–10 days. Several clinical trials have evaluated the efficacy and safety of extending VTE prophylaxis after THR surgery.^{5–11}

A randomized trial was conducted to evaluate extended prophylaxis with enoxaparin after discharge in patients who underwent THR.⁵ All patients received enoxaparin 40 mg/day, with the first dose administered 12 hours before surgery, for 9 ± 2 days. Patients without symptomatic VTE then were randomly assigned either to continued therapy with enoxaparin 40 mg/day or placebo for another 21 days (total treatment period of about 30 days). All patients were intended to undergo bilateral venography, and adequate results were available for 233 of the patients. Patients receiving extended prophylaxis with enoxaparin experienced a significant reduction in both total and proximal DVT (Table 1).

Another similar trial was conducted, with a few important differences.⁶ The inpatient therapy of enoxaparin 40 mg/day was the same but was slightly longer in duration (14 days). An important difference in this trial was the requirement for all patients to undergo venography before randomization to the extended prophylaxis period. Thirteen percent of patients were found to have venographic DVT, preventing them from progressing to the randomization phase of the trial. The remaining patients then were randomly assigned either to enoxaparin 40 mg/day or to placebo. As with the previous trial,⁵ patients underwent bilateral venography after an additional 21 days of therapy (total treatment period of about 35 days). Patients receiving extended enoxaparin

Table 1. Clinical Evidence with Extended Prophylaxis After Total Hip Replacement Surgery

No. of Patients	LMWH Extended Prophylaxis Regimen ^a vs Placebo	Total DVT (%)		Proximal DVT (%)		Symptomatic VTE (%)	
		LMWH	Placebo	LMWH	Placebo	LMWH	Placebo
233 ⁵	Enoxaparin 40 mg/day x 21 days	18	39	7	24	1.7	8.6
173 ⁶	Enoxaparin 40 mg/day x 21 days	7.1	19.3	5.9	7.9	3.3	7.8
218 ⁷	Dalteparin 5000 IU/day x 28 days	19.3	31.7	8.3	13.4	4.3	3.4
215 ⁸	Dalteparin 5000 IU/day x 28 days	4.4	11.8	0.9	5.0	NA ^b	NA ^b
472 ^{9,c}	Ardeparin 100 IU/kg/day x 42 days	NA	NA	NA	NA	1.7	2.6
533 ¹⁰	Dalteparin 5000 IU/day x 29 days	19.7	36.7	2.6	9.2	1.4	2.3
435 ¹¹	Enoxaparin 40 mg/day x 21 days	8.0	23.2	2.7	12.8	0.0	3.3

LMWH = low-molecular-weight heparin; DVT = deep vein thrombosis; VTE = venous thromboembolism; NA = data not available.

^aProphylaxis regimen followed an in-hospital course of therapy in which all patients received active treatment for 4–14 days (depending on the trial).

^bFive cases of symptomatic VTE occurred but were not reported for the individual groups.

^cStudy included patients undergoing elective hip and knee replacement surgeries. This no. of patients represents those undergoing elective hip replacement.

prophylaxis experienced a significant reduction in risk of DVT. The 25% reduction in risk of proximal DVT did not achieve statistical significance (Table 1).

A major difference between these two trials^{5,6} was the evaluation of either symptomatic DVT or venographic DVT after in-hospital therapy and before randomization to extended VTE prophylaxis. Evaluation of only symptomatic DVT may be described as more “real world” since patients do not typically undergo DVT screening before discharge. On the other hand, when DVT is assessed at the conclusion of the follow-up period, it is unknown whether the DVT originated before discharge or during the extended prophylaxis period. Some may argue it does not matter when the DVT occurs once it is discovered. If all patients are screened with venography before randomization, the true frequency of DVT during the extended prophylaxis time period can be determined. This may explain why the rate of total DVT in the treatment and placebo groups is twice as high in the first trial⁵ than in the second trial.⁶ The screening of asymptomatic patients before randomization also introduces the possibility of the venographic procedure itself leading to the development of DVT, which may not have occurred if the procedure had been avoided.¹²

Several trials have evaluated the role of dalteparin for VTE prophylaxis after discharge in patients who underwent THR. Two of the trials used in-hospital dalteparin for all patients. Similar to the enoxaparin trials, one trial excluded patients with symptomatic DVT at discharge, whereas the other excluded patients with venographic DVT from randomization.^{7,8} Both trials showed a significant reduction in total

DVT and a greater than 50% relative risk reduction in proximal DVT (Table 1). In the North American Fragmin Trial, patients were randomly assigned before in-hospital therapy to either dalteparin or warfarin.¹³ After the in-hospital phase, venography was performed. Patients who had received dalteparin and were free of DVT continued to receive dalteparin for a total of 35 days.¹⁰ Patients who had received warfarin and were free of DVT were switched to placebo until venography on day 35. Patients receiving dalteparin for the 35 days had significantly less total and proximal DVT compared with that of patients receiving 6 days of warfarin and then placebo (Table 1).

Most of these trials of LMWH for extended VTE prophylaxis after THR surgery enrolled less than 150 patients/arm and, therefore, lacked the statistical power to detect a significant reduction in symptomatic DVT. One relatively large trial (1195 patients) that included patients undergoing THR or TKR attempted to evaluate symptomatic events as its primary end point.⁹ All patients in this trial received ardeparin 50 IU/kg twice/day as in-hospital treatment for 4–10 days. Patients without clinical DVT then were randomly assigned to either placebo or ardeparin 100 IU/kg/day for 6 weeks. Symptomatic DVT or death occurred in 1.5% of patients receiving extended VTE prophylaxis with ardeparin compared with 2.0% of patients receiving placebo ($p=NS$). This study had several methodologic problems. The duration of in-hospital therapy may have been too short, and the dose of ardeparin may not have been sufficient. The dose of ardeparin was capped at 10,000 IU, the calculated dose for patients weighing 100 kg, whereas patients weighing up to 140 kg were

enrolled. Therefore, anyone weighing more than 100 kg may have received an insufficient dose of anticoagulant. The fact that 60% of the patients in this trial were undergoing TKR surgery is also important. In this trial, as in others, the results of extended prophylaxis have been less impressive for TKR than THR. The relative risk reduction for VTE or death was 18% (1.4% ardeparin vs 1.7% placebo) for patients who underwent TKR as opposed to 35% (1.7% vs 2.6%) for patients who underwent THR. The difference in the THR group was not statistically significant, but because the THR group represented only 40% of the total patient population, the power of this analysis is greatly reduced.

At least two well-conducted meta-analyses are available on this issue of extended VTE prophylaxis after THR surgery.^{14, 15} The first compiled data from six trials that compared LMWH, either dalteparin or enoxaparin, with placebo.¹⁴ In this meta-analysis of more than 1500 patients, a significant reduction was noted in risk of developing any DVT by almost 60% (7.9% LMWH vs 22.5% placebo, relative risk [RR] 0.41, 95% confidence interval [CI] 0.32–0.54, $p < 0.001$). Even more important, significant reductions were noted in proximal DVT (3.0% LMWH vs 11.2% placebo, RR 0.31, 95% CI 0.20–0.47, $p < 0.001$) and even in symptomatic VTE (1.4% LMWH vs 4.2% placebo, RR 0.36, 95% CI 0.20–0.67, $p = 0.001$) with the use of LMWH extended prophylaxis. Minor bleeding occurred in about 2.5% of patients in each group, whereas only one case of major bleeding occurred, in a patient in the placebo group.

The other meta-analysis used the same six trials as the previously discussed meta-analysis, but included three additional trials.¹⁵ These three additional trials used nadroparin, ardeparin, or unfractionated heparin as the anticoagulant compared with placebo.^{9, 16, 17} This meta-analysis included patients who underwent TKR surgery, but results for THR surgery were separated out. In this meta-analysis of almost 2000 patients, extended prophylaxis provided a significant reduction in asymptomatic VTE (7.7% prophylaxis vs 18.6% placebo, RR 0.39, 95% CI 0.28–0.54) as well as a significant reduction in symptomatic VTE (1.4% prophylaxis vs 4.3% placebo, RR 0.33, 95% CI 0.19–0.56) in the THR surgery group. Minor bleeding was significantly higher in patients receiving extended prophylaxis, whereas no difference was noted in major bleeding.

Overall, the clinical evidence supports the use

of extended prophylaxis in patients undergoing THR surgery. In the clinical trials using an LMWH, the total DVT rate decreased to approximately 10% and the proximal DVT rate to about 4%. These benefits were provided with no increase in major bleeding. There was an increase in minor bleeding, which was usually injection-site hematoma. The rate of symptomatic VTE was reduced from about 4% with placebo to about 1.6% with LMWH.^{5–11} As previously discussed, these trials were not designed to evaluate symptomatic VTE, and the reduction was not commonly statistically significant in the individual trials. The meta-analyses do suggest such a benefit, however.^{14, 15} The lack of strong data supporting a reduction in symptomatic VTE and cost-effectiveness with extended prophylaxis are the justifications for a grade 2A, instead of a grade 1A, recommendation from the ACCP.¹

Knee Replacement Surgery

A limited number of clinical trials have examined the role of extended VTE prophylaxis in patients undergoing TKR surgery. In one study, 438 patients undergoing TKR surgery received enoxaparin 30 mg twice/day until hospital discharge (7–10 days).¹¹ Patients without symptomatic VTE then were randomly assigned to either continued therapy with enoxaparin 40 mg/day or placebo for an additional 21 days. Bilateral venography was then performed to assess the occurrence of DVT. Patients receiving the extended prophylaxis regimen did not experience a significant reduction in total DVT (17.5% enoxaparin vs 20.8% placebo) or proximal DVT (4.1% vs 7.7%). This trial also included patients undergoing THR surgery (435 patients). Patients receiving extended prophylaxis after THR did experience a significant reduction in both total and proximal DVT.

Ardeparin also has been evaluated for extended VTE prophylaxis in patients undergoing TKR surgery.⁹ The trial evaluated in-patient treatment with ardeparin and then randomly assigned patients to 6 weeks of ardeparin or placebo. As previously discussed, this trial included both TKR (60%) and THR (40%) surgery groups. The 18% reduction (1.4% vs 1.7%) in death or symptomatic VTE in patients undergoing TKR surgery was not statistically significant and was only about half the reduction seen in patients undergoing THR surgery (35%).

Finally, a meta-analysis included trials in patients with both TKR and THR surgery.¹⁵ The TKR surgery trials included in this analysis are the two trials just previously discussed.^{9, 11} Although a significant reduction was noted with extended prophylaxis in asymptomatic and symptomatic VTE in patients who underwent THR surgery, the TKR surgery group did not experience this significant benefit in either asymptomatic (20.5% vs 24%, RR 0.82, 95% CI 0.49–1.4) or symptomatic (1% vs 1.4%, RR 0.74, 95% CI 0.26–2.15) VTE.

As previously discussed, VTE usually occurs earlier in patients with TKR surgery than in those with THR surgery.⁴ Owing to this earlier presentation of VTE in patients who underwent TKR surgery, extending the prophylaxis period outside the 7–10-day period may not provide significant benefits.

Current Data with Hip Fracture Surgery

Current ACCP guidelines for prevention of VTE in patients undergoing hip fracture surgery do not contain any grade 1A recommendations.¹ The guidelines do make a grade 1B recommendation for the use of LMWH or adjusted-dose warfarin for prophylaxis against VTE after hip fracture surgery. The use of low-dose unfractionated heparin is given a level grade 2B recommendation based on the limited data available (two trials). Aspirin alone is not recommended since trials comparing it with warfarin and danapranoid showed aspirin to be less efficacious.

The data supporting the use of LMWH after hip fracture surgery come from the results of five clinical trials.^{18–22} Only two of these trials used a traditional LMWH,^{18, 19} whereas the other three trials used heparinoids.^{20–22} One of these trials used an unidentified LMWH that was apparently less efficacious than unfractionated heparin 5000 U 3 times/day.¹⁸ This trial had several flaws. For example, venography initially was used only to confirm symptomatic events but was performed for all of the first one third of the patient population. The authors also suggest that the dose of LMWH may have been too low. The other trial evaluated enoxaparin 20 or 40 mg started 8 hours before hip fracture surgery.¹⁹ After 10–15 days, enoxaparin 40 mg/day provided a relative risk reduction in total DVT and proximal DVT by 43% and 66%, respectively, compared with enoxaparin 20 mg/day. No placebo group comparison was performed in this trial.

There are also five trials supporting the recommendation for the use of warfarin for prevention of VTE after hip fracture surgery.^{23–27} These trials collectively show a 40–45% reduction in total DVT with warfarin. Four of these five trials were conducted before 1972^{23–26} and the fifth was published in 1989.²⁷ Advances in surgical technique and improvements in early mobilization of patients after surgery should be considered when evaluating these data. Two of these trials compared warfarin (dicoumarol) with dextran 70 and showed no significant difference in VTE.^{25, 26}

Since the last publication of the ACCP guidelines (January 2001), the PENTHIFRA study evaluated the efficacy and safety of fondaparinux 2.5 mg/day compared with enoxaparin 40 mg/day for up to 11 days after hip fracture surgery.³ The rate of VTE was reduced by more than 50% with the use of fondaparinux (8.3% vs 19.1%, $p < 0.001$). This reduction in VTE came without an increase in major bleeding. These results should lead to a grade 1A recommendation for the use of fondaparinux for prophylaxis of VTE after hip fracture surgery in the future ACCP guidelines.

Although there are no ACCP recommendations on the use of extended prophylaxis of VTE after hip fracture surgery, some insight into the risk for these patients can be gained from some of the earlier warfarin trials. Three of the trials that evaluated vitamin K antagonist versus placebo included venographic evaluation 21 days after surgery.^{23, 24, 27} In these trials, the rate of VTE among patients receiving placebo was 46–56%. The rates of VTE with therapy were reduced but were still 10–25%. Unfortunately, in these trials how long the prophylactic therapy was continued was not well described.

Data from these early trials, along with information about clinical VTE events in the PENTHIFRA study, suggest that patients undergoing hip fracture surgery continue to be at risk for several weeks beyond the hospitalization period. Because of the success of up to 11 days of fondaparinux in the PENTHIFRA study, it was logical to undertake a clinical trial of fondaparinux for extended VTE prophylaxis in this patient population.

PENTHIFRA Plus Study

Patients enrolled in the PENTHIFRA Plus study²⁸ had to be at least 18 years of age and undergoing hip fracture surgery within 48 hours

of admission. Specifically, the fracture needed to be in the upper third of the femur, which included the femoral head and neck. Patients who came to the hospital more than 24 hours after the trauma, or patients with multiple traumas, were excluded from the study. Other significant exclusion criteria were patients at risk of bleeding, the need for chronic anticoagulation for a comorbid condition, planned indwelling intrathecal or epidural catheter for more than 6 hours after surgery, serum creatinine level above 2.0 mg/dl, or receipt of another anticoagulant or a fibrinolytic agent after admission to the hospital. The PENTHIFRA Plus study was not a continuation of the PENTHIFRA study. Although the PENTHIFRA Plus study involved many of the same study sites and study investigators as PENTHIFRA and the patient populations in the two studies were demographically similar, none of the patients from PENTHIFRA participated in PENTHIFRA Plus.

All 737 patients received fondaparinux 2.5 mg/day starting 6–8 hours after surgery, similar to the fondaparinux arm of the PENTHIFRA study. Open-label fondaparinux was to be given for 7 ± 1 days. Patients without symptomatic VTE, significant bleeding, or need for repeat surgery then were randomly assigned to either extended prophylaxis with the same dose of fondaparinux (326 patients) or placebo (330 patients) for an additional 21 ± 2 days. This provided a total duration of treatment of 25–31 days.

The primary outcome of the study was the frequency of total VTE. This included the evaluation of DVT by bilateral venography between days 25 and 32, and confirmation of symptomatic pulmonary embolism by lung scanning, pulmonary angiography, or spiral computed tomography, or at autopsy. Other efficacy outcomes included a breakdown of the location of the DVT (distal or proximal) and the frequency of symptomatic VTE. Major and minor bleeding, as well as platelet counts, were assessed as safety outcomes. Major bleeding was defined as bleeding that was fatal, involving a critical organ (e.g., retroperitoneal, intracranial, intraspinal bleeding); led to repeat surgery; or was associated with a bleeding index of 2 or greater. As in other orthopedic trials using fondaparinux,²⁹ the bleeding index was calculated as the number of units of packed red blood cells or whole blood transfused plus the prebleeding minus postbleeding hemoglobin level values. Additional data collected were the rate of death, need for transfusion, and any other

Table 2. PENTHIFRA Plus Efficacy Outcomes²⁸

End Point	Fondaparinux (n=326) ^a	Placebo (n=330) ^a	p Value
All venographic VTE	1.4	35	<0.001
All venographic DVT	1.4	33.9	<0.001
Proximal DVT	0.9	15.8	<0.001
Distal DVT	0.5	19.9	<0.001
Symptomatic VTE	0.3	2.7	0.021
DVT	0.3	1.8	
Nonfatal PE	0.0	0.6	
Fatal PE	0.0	0.3	

PENTHIFRA Plus = Pentasaccharide in Hip-Fracture Surgery Plus; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism.

^aData are percentages.

adverse events.

Baseline patient characteristics were not different between the groups. In this trial, mean age was 79 years and mean weight about 65 kg (range 39–127 kg); 71% were women. Mean duration of open-label fondaparinux was 7 days in both groups. The duration between surgery and hospital discharge was 13.9 days for the fondaparinux group and 13.1 days for the placebo group. No difference was noted between the groups in the type of fracture, type of surgery, use of cement, type of anesthesia, or duration of surgery (median 1.5 hrs).

At the end of the 25–32-day follow-up, the primary end point of total VTE was significantly reduced by 96% with the use of extended prophylaxis with fondaparinux (1.4% fondaparinux vs 35% placebo, $p < 0.001$). This reduction was not only due to a 97% reduction in distal DVT, but also to a significant reduction of almost 95% in more serious proximal DVT (Table 2). Although the trial was not expected to have the statistical power to demonstrate a difference in symptomatic events, extended prophylaxis with fondaparinux virtually eliminated the risk of symptomatic VTE (0.3% vs 2.7%, $p = 0.021$). It is also interesting to note that the magnitude of the benefit in reducing symptomatic VTE was similar to the reduction in venographic VTE (89% vs 96%). Although there were three pulmonary embolisms in the placebo group compared with none in the fondaparinux group, these numbers are too small to establish any type of conclusions.

Major and minor bleeding occurred infrequently, and no significant differences were noted between the groups (Table 3). Most of the major bleeding was due to an increase in the bleeding events with a bleeding index of 2 or greater, but such an event occurred in only six patients and

Table 3. PENTHIFRA Plus Safety Outcomes²⁸

End Point	Fondaparinux (n=326) ^a	Placebo (n=330) ^a
Major bleeding	2.4	0.6
Fatal bleeding	0.0	0.0
Nonfatal bleeding in a critical organ	0.0	0.0
Surgical-site bleed leading to repeat surgery	0.6	0.6
Bleeding index ≥ 2	1.8	0.0
Minor bleeding	1.5	0.6
Need for transfusion	8.9	6.1
Death from any cause	1.8	2.4

PENTHIFRA Plus = Pentasaccharide in Hip-Fracture Surgery Plus.

^aData are percentages.

No statistically significant difference was noted between the groups for any end point.

led to discontinuation of fondaparinux in only one patient. No differences were noted between the groups with regard to need for transfusion and death from any cause (Table 3).

The results from the PENTHIFRA Plus study broke new ground in the area of extended VTE prophylaxis. As previously stated, PENTHIFRA Plus was the first trial to evaluate the role of extended VTE prophylaxis in patients undergoing hip fracture surgery. The magnitude of the benefits seen with extended prophylaxis with fondaparinux can be put into some perspective by comparing them with some of the extended prophylaxis THR surgery data. Although the total VTE rate in the placebo group of PENTHIFRA Plus was similar to that seen in the THR surgery trials (35% vs ~30%), the impact of the extended prophylaxis was much more impressive (1.4% PENTHIFRA Plus vs 10–12% in THR surgery). These data suggest that there is almost a 10-fold greater reduction in total VTE with fondaparinux compared with LMWH for extended prophylaxis. The rate of total DVT with extended use of fondaparinux (1.4%) is reduced to a similar rate of symptomatic VTE with the use of extended prophylaxis with LMWH (1.6%) in patients undergoing THR surgery. The rate of symptomatic VTE in the fondaparinux group was less than one fifth of that seen with LMWH (0.3% vs 1.6%). In PENTHIFRA Plus, all these remarkable results are seen without an increase in major or minor bleeding.

One reason why extended prophylaxis with LMWH after THR surgery has received only a grade 2A recommendation from the ACCP is a lack of a significant reduction in symptomatic VTE in individual trials. Also, there is a question

about the cost-effectiveness of extended prophylaxis therapy. The 89% statistically significant reduction in symptomatic VTE with the extended use of fondaparinux in the PENTHIFRA Plus study should lead to a grade IA recommendation from the ACCP for this indication.

Thrombus-Riddance Effect

Results of the PENTHIFRA Plus trial and other orthopedic trials using fondaparinux suggest an ability of the agent to reduce thrombus over time. This reduction in thrombotic burden has been referred to as the “thrombus-riddance effect.” Data from a meta-analysis of the four previously published fondaparinux versus enoxaparin orthopedic trials shows a gradual and consistent reduction in the rate of total VTE with longer durations of fondaparinux administration (Figure 1).²⁹ The consistent reduction is even more dramatic when the data from the PENTHIFRA Plus trial are added.²⁸ Extended prophylaxis with fondaparinux apparently exerts a thrombus-riddance effect in patients who have undergone hip fracture surgery. Patients receiving fondaparinux in the PENTHIFRA study had a total VTE rate of 8.3% after in-hospital prophylaxis (~11 days). This rate of total VTE was reduced to 1.4% with extended prophylaxis in the PENTHIFRA Plus study, providing a 6.9% absolute reduction in detectable thrombus with an increased duration of therapy.

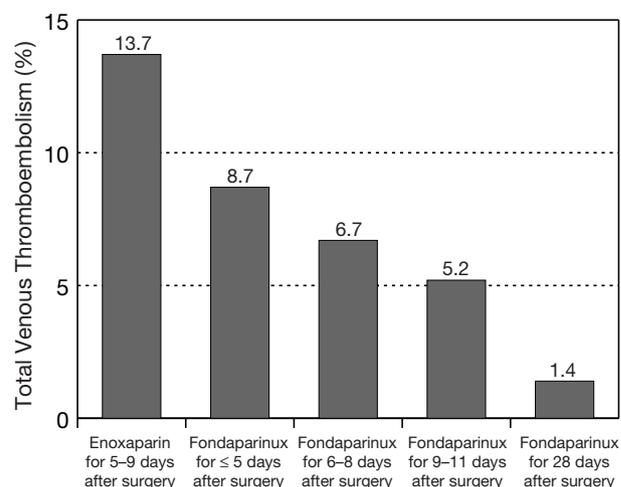


Figure 1. Thrombus-riddance effect. Data from the meta-analysis of four phase III trials²⁹ and the PENTHIFRA Plus study²⁸ that used fondaparinux show a greater reduction in total venous thromboembolism with longer durations of prophylaxis.

This phenomenon does not seem to be apparent with LMWH for extended prophylaxis after THR surgery. Patients undergoing THR surgery who received enoxaparin for up to 11 days in the European Pentasaccharide Elective Surgery Study³⁰ and the Pentasaccharide in Total Hip Replacement Surgery Study³¹ had a collective total VTE rate of 8.8%. Extended prophylaxis trials using enoxaparin report a total VTE rate of about 12%.^{14, 15} Although the VTE rates were lower after extended prophylaxis with LMWH than with placebo, there is less evidence of a reduction or a thrombus-riddance effect as seen with fondaparinux. Whether the reduction in VTE rate is due to the selective antifactor Xa activity of fondaparinux or something else remains to be determined. Despite the attractiveness of the hypothesis, the limitations of these cross-trial comparisons prevent firm conclusions about fondaparinux's true thrombus-riddance effect. Clinical trial data with fondaparinux as extended prophylaxis after THR surgery would be helpful in drawing additional conclusions.

Conclusion

Despite adequate VTE prophylaxis during hospitalization, patients undergoing orthopedic surgery remain at high risk for VTE for several weeks after discharge. This is especially true for patients undergoing THR or hip fracture surgery. Although LMWH has proved to be useful as extended prophylaxis after THR surgery, the current evidence supports a grade 2A recommendation from the ACCP. No recommendations exist for the use of extended prophylaxis after hip fracture surgery. New data from the PENTHIFRA Plus trial using fondaparinux showed not only a significant reduction in total VTE, but also a significant reduction in symptomatic VTE. Based on these results, fondaparinux is the only agent to receive FDA approval for the indication of extended prophylaxis in patients undergoing hip fracture surgery. This important clinical evidence should move the ACCP to add a grade 1A recommendation for fondaparinux for extended prophylaxis after hip fracture surgery.

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