Efficacy of Fondaparinux compared to Enoxaparin for Deep Vein Thrombosis Prophylaxis in Lower Extremity Orthopedic Surgery

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Efficacy of Fondaparinux compared to Enoxaparin for Deep Vein Thrombosis Prophylaxis in Lower Extremity Orthopedic Surgery

Abstract
Background: Deep vein thrombosis (DVT) or venous thromboembolus (VTE), is a common complication with orthopedic surgery and remains a serious problem even with multiple medications available for prophylaxis. Enoxaparin and fondaparinux are widely accepted in North America, Australia, and Europe although, a lack of evidence still remains to determine which is more effective in DVT prophylaxis in orthopedic surgery. This systematic review seeks to determine whether fondaparinux is more effective than enoxaparin in DVT prophylaxis.

Methods: A systematic literature search using multiple databases focusing on articles from professional journals, position statements, information from pharmaceutical manufacturers and CDC statistics were the primary sources for this study.

Hypothesis: Fondaparinux is more effective than enoxaparin in DVT prophylaxis, with a lower bleeding risk, and reduction of patient death.

Results: Six studies were evaluated to determine the effectiveness of fondaparinux compared to enoxaparin. Fondaparinux was compared to enoxaparin in double-blinded randomly assigned trials using subjects over 18 years of age who were scheduled to undergo orthopedic surgery of the lower extremity within 48 hours of admission. Potential subjects were excluded from the studies if they were involved in multiple trauma affecting more than one organ system, pregnancy, active bleeding, history of hemorrhagic stroke, bleeding disorder, hypersensitivity to heparin, serum creatinine above 2 mg/dl, and a platelet count below 100,000 per cubic millimeter. In all studies day 1 was defined as the day of surgery.

Conclusion: Fondaparinux is more effective at DVT prophylaxis than enoxaparin and should be considered a preferential agent in high DVT risk orthopedic surgery. Further randomized trials with long term outcomes (>30 days), are needed to evaluate benefit to risk of longer term prophylaxis post orthopedic surgery.

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Efficacy of Fondaparinux compared to Enoxaparin for Deep Vein Thrombosis Prophylaxis in Lower Extremity Orthopedic Surgery

By:

Gregg A. Fletcher

A Clinical Research Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Forest Grove, OR For the Masters of Science Degree August, 2009

Faculty Advisor: James Ferguson, MS PA-C Clinical Project Advisor: Annjanette Sommers, MS PA-C and Robert Rosenow, OD
**Biography**

Gregg Fletcher is a native of Pennsylvania coal and farm country, the oldest of 5 children. He received his Bachelors degree from Indiana University of Pennsylvania and a Masters degree from East Stroudsburg University. He worked in Cardiac Rehabilitation in Dallas, Texas for 15 years before PA school. His experiences at Medical City Dallas Hospital prepared him well for what lay ahead. He needed a new challenge and direction in life and knew PA school would provide both. He was accepted for admission into Pacific’s PA Program in 2007. Rotations took him many places and introduced him to many incredibly talented clinicians. He thanks his wife, Casey, for being strong and taking care of things at home while he was in school and traveling the country and Ecuador for rotations. He resides in Frisco, Texas with his wife Casey and daughters Ashley and Riley.
Abstract

Background: Deep vein thrombosis (DVT) or venous thromboembolus (VTE), is a common complication with orthopedic surgery and remains a serious problem even with multiple medications available for prophylaxis. Enoxaparin and fondaparinux are widely accepted in North America, Australia, and Europe although, a lack of evidence still remains to determine which is more effective in DVT prophylaxis in orthopedic surgery. This systematic review seeks to determine whether fondaparinux is more effective than enoxaparin in DVT prophylaxis.

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Conclusion: Fondaparinux is more effective at DVT prophylaxis than enoxaparin and should be considered a preferential agent in high DVT risk orthopedic surgery. Further randomized trials with long term outcomes (>30 days), are needed to evaluate benefit to risk of longer term prophylaxis post orthopedic surgery.

Keywords: hip fracture, total hip arthroplasty, total knee arthroplasty, venous thromboembolism, pulmonary embolism, enoxaparin (Lovenox), fondaparinux (Arixtra), orthopedic surgery, factor Xa inhibitor.
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Figure I: Coagulation Cascade and fondaparinux mechanism of action
List of abbreviations

CDC.................................................................Center for Disease Control
DVT.................................................................deep vein thrombosis
HFS.................................................................hip fracture surgery
PE.................................................................pulmonary embolus
RRR.................................................................relative risk reduction
THA...............................................................total hip arthroplasty
TKR...............................................................total knee replacement
Efficacy of Fondaparinux Compared to Lovenox for Deep Vein Thrombosis Prophylaxis in Lower Extremity Orthopedic Surgery

**Introduction**

Patients undergoing lower extremity orthopedic surgery (hip fracture, hip replacement, knee replacement), are in the highest category for postoperative venous thromboembolism and pulmonary embolus. This exaggerated risk for postoperative deep vein thrombosis\(^2\)\(^-\)\(^3\) where 45-57% of total hip replacement (THR) patients, 40-84% of total knee replacement (TKR), and 36-60% of hip fracture surgery (HFS) patients develop DVT, often presents even with appropriate prophylaxis.\(^4\)

The US Center for Disease Control (CDC) estimated in 2004, that there were over 320,000 hospital admissions for HFS, 234,000 THR surgeries, and 478,000 TKR surgeries.\(^2\) Approximately 1 in 5 hip fracture patients dies within a year of their injury, often from pulmonary embolus (PE), with higher mortality seen in elderly female patients in the first 4 months after surgery.\(^2\) With the aging of the US population, HFS alone is expected to double over the next 30 years.\(^3\)

Still, DVT prophylaxis is somewhat surprisingly underutilized in the orthopedic setting, for those at highest risk, the elderly. Ennis, et al reported, in a retrospective study that, over 46% of patients received either no pharmacological prophylaxis, or only aspirin for DVT prophylaxis. The study’s female subjects’ average age was 83 years while the male subjects’ average age was 78 years.\(^5\)

Postoperative bleeding risk is often the largest concern in orthopedic surgery, with some evidence pointing to DVT or PE as a more likely occurrence. Lopez-Jimenez, et al found in a study of VTE in the very elderly, a low incidence of fatal bleeding (0.8%) but a
significantly higher incidence of fatal PE (3.7%). The authors concluded, “there seems to be more reason to be concerned about fatal PE than about bleeding in elderly patients with VTE”.6

Returning patients to active, healthy productive lives is the goal of any procedure and those mentioned in this paper are no different. Aging of the U.S. population will undoubtedly increase HFS, THA, TKR rates underlining the need for more effective DVT prophylaxis perioperatively.

**Purpose of study**

This systematic review was done to evaluate the effectiveness in lower extremity orthopedic surgery patients, of fondaparinux (Arixtra) compared to enoxaparin (Lovenox) in DVT prophylaxis. Fondaparinux (Arixtra) was the first pentasaccharide, a class of medications that cause the selective inhibition of factor X without direct activity against thrombin, to be approved, for use in the US. Fondaparinux is 100% bioavailable, exhibits a linear pharmacokinetic profile, reaches half maximal plasma concentration within 25 minutes, and has a half life of 15 -17 hours, allowing for once daily administration.7 This novel approach to therapy is not without concern, as there is no known antidote to reverse the effects of fondaparinux at this time.

Due to its ease of administration and mechanism of action, fondaparinux is the focus of thrombosis prophylaxis in orthopedic surgery, cardiology, oncology, and abdominal surgery programs throughout the US and Europe. It should be noted that, pulmonary embolism (PE), was not the primary focus of this systematic review but is addressed because it was considered a venous thromboembolus in the majority of the literature reviewed.
**Significance**

The aging of the US population represents an opportunity for clinicians and researchers to determine efficacious treatments that benefit the patient, improve outcomes, and decrease the incidence of DVT, PE, and death after orthopedic surgery. Perioperative outcomes are the focus of this paper however, Gordois, et al found that the use of fondaparinux led to long term cost savings (5 years post surgery) in the UK Public Health System. Fondaparinux was found to have a lower rate of clinical VTE (33.4 vs 53.4 per 1000 patients), lower VTE-related deaths (3.9 vs 7.1 per 1000 patients), and discounted cost (£219 vs £246 per patient at 5 years). It was also found to prevent 2640 VTE events and 400 VTE-related deaths annually.\(^8\) Fondaparinux is now the preferred agent for DVT prophylaxis in the UK.\(^8\)

The fastest growing segment of the US population is those 80 years and older. Enders, et al report, that the incidence of VTE increases with age, with an estimated 200-fold increase in risk between the ages of 20 and 80 years, the sharpest increase being noted after 40 years of age.\(^9\) Treatments for the prevention of DVT and PE in the elderly population are especially important to improve outcomes after orthopedic surgery.

**Methods and Materials**

An exhaustive literature search was conducted, using the following search engines CINAHL, Web of Science, Ovid, Medline, and MD Consult. Inclusion criteria: randomized control trials published since 2000 comparing fondaparinux and enoxaparin in orthopedic surgery, English language, and multicenter multicountry randomized control trials were preferred for this study. Exclusion criteria included meta-analyses, retrospective studies, and
articles published prior to 2000. All randomized control trials available were used for this review due to the limited number of studies. Literature review included information from professional journals, the US Center for Disease Control, and pharmaceutical manufacturers.

**Results**

A dose-ranging study authored by Turpie, et al, looked at using fondaparinux in the prevention of deep vein thrombosis after total hip replacement. The study was performed to determine the optimal dosing for Phase III Clinical trials and included information which was used in future studies involving fondaparinux.

Patients were randomized during the double-blinded trial and consisted of 933 subjects, undergoing total hip replacement surgery. Study drugs were given for 10 days or until mandatory bilateral venography was performed, after a minimum of 5 days. Subjects were placed on 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, or 8.0 mg of fondaparinux once daily or enoxaparin 30 mg every 12 hours.

This trial showed RRR of 82% (P=0.01) for the 3.0 mg fondaparinux group and 29% (P=0.51) for the 1.5 mg fondaparinux group. Enrollment in the 6.0 mg and 8.0 mg groups was discontinued because of major bleeding episodes. In the comparison between the 3.0 mg fondaparinux group and the 30 mg enoxaparin group little difference was noted. The authors determined fondaparinux has the potential to significantly improve the prevention of VTE compared with low molecular weight heparin (LMWH).

Another article, the European Pentasaccharide Hip Elective Surgery Study (EPHESUS), was the first large scale trial to compare the effectiveness of fondaparinux to enoxaparin in orthopedic surgery. The double-blinded, randomly assigned study enrolled
2309 patients from 73 medical centers in 16 European countries, and placed them into two groups: enoxaparin 40 mg once daily with the first dose given before surgery, or fondaparinux 2.5 mg once daily started postoperatively. The trial arm groups were equally divided between the two regimens (fondaparinux n=1140 and enoxaparin n=1133). Each medication was administered through day 9 and patients followed through day 11. Patients qualified for the protocol if they were age 18 or older, having primary elective hip replacement, or revision of at least 1 component of a previously implanted total hip prosthesis. Subjects were assessed for DVT by bilateral venography, between day 5 and 11 (no longer than 2 days after the last dose of study medication), and for symptomatic PE by lung scan, pulmonary angiography, helical CT, or at autopsy.

Use of sequential compression devices (SCDs), dextran, thrombolytic treatment, and any other anticoagulant agents were prohibited. Centers were also instructed to avoid giving patients aspirin or non-steroidal anti-inflammatory agents when possible. Compression stockings and physical therapy and early mobilization were recommended. The findings showed fondaparinux caused a RRR of 55.9% (95% CI, 33.1-72.8; p<0.0001) with no difference in incidence of major bleeding or death (11).

The PENTATHLON 2000 Trial\textsuperscript{12} was the next in this series of studies to compare fondaparinux and enoxaparin for the prevention of VTE. This trial enrolled 2275 patients in 149 medical centers in North America and Australia, and compared enoxaparin 30 mg twice daily to 2.5 mg fondaparinux once daily. Medications given in this trial were administered after surgery, with the first dose of fondaparinux given 4-8 hours post surgery and first dose of enoxaparin given between 12-24 hours post surgery, in accordance with manufacturer’s recommendations. Subjects received study medication for 5-9 days post surgery and were
followed through day 11. Mandatory bilateral venography was performed between day 5-11 post surgery with symptomatic PE evaluated by lung scan, pulmonary angiography, helical CT, or at autopsy. Follow-up was completed between day 35 and day 49 post procedure. This was the first trial to compare both medications in the postoperative setting. Approximately 70% of subjects were included in the efficacy analysis, an improvement over the EPHESUS trial.

Study results showed that fondaparinux caused a RRR of 26.3% (95% CI, -10.8-+52.8; p=0.099), but was not significantly more effective than enoxaparin in reducing the risk of symptomatic VTE. Fondaparinux was however, significantly more effective in reducing the total number of VTE by day 11. The authors found a clinically important lower risk with fondaparinux, where no increase in clinically relevant bleeding or incidence of major bleeding or death was noted.

The Pentasaccharide in Hip-Fracture Surgery Study (PENTHIFRA)\(^1\), a randomly assigned, double-blinded trial, released in November 2001, compared enoxaparin 40 mg once daily, administered preoperatively to fondaparinux 2.5 mg once daily, administered postoperatively. Subjects were enrolled through 100 medical centers in 21 countries and included 1711 consecutive patients aged 18 or older. Subjects received study medications up to day 9 and were followed through day 11. As with the PENTATHLON study, mandatory bilateral venography was performed between day 5 and day 11 to determine the presence of DVT. Patients were followed up in person, by phone, or mail between day 35 and 49. Again, investigators could extend prophylaxis with any appropriate therapy but only after venography had been done. Symptomatic PE was evaluated by lung scan, pulmonary
angiography, helical CT, or at autopsy. If VTE was present at any point during the study, the
treatment course was decided by the investigator.

The authors found the VTE rate by day 11 was 8.3% in the fondaparinux group and
19.1% in the enoxaparin group, yielding a RRR of 56.4% (95% CI, 39.0 to 70.3%; p<0.001).
They found no difference in major bleeding or death and no difference between the groups in
symptomatic VTE with a low rate of 6.5%. The number of patients treated for VTE by day
11 was lower in the fondaparinux group (6.1%) than in the enoxaparin group (11.7%). By
day 49 the incidence of symptomatic VTE was similar in both groups (2.0% in fondaparinux
and 1.5% in enoxaparin). It should be noted that, even with appropriate use of study
medications, 38 patients (4.6%) in the fondaparinux group, and 42 patients (5.0%) in the
enoxaparin group had died by day 49. The authors attribute the efficacy of fondaparinux to
“its ability to inhibit factor Xa rapidly and selectively, its predictable linear
pharmacokinetics, and its relatively long half-life, which permits the drug to achieve an
antithrombotic effect for 24 hours” (PENTHIFRA Study).

The Pentasaccharide in Major Knee Surgery Trial (PENTAMAKS)\textsuperscript{14} compared
fondaparinux 2.5 mg daily, initiated 6 ± 2 hours postoperatively (second dose given 12 hours
or more after the first), to enoxaparin 30 mg twice daily, initiated 12-24 hours
postoperatively (based on manufacturer’s recommendations), for 5-9 days. The randomized
double-blinded study enrolled 1049 patients from 64 centers in North America. Patients were
followed through day 11 and had mandatory bilateral venography performed between day 5
and 11, but no longer than 2 days after the final dose of study medication. Patients in the trial
were at least 18 years old and were undergoing elective major knee surgery.
Symptomatic PE was evaluated by lung scan, pulmonary angiography, helical CT, or at autopsy. Follow-up, as in the previously mentioned trials, was performed between day 35 and day 49 post surgery via telephone, mail, or in person. Also, patients were to report any signs or symptoms of VTE or bleeding. Investigators could extend prophylaxis during follow-up with any available therapy after venography had been performed. In the presence of VTE during the study, treatment was determined by the investigator.

Results of the PENTAMAKS showed fondaparinux was superior to enoxaparin in the prevention of VTE. The fondaparinux group had an incidence of VTE of 12% compared to 27.8% in the enoxaparin group, yielding an ARR of 55.2% (95% CI, 36.2 to 70.2%; P<0.001). The superiority of fondaparinux in primary efficacy was consistent according to age, sex, BMI, type of anesthesia, type of surgery (primary or revision), use or nonuse of cement, and whether or not patients experienced previous VTE. The number of patients treated for VTE by day 11 was significantly lower in the fondaparinux group (15.1 %) when compared to the enoxaparin group (25.1%, P<0.001). No instances of fatal bleeding were seen, in either group, and no difference in mortality was noted between the 2 medication groups. The authors concluded fondaparinux is significantly more effective than enoxaparin in preventing VTE after elective major knee surgery.

The trials previously mentioned, looked at the immediate postoperative course in DVT prevention. None addressed the issue of appropriate duration of DVT prophylaxis. The PENTHIFRA Plus Trial\textsuperscript{15}, released in 2003 did investigate this topic. The study authored by Ericksson, et al, enrolled 656 patients undergoing hip fracture surgery in a randomly assigned, placebo-controlled, double-blinded fashion, from 57 centers in 16 countries. Subjects received fondaparinux 2.5 mg daily or placebo, for an additional 19 to 21 days (after
initial 1 week, 6 to 8 days, prophylaxis with fondaparinux) post surgery to determine the efficacy of fondaparinux in extended DVT prophylaxis. Total DVT prophylaxis was 25 to 31 days post surgery.

While this trial did not compare fondaparinux to enoxaparin in DVT prophylaxis, the important information regarding extended prophylaxis can not be overlooked. Several studies have shown the benefit of extended prophylaxis using enoxaparin but no other study has addressed this concerning fondaparinux. The authors found fondaparinux reduced the incidence of VTE from 35.0% (77/220) to 1.4% (3/208) with a RRR of 95.9% (95% CI, 87.2%-99.7%; P<0.001) when compared to placebo. The fondaparinux group had a higher bleeding rate than the placebo group but, there were no differences between the 2 groups in regards to the incidence of clinically relevant bleeding.

The authors stated that, the results of this study would be easily reproducible because they chose not to exclude subjects with asymptomatic DVT at 7 days post surgery. They further stated that all patients with hip fracture surgery, not only high-risk groups, would benefit from an additional 1 month treatment with fondaparinux. Additionally, fondaparinux requires no monitoring of PT/INR or dose adjustment, with a high level of subject compliance being achieved.

Discussion

The studies utilized in this systematic review were high quality, randomized, double-blinded, and had good sample sizes. All of the studies used were multi-center, multi-country in nature and considered many possible outcomes and exclusion criteria for therapy. The studies relied on similar treatment regimens and the medications, fondaparinux and
enoxaparin, length of prophylaxis during hospital stay, evaluation techniques, and length of follow-up.

Several areas of concern were noted with the dose-ranging trial (Turpie, et al). The most easily identified problem is the number of subjects in the various treatment groups. The enoxaparin group had 260 subjects while the fondaparinux groups ranged from 52 (8.0 mg group) to 188 (1.5 mg group) subjects. Another concern is the number of potential subjects not included in the efficacy analysis. Only 64% of the original study subjects met the criteria for intention-to-treat and per-protocol analysis. Other studies reviewed for this paper used approximately 70% of subjects in the efficacy analysis. A larger percentage of subjects included in the analysis would make the results more accurate.

The EPHESUS Trial limitations were common to others presented. It is important to note that 6 out of 10 steering committee members were on the payroll of the sponsor of the study (GlaxoSmithKline - GSK), who was also responsible for performing the statistical analysis. This issue might lead one to question the objectivity of the study. Also, only 80% of patients had an adequate venogram which resulted in over 400 subjects being left out of the final statistical analysis. Finally, prolonged prophylaxis in over 50% of patients, likely prevented symptomatic VTE outside of the initial therapy window (day 5-11) but still within the prolonged follow-up period (day 35-49). Investigators could and did extend prophylaxis during follow-up with any available treatment and at the discretion of the investigator, leading to the potential that the follow up results may be skewed that future studies may reach inaccurate results and conclusions.

Problems with the PENTATHLON Trial are similar to those found in the EPHESUS trial where 6 of 10 members of the steering committee were again from the
sponsor with the sponsor likewise completing the statistical analysis. Additionally, a large number of patients (650 or 28.5%) in both treatment groups had no venography performed by day 11 or had a study that was inadequate. Moreover, subjects receiving a minimum of 1 dose of study drugs were included in the analysis, possibly altering the VTE rate and the conclusions the authors reached.

The PENTIFRA Study\textsuperscript{13} had similar shortcomings in that only 1 dose of study drugs was required to be included in the efficacy analysis. The potential bias on the steering committee, where 6 of 10 people were from the drug manufacturer (GSK) with the final statistical analysis also being done by the sponsor, remained present. Additionally in this study, only 25.6\% of patients received the preoperative injection of enoxaparin due to emergent situations but these subjects were still included in the efficacy analysis. Lastly, 421 patients or 24.6\% had not been assessed by venography by day 11. This is a similar percentage seen in both the EPHESUS\textsuperscript{11} (20\%) and PENTATHLON\textsuperscript{12} (28.5\%) trials.

Limitations of the PENTAMAKS Trial\textsuperscript{14} are similar to those presented in this systematic review. Namely patients receiving only 1 dose of study medication were included in the efficacy analysis. The drug manufacturer was represented by 7 of 11 members of the steering committee and was responsible for final statistical analysis. Venography was not performed by day 11 in 310 out of 1049 patients (~30\%), which is in line with other studies mentioned in this review.

The PENTIFRA Plus Trial\textsuperscript{15} was not immune to areas of concern. Patient compliance was determined by reviewing written records from patients, caregivers, and community nurses. Alternatively, patients had to receive at least 19 doses of study drug to be
included in the efficacy analysis. However, when VTE was confirmed, study treatment was
discontinued and replaced by another regimen at the investigator’s discretion.

This study had an open-label portion (initial 1 week prophylaxis) using fondaparinux.
The authors did not use subjects that received other DVT prophylaxis, possibly exaggerating
the results of the additional 3 weeks of prophylaxis with fondaparinux. The authors do report
using a steering committee which designed the study, interpreted the results, and wrote the
article, and a data monitoring committee and central adjudication committee which were
independent of the sponsor.

All studies (except PENTHIFRA Plus) in this systematic review permitted
prophylaxis at the discretion of the investigator once outside the treatment window (Day 5-9
or follow-up at Day 11). While clinically and ethically appropriate, this may have altered
results during the follow-up period (between day 35-49) and effected VTE rates in both
groups.

Timing of medication administration with different recommendations from
manufacturers, European (40 mg 12 h before surgery) compared to US (30 mg bid 12-24 h
after surgery) dosing regimens, may produce results that cannot be standardized. Although,
the dosing regimens were standardized for study purposes, the fact that the approved
European regimen differs from the approved US dosage yields different results in clinical
practice than those found in the study.

The majority of studies found a slightly higher bleeding risk with fondaparinux, likely
due to its targeted mechanism of action in the coagulation cascade. On the other hand, the
risk of heparin induced thrombocytopenia (HIT) is non-existent with fondaparinux.
Warkintin, et al\textsuperscript{16}, found poor reactivity of antibodies against platelet factor 4 (PF4) and also
determined that HIT would occur less frequently with fondaparinux compared with LMWH without developing thrombocytopenia. The authors also theorized, fondaparinux might be safe for patients with HIT induced by either LMWH or unfractionated heparin (UFH). They found that a low capacity for fondaparinux to form the antigens on PF4, may contribute to further reduce the most frequent immune-mediated adverse drug reaction associated with anticoagulant therapy.16

**Limitations of Study**

Several limitations are noted in the systematic review of this topic. First and foremost, is the lack of studies to adequately assess the potential outcomes of using fondaparinux in the orthopedic surgery setting. The extensive literature review using multiple databases yielded less than 10 articles, one of which was a dose-ranging trial, with several having the same author as lead investigator (Eriksson and Lassen in particular).

It is difficult to overlook the possible influence which drug manufacturers held over the results of studies published on the use of fondaparinux in orthopedic surgery. All studies were sponsored by the manufacturer of fondaparinux (Sanofi, now GlaxoSmithKline) and had statistical analysis done by the sponsor. While this may be commonplace in research the impression it presents, is concerning.

Assessment of DVT by venography and PE by various tests is open to error, based on technique and interpretation by a radiologist. While venography remains the gold standard in determining DVT, other diagnostic tools, could appropriately be considered. The large number (up to 36%) of patients not receiving the *mandatory venography* by day 11 post surgery, in the studies presented here, carries a significant potential for error.
Although the studies mentioned in this review differentiated between total, distal, and proximal DVT (which is more likely to embolize), the author chose not to provide a breakdown based on these categories. The focus of this review was to determine efficacy in DVT prophylaxis, not to determine which medication limited distal or proximal DVT individually.

Areas of future study with fondaparinux should focus on elderly patients who are at greater risk of DVT, closer evaluation of its use in pulmonary embolus, and post coronary stent (these trials are ongoing at this time). Additionally, a comparison of fondaparinux to enoxaparin in traumatic versus elective surgery may provide quality information for use in emergent situations. Trials determining the safety and efficacy of fondaparinux in the elderly population with renal impairment may be of paramount importance in the future.

**Conclusion**

Based on the results of the articles reviewed for this study, fondaparinux provides greater DVT prophylaxis when compared to enoxaparin in lower extremity orthopedic surgery. Fondaparinux caused no increase in major or clinically relevant bleeding. Its ease of administration (once daily compared to twice daily with enoxaparin), linear pharmacokinetics, and long half-life (17 hours) improve patient and clinician compliance and outcomes. As of this writing, both enoxaparin (7 to 10 days with extended prophylaxis to 35 days) and fondaparinux (5 to nine days) are approved for DVT prophylaxis in hip and/or knee surgery patients.

Current clinical trials are investigating the efficacy of fondaparinux in coronary surgery and stent placement, abdominal surgery, DVT prophylaxis in cancer treatment, and
extended DVT prophylaxis in orthopedic surgery. Finally, fondaparinux received a Grade Ia recommendation for DVT prophylaxis in hip fracture surgery, total hip arthroplasty, and total knee replacement in the 8th Edition of Antithrombotic and Thrombolytic Therapy guidelines by the American College of Chest Physicians. Lastly, and maybe most importantly, government agencies as noted by Gordois, et al and insurance companies (Blue Cross Blue Shield in particular) have noted evidence of cost savings in the short and long-term with the use of fondaparinux, even to the extent that this medication is now considered “medically necessary” in the prevention of DVT for hip and knee surgery patients. Undoubtedly, cost savings along with improved patient outcomes will provide the incentive for increased use of fondaparinux as well as additional impetus for further study.
<table>
<thead>
<tr>
<th>Study</th>
<th>Published</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Comparison</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Dose-ranging trial(^{10})</td>
<td>2001</td>
<td>Double blind</td>
<td>933 hip replacement patients</td>
<td>Various doses of fondaparinux (up to 8 mg daily) to enoxaparin 30 mg twice daily</td>
<td>Fondaparinux effective in DVT prevention in THR patients; lower bleeding risk than enoxaparin</td>
</tr>
<tr>
<td>PENTAMAKS(^{14})</td>
<td>2001</td>
<td>Double blind, randomly assigned</td>
<td>1049 major knee surgery patients</td>
<td>Fondaparinux 2.5 mg once daily compared to enoxaparin 30 mg twice daily; both given postoperative</td>
<td>Fondaparinux produced RRR of 55.2% compared to enoxaparin</td>
</tr>
<tr>
<td>EPHESUS(^{11})</td>
<td>2002</td>
<td>Double blind, randomly assigned</td>
<td>2309 hip replacement patients</td>
<td>Postoperative fondaparinux 2.5 mg once daily to preoperative enoxaparin 40 mg once daily</td>
<td>Fondaparinux produced RRR of 56% compared to enoxaparin</td>
</tr>
<tr>
<td>PENTATHLON 2000(^{12})</td>
<td>2002</td>
<td>Double blind, randomly assigned</td>
<td>2275 hip replacement patients</td>
<td>Fondaparinux 2.5 mg once daily to enoxaparin 30 mg twice daily; both started postoperative</td>
<td>Fondaparinux produced RRR of 26.3% compared to enoxaparin</td>
</tr>
<tr>
<td>PENTHIFRA(^{13})</td>
<td>2002</td>
<td>Double blind, randomly assigned</td>
<td>1711 hip fracture surgery patients</td>
<td>Postoperative fondaparinux 2.5 mg once daily to preoperative enoxaparin</td>
<td>Fondaparinux produced RRR of 56.4% compared to enoxaparin</td>
</tr>
<tr>
<td>PENTHIFRA Plus(^{15})</td>
<td>2003</td>
<td>Double blind</td>
<td>656 hip fracture surgery patients</td>
<td>Postoperative fondaparinux 2.5 mg once daily to placebo</td>
<td>Fondaparinux produced RR of 96% versus placebo</td>
</tr>
</tbody>
</table>
**Figure I:** Coagulation cascade and mechanism of action of fondaparinux\textsuperscript{20}.

**Intrinsic System**
- Surface contact
- XII → XIIa
  - XI → Xla
  - IX → IXa
  - VIII → VIIIa
  - V → Va
  - II → IIa (thrombin)

**Extrinsic System**
- Tissue damage
  - Tissue factor
  - VIIa → VII
  - IXa
  - V → Va
  - II → IIa (thrombin)

Fondaparinux
References


