Cost-Effectiveness of Fondaparinux Compared with Enoxaparin as Prophylaxis against Venous Thromboembolism in Patients Undergoing Hip Fracture Surgery

Sean D. Sullivan, PhD1, Louis Kwong, MD2, Edith Nutescu, PharmD3

1Pharmaceutical Outcomes Research and Policy Program, University of Washington, Seattle, WA, USA; 2Department of Orthopedics, Harbor/ UCLA Medical Center, Torrance, CA, USA; 3Department of Pharmacy Practice, University of Illinois, Chicago, IL, USA

ABSTRACT

Objective: To evaluate the cost-effectiveness of fondaparinux relative to enoxaparin as prophylaxis against venous thromboembolism (VTE) in patients undergoing hip fracture surgery.

Methods: A decision analysis model was created to simulate the impact of fondaparinux 2.5 mg once daily relative to enoxaparin 30 mg twice daily on patient outcomes and costs over various time points up to 5 years after surgery. Probabilities for the analysis were estimated for a hypothetical cohort of 1000 patients undergoing hip fracture surgery in the United States receiving either fondaparinux or enoxaparin according to comparative trial results. Resource use and costs (2003 dollars) were obtained from large healthcare databases. Outcome measures were rates of symptomatic VTE events, health-care costs, and incremental cost-effectiveness ratios.

Results: Fondaparinux is estimated to prevent an additional 30 VTE events (per 1000 patients) at 3 months compared with enoxaparin, producing savings of $103 at discharge, $290 over 1 month, $361 over 3 months, and $466 over 5 years. The results remain robust to clinically plausible variation in input parameters and assumptions.

Conclusions: Fondaparinux improves outcomes and is cost-saving over a broad range of assumptions compared with enoxaparin for prophylaxis of VTE after hip fracture surgery.

Keywords: cost-effectiveness, fondaparinux, hip fracture surgery, venous thromboembolism.

Introduction

Venous thromboembolism (VTE), encompassing deep-vein thrombosis (DVT) and pulmonary embolism (PE), remains an important cause of morbidity and mortality among patients undergoing hip fracture surgery [1]. Without prophylaxis, the incidence of DVT approaches 50% while fatal PE occurs in up to 12% of patients [1]. Because of this, thromboprophylaxis is routinely used in the majority of patients. Fondaparinux, a novel synthetic antithrombotic has recently been approved in the United States for prevention of VTE in patients undergoing hip fracture surgery. In a pivotal trial known as PENTHIFRA (PENTasaccharide in HIp FRActure surgery), fondaparinux, when administered for 7 to 10 days, was significantly more effective than the widely used low-molecular-weight heparin enoxaparin, with VTE reduced from 19.3% (119/624) to 8.3% (52/626), representing a relative risk reduction of 58% ($P < 0.001$), with no difference in clinically relevant bleeding [2].

In 2002, 315,000 hip fractures occurred in the United States [3], a figure which is expected to increase, in persons aged 50 years or above, by 70% over the next 40 years [4]. This increase, explained primarily by the aging of the population, has resulted in more attention being placed on the economic consequences of hip fracture surgery and its associated treatments [5]. The introduction of new prophylactic therapies, such as fondaparinux, has implications for hospital and pharmacy budgets and as a result, the economic costs and benefits need to be examined.

Based on guidelines for assessing outcomes of prophylaxis after major orthopedic surgery [6], an economic model has been developed to compare the cost-effectiveness of fondaparinux with enoxaparin, for patients undergoing major orthopedic surgery in the United States, including hip fracture surgery [7]. Using a 5-year decision analysis model, the outcomes and costs of VTE-related care were assessed. In the main analysis, for a hypothetical cohort of patients undergoing total hip replacement, total knee replacement or hip fracture surgery, fondaparinux was cost-saving compared with enoxaparin over a broad range of assumptions evaluated [7]. The greatest savings were demonstrated in patients undergoing hip fracture surgery.

Address correspondence to: Sean D. Sullivan, Pharmaceutical Outcomes Research and Policy Program, Department of Pharmacy and Health Services, Box 357630, University of Washington, Seattle, WA 98195, USA. E-mail: sdsull@u.washington.edu 10.1111/j.1524-4733.2006.00085.x

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In view of the cost implications associated with the high VTE risk after hip fracture surgery, we used the same economic model to concentrate on a cohort of patients undergoing hip fracture surgery and determine the cost-effectiveness of fondaparinux from the perspective of the US health-care payer.

**Methods**

**Decision Model**

A full description of the economic model has been published [7], with the main outcomes for each time period shown in Figure 1. Briefly, the decision analytic model enables translation of clinical trial end points (venographic DVT) into end points relevant to routine practice (clinical DVT and PE), and extrapolates the economic consequences beyond the time horizon of clinical trials. In particular, shorter postoperative hospital admissions mean that a greater proportion of VTE events occur after hospital discharge. The model relies on several key assumptions. First, hospitalized patients may develop a clinically apparent (symptomatic) or silent (asymptomatic) thrombotic event. In line with daily clinical practice, detection of DVT or PE is based on symptomatic presentation, which is subsequently confirmed by objective testing. Second, it accounts for those patients who may be incorrectly suspected of having a DVT or PE. Third, patients with confirmed VTE who undergo treatment are assumed to remain at risk of long-term complications (recurrent VTE or post-thrombotic syndrome [PTS]). Finally, patients with undetected and untreated DVT are assumed to be at risk of PTS. In addition, the model considers the risk of death and reflects the risk of major bleeding, fatal or nonfatal, during either prophylaxis or treatment of a VTE event.

Two distinct periods exist in the model: an acute phase, beginning with surgery and ending at 90 days (3 months); and a chronic phase, beginning on day 91 and ending 5 years after surgery. In the acute phase, “early” thrombi are defined as those developing during the period of hospitalization, and “late” thrombi as those developing between hospital discharges and day 30. Patients with early or late thrombi can present with clinical VTE before day 90 or can remain asymptomatic with future consequences. During the chronic phase patients are assumed to be at risk of long-term complications (recurrences, PTS) based on outcomes during the acute phase, even if they had subclinical events during the acute phase.

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**Figure 1** The cost-effectiveness decision model. A decision analytic model showing the range of clinical alternatives and outcomes that may occur in the prevention of venous thromboembolism (VTE) after hip fracture surgery. The circles represent chance nodes for a particular event. Thrombi (early or late) that would have been detected on bilateral systematic venography can remain as asymptomatic thrombi or develop into symptomatic VTE. Patients with detected (and confirmed) VTE are assumed to undergo treatment and remain at risk of long-term complications (Box 1). Patients with undetected (silent, or asymptomatic) and hence untreated VTE are also assumed to be at risk of long-term complications (Box 2). Suspected but not confirmed deep-vein thrombosis or pulmonary embolism, and major bleeding related to treatment of VTE, are included in the model but not represented on this figure.

*Long-term complications include VTE recurrences and post-thrombotic syndrome.*
Economic Analysis

The model compares the costs and outcomes of 7 days of fondaparinux 2.5 mg (Arixtra, GlaxoSmithKline, London, UK) administered once daily with 7 days of enoxaparin 30 mg (Lovenox, Aventis Pharma, Bridgewater, NJ, the United States) administered twice daily in patients undergoing hip fracture surgery. Enoxaparin is used as the comparator because it was the reference therapy used in the PENTHIFRA study [2], and is a standard of care recommended by the American College of Chest Physicians [1]. It also has been found to be cost-effective in numerous analyses, compared with either warfarin [8–11] or unfractionated heparin [12]. The balance between costs and effects is assessed by computing the incremental cost-effectiveness ratios, being the costs per symptomatic VTE event avoided, at various time points. The time horizon of the analysis includes hospital discharge, 30 and 90 days, and extends out to 5 years after surgery. The main outcome data are presented at discharge and at 90 days (3 months), because this is the period when the majority of thrombi manifest clinically.

The analysis is conducted on a hypothetical cohort of 1000 patients undergoing hip fracture surgery in the United States using the recommended dosing regimen of enoxaparin of 30 mg twice daily and commenced postoperatively. In the PENTHIFRA study enoxaparin was administered as 40 mg once daily preoperatively. It is assumed that the mean length of hospital stay is 7 days for patients undergoing hip fracture surgery, which is consistent with national statistics [3].

Event Probabilities

Because of a paucity of various outcomes for patients undergoing hip fracture surgery, data were extrapolated from patients undergoing hip replacement when information was not available. In particular, using data from the PENTHIFRA study and the more recent PENTHIFRA-Plus study, which evaluated the use of fondaparinux for up to 4 weeks after hip fracture surgery, the probability of symptomatic VTE events in patients undergoing hip fracture surgery was estimated to be 2.2 times that after hip replacement [2,13]. In the previous analysis [7], a more conservative hip fracture multiplier of 1.7 was used, which is now updated based on more recently available evidence.

Enoxaparin. Early thrombi rates were based on results from the PENTHIFRA study whereas the occurrence of symptomatic VTE at 90 days was estimated from a cohort study and randomized trial of patients undergoing total hip replacement [14,15]. The risk of late thrombi was estimated from a study of total hip replacement patients who had negative findings on venography at the time of hospital discharge [16], applying the above-mentioned multiplier (2.2) to extrapolate to a hip fracture population. Rates of symptomatic VTE occurring from late thrombi were estimated from a study by Hull and colleagues [17]. The temporal distribution of symptomatic VTE events after hip fracture surgery is similar to that after hip replacement [18] and was extrapolated from a large cohort study by White and colleagues [19] (Table 1).

Fondaparinux. The probabilities of early thrombi were based on the venographic results from the PENTHIFRA study [2], which showed the relative risk of early thrombi (venographic DVT) relative to enoxaparin to be 0.58. The probabilities of clinical VTE were estimated by assuming that the ratios of venographic DVT that become symptomatic were similar to that for enoxaparin. Despite a lack of conclusive information concerning the occurrence of late thrombi and subsequent clinical events, it is assumed that there was no difference compared with enoxaparin.

Bleeding risk. The risk of prophylaxis-related major bleeding was based on the observed rates seen in the PENTHIFRA study [2]. The risk of major bleeding related to the treatment of clinical VTE was estimated from pooled data of randomized clinical trials involving heparin, and/or warfarin where there was at least 3 months follow-up [20–27].

Other probability estimates. Rates of suspected but unconfirmed DVT (10%) and PE (2%) were obtained from the literature and assumed not to differ by type of prophylaxis received [28]. The risk of recurrent VTE over 5 years was based on methods described in the original cost-effectiveness model [7]. Briefly, outcomes for long-term follow-up study of patients with objectively verified symptomatic DVT was adjusted from a hip fracture surgery cohort [29] This estimate was apportioned between the acute and chronic phases, with the risk of recurrence assumed to begin immediately after an initial DVT or PE. Data from VTE treat-

### Table 1  Key baseline event probabilities

<table>
<thead>
<tr>
<th>Event</th>
<th>Fondaparinux</th>
<th>Enoxaparin</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early thrombi&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.0785</td>
<td>0.1878</td>
<td>[2]</td>
</tr>
<tr>
<td>Early clinical DVT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.0057</td>
<td>0.0375</td>
<td>[2,14,15,19]</td>
</tr>
<tr>
<td>Early clinical PE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.0089</td>
<td>0.0212</td>
<td>[2,14,15,19]</td>
</tr>
<tr>
<td>Late thrombi&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.1932</td>
<td>0.1932</td>
<td>[16,19]</td>
</tr>
<tr>
<td>Late clinical DVT&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.0251</td>
<td>0.0221</td>
<td>[2,14,15,17]</td>
</tr>
<tr>
<td>Late clinical PE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.0031</td>
<td>0.0028</td>
<td>[2,14,15,17]</td>
</tr>
<tr>
<td>Prophylaxis-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.0451</td>
<td>0.0451</td>
<td>[20–27,29,30]</td>
</tr>
<tr>
<td>After clinical VTE</td>
<td>0.2800</td>
<td>0.2800</td>
<td>[31]</td>
</tr>
<tr>
<td>After subclinical VTE</td>
<td>0.1168</td>
<td>0.1168</td>
<td>[32,33]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Thrombi refers to DVT detected by systematic venography.
<sup>b</sup>Cumulative to day 90.
<sup>c</sup>Probabilities are presented at 5 years.

Note: Rounding has been applied to some figures.

DVT, deep-vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.
ment trials [20–27,30] were used to estimate the risk of recurrence during the first 90 days versus later and recurrence during the chronic phase was distributed according to the temporal pattern observed in the long-term study [29]. The risk of PTS was assumed to begin at day 91 (chronic phase) and estimates were made separately depending on the development of clinical or subclinical DVT within 3 months of surgery. Cumulative risks of PTS after acute DVT were derived from a long-term outcome study [31]. Because of inconsistent data concerning the incidence of PTS after untreated subclinical DVT we used a weighted incidence from two studies (12%) [32,33] reporting the incidence of PTS among patients developing venographic DVT that is subsequently treated.

In view of a lack of epidemiological data, the risk of fatal PE was derived from the PENTHIFRA study (68.2%) [2]. The risk of death after major bleeding (0.63%) was derived from the percentage of patients with major bleeding from four large fondaparinux orthopedic clinical trials whose bleeding was deemed to be the cause of death after adjudication [2,34–36]. The probabilities of death from other causes (i.e., deaths unrelated to VTE) were estimated from US National Statistics.

**Estimates of Resource Use and Costs**

The costs of managing VTE, including the costs of investigations for suspected VTE events, treatment of confirmed cases, management of major bleeding, and the long-term sequelae of VTE were determined from various sources, as previously described (Table 2) [7]. Patients developing clinical VTE during the initial hospitalization were assumed to require extended stays in hospital, whereas those developing VTE after discharge are either readmitted or treated at home. The proportion of patients treated either in the inpatient and outpatient setting was determined from a claims database.

Work-up costs for suspected but unconfirmed VTE were based on a previous economic evaluation [12]. In-hospital VTE management costs were derived from a large multihospital Clinical Pathways Data Base (CPDB) [37], updated to 2003 prices [38]. VTE events costs after hospital discharge was derived from a US health-care claims database [39].

Prophylaxis-related major bleeding costs were similarly derived from the CPDB database [37]. Here, patients undergoing hip fracture surgery were stratified according to whether or not they had coded secondary diagnoses of bleeding with total estimated costs of inpatient care then compared between groups. Patients with diagnoses of DVT or PE were excluded from the sample to minimize the possibility that bleeding was treatment-related. Minor bleeding costs were not included in the analysis because of difficulty in obtaining precise estimates, and the fact that no difference was seen in this outcome between fondaparinux and enoxaparin in the clinical trial. In the absence of reliable US studies, the costs of treating PTS were estimated from a Swedish study of long-term consequences of VTE [40]. Costs were converted from Swedish kroner using average exchange rates and updated to 2003 price levels. All costs parameters were expressed in 2003 US dollars and all costs and effects beyond 1 year were discounted at 3%.

**Sensitivity Analyses**

One-way sensitivity analyses were performed at day 90 to test parameter uncertainty. The baseline assumptions were varied to examine the effect of credible variations. Where possible the reported 95% confidence intervals were used, otherwise 50% was added or subtracted to the values.

**Results**

The number of clinical VTE events prevented and costs savings at 1 and 3 months when fondaparinux is used instead of enoxaparin in a cohort of US patients undergoing hip fracture surgery are shown in Table 3. Fondaparinux prevents an additional 24.1 clinical events per 1000 patients at 1 month when used in place of enoxaparin, and 30 clinical events (18.4 DVT, 11.7 PE) are prevented after 3 months (number needed to treat [NNT] = 33). In addition, 7.9 deaths from PE (reduced from 15.9 to 8.0 per 1000 patients) will be prevented after 3 months. The reduction in VTE events

<p>| Table 2 | Costs of individual procedures and events for patients undergoing hip fracture surgery |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Event cost ($)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost of prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>265</td>
<td>[44]</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>242</td>
<td></td>
</tr>
<tr>
<td><strong>Cost of treating confirmed DVT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital</td>
<td>16,426</td>
<td>[12,37]</td>
</tr>
<tr>
<td>Post-discharge</td>
<td>11,210</td>
<td>[12]</td>
</tr>
<tr>
<td><strong>PE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital</td>
<td>12,361</td>
<td>[12,37]</td>
</tr>
<tr>
<td>Post-discharge</td>
<td>12,969</td>
<td>[12]</td>
</tr>
<tr>
<td><strong>Costs of excluding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspected but unconfirmed DVT</td>
<td>756</td>
<td></td>
</tr>
<tr>
<td>Suspected but unconfirmed PE</td>
<td>957</td>
<td></td>
</tr>
<tr>
<td><strong>Cost of adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4,788</td>
<td>[G. Oster, pers. comm.]</td>
</tr>
<tr>
<td><strong>Costs of long-term complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute PTS (1st quarter)</td>
<td>2,133</td>
<td>[31–33]</td>
</tr>
<tr>
<td>Chronic PTS (subsequent quarters)</td>
<td>355</td>
<td>[31–33]</td>
</tr>
</tbody>
</table>

*Prophylaxis costs included the acquisition cost of each drug (fondaparinux $34.8/day, enoxaparin $30.8/day), as well as the administration ($0.65/day) and monitoring costs ($16.8 per patient) of each therapy for 7 days.

†Includes cost of treating varicose veins, venous ulcer, chronic venous insufficiency, and cellulitis. First quarter is from days 1–90; subsequent quarters yearly.

DVT, deep-vein thrombosis; PE, pulmonary embolism; PTS, post-thrombotic syndrome.
continue to increase over the 5-year period (Data not shown). Savings per patient with the use of fondaparinux are: $103 at hospital discharge, $290 1 month after surgery, and $361 3 months after surgery. When long-term consequences of clinical events are included, the economic benefits increase with savings of $387 at year 1 and $466 at year 5 (Table 4, Fig. 2). At all time points the greatest cost savings with using fondaparinux are seen in reduced requirement for treatment for clinical VTE events, exceeding the costs of prophylaxis or any adverse events (Fig. 3).

**Sensitivity Analysis**

The results of the one-way sensitivity analyses at day 90 are illustrated in Table 5. The results are generally robust to plausible changes in all values tested. Fondaparinux remains cost-saving in all assumptions, even with wide variations in the overall main variables.

**Discussion**

Patients who undergo hip fracture surgery are at the highest risk of VTE. For patients receiving low-molecular weight heparin, fatal PE occurs in up to 2% of patients [41]. In the PENTHIFRA study, the synthetic factor Xa inhibitor fondaparinux was significantly more effective at reducing VTE than enoxaparin after hip fracture surgery [2]. This economic analysis suggests that in addition to its clinical benefits, prophylaxis of VTE with fondaparinux is cost-saving compared with enoxaparin when administered to a cohort population of US patients undergoing hip fracture surgery. Cost savings of $103 per patient are seen during hospitalization, which increases after hospital discharge.

The economic model developed for this analysis is dynamic, in that outcomes can be presented at different time points and assessed for different populations of patients undergoing major orthopedic surgery. Here we have concentrated on a hip fracture surgery population and used a trial-based analysis to maintain trial validity and reduce uncertainties concerning outcomes. The majority of cost savings seen with use of fondaparinux are due to the reduced number of clinical VTE events requiring treatment. In particular, each PE or DVT event after hip fracture surgery requires an
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addition of 7- to 9-day hospitalization for the associated treatment of each event [37]. Treatment costs for these events range from $11 to $16,000 per event, with the range being dependent on the nature of the event (DVT or PE) and its occurrence either in or out of hospital. The additional costs of prophylaxis, diagnosis of suspected events and bleeding complications comprise only a small proportion of overall costs.

In general terms, hospital pharmacies and insurers have a tendency to bear the cost of prophylaxis whereas patients accrue some or all of the benefits. At present, hospital pharmacies and pharmacy benefit programs of health insurance providers often work from capitated drug budgets. This practice, termed silo budgeting, means that paying for expensive drugs beyond some anticipated level may lead to budget shortfalls in other areas unless cutbacks are made or additional funds are identified [42]. Often a critical issue in decision-making is whether the “improvement” in a drug therapy warrants an associated increase in cost. In this regard, the price difference between fondaparinux and enoxaparin is $23 when administered for 7 days, a modest increase compared with the overall cost savings of $103 at hospital discharge. Therefore, with a small incremental price difference in cost between fondaparinux and enoxaparin, savings are recouped within 7 days.

As with all economic analyses, several assumptions were made. The findings are based on the results of a single large study [2], in which the efficacy of fondaparinux over enoxaparin was clearly demonstrated. In the PENTHIFRA study [2], enoxaparin was used as the comparator at a dose of 40 mg once daily, commenced preoperatively. In line with current US practice, this analysis, however, assesses the use of enoxaparin at a dose of 30 mg twice daily, commenced postoperatively. We think it is unlikely that the differ-

![Figure 2](image-url) Distribution of hip fracture surgery costs (per patient) at various time points.

![Figure 3](image-url) Distribution of combined and individual surgical group costs (2003 US dollars) at day 90. VTE, venous thromboembolism.

Table 5  Sensitivity analysis—cost savings with use of fondaparinux compared with enoxaparin per patient at day 90

<table>
<thead>
<tr>
<th>Test performed</th>
<th>Cost savings ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>361</td>
</tr>
<tr>
<td>Efficacy of fondaparinux vs. enoxaparin varied with 95% CI (Base case 58.2% [95% CI 45.0–71.34%])</td>
<td>276–448</td>
</tr>
<tr>
<td>Major bleeding of fondaparinux vs. enoxaparin varied ±50%</td>
<td>307–416</td>
</tr>
<tr>
<td>Cost of treating confirmed VTE varied ±50%</td>
<td>169–554</td>
</tr>
<tr>
<td>Price of fondaparinux vs. enoxaparin varied (low: enoxaparin–20%; high: fondaparinux–20%)</td>
<td>318–410</td>
</tr>
<tr>
<td>Hip fracture multiplier varied form 1.7–2.7 (Base case 2.2)</td>
<td>274–449</td>
</tr>
<tr>
<td>Cost of confirming VTE varied ±50%</td>
<td>358–365</td>
</tr>
<tr>
<td>Rate of false-positive VTE diagnosis varied ±50%</td>
<td>358–365</td>
</tr>
<tr>
<td>Cost of prophylaxis-related bleeding varied ±50%</td>
<td>359–364</td>
</tr>
</tbody>
</table>

CI, confidence interval; VTE, venous thromboembolism.
ent enoxaparin dosing regimens will have any substantial impact on the efficacy and safety outcomes demonstrated in this analysis. This is highlighted by the sensitivity analysis where variations of 50% in relative efficacy and safety had no substantial impact on the results. Furthermore, a meta-analysis of four similarly designed studies in which fondaparinux was compared with different dosing regimens of enoxaparin in different orthopedic populations showed consistent efficacy and safety results [43]. To maintain external validity for the clinical outcome probabilities used in this analysis a wide spectrum of randomized controlled trials and cohort studies were assessed and incorporated, reflecting contemporary clinical practice in which patients do not routinely undergo venography as in clinical trials. The assumptions were further validated by an international advisory board. Furthermore, because the analysis only examines direct costs related to the health-care system, incorporation of indirect costs and patient focused issues such as quality of life impairment would likely improve the cost-effectiveness of fondaparinux.

In conclusion, this analysis demonstrates that in patients undergoing hip fracture surgery, thromboprophylaxis with fondaparinux, compared with enoxaparin, is cost-saving with reduced clinical events compared with enoxaparin. The results of the analysis, in conjunction with the associated clinical trial results, strengthen the claim of fondaparinux as the standard of care for VTE prevention after hip fracture surgery.

The economic model on which this analysis is based was constructed with the assistance of an International Economic Advisory Board including: Chair—Sean Sullivan (Health Economist, USA), Lars Borris (Orthopedic Surgeon, Denmark), Patrick Bossuyt (Clinical Epidemiologist, the Netherlands), Bruce Davidson (Pulmonary and Critical Care Medicine, USA), Bengt Jonsson (Health Economist, Sweden), Susan Kahn (Clinical Epidemiologist, Canada), Emile Levy (Health Economist, France), James E. Muntz (Health Economist, France), Lars Borris (Orthopedic Surgeon, Denmark), Gerard de Pouvourville (Health Economist, France), Gary E. Raskob (Clinical Epidemiologist, USA). We also thank John Posnett, Adam Gordois, and Dan Ollendorf for their assistance in the construction of the economic model. The Advisory Board was supported by a grant from Sanofi-Synthelabo Inc, New York, USA. A poster of the results was presented in December 2003 at the mid-year clinical meeting of the American Society of Health-System Pharmacists (ASHP) in New Orleans, LA.

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