Superiority of Fondaparinux Over Enoxaparin in Preventing Venous Thromboembolism in Major Orthopedic Surgery Using Different Efficacy End Points*

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**Study objectives:** To assess the relevance of various efficacy end points established for thromboprophylaxis trials, we compared the results of the fondaparinux phase III program in major orthopedic surgery using the original primary efficacy end point with those obtained when the efficacy end points recently suggested by the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy and the European Committee for Proprietary Medicinal Products (CPMP) were used.

**Setting and patients:** Fondaparinux was compared with enoxaparin in four multicenter, randomized, double-blind trials of major orthopedic surgery. The original primary efficacy end point consisted of a composite of deep-vein thrombosis detected by mandatory bilateral venography, documented symptomatic deep-vein thrombosis, or pulmonary embolism up to day 11. The efficacy end point established by the ACCP Consensus Conference on Antithrombotic Therapy comprises any proximal deep-vein thrombosis, symptomatic proven deep-vein thrombosis or pulmonary embolism, or fatal pulmonary embolism, and that established by the European CPMP comprises any proximal deep-vein thrombosis, symptomatic proven pulmonary embolism, or death from any cause.

**Interventions:** Patients were randomized to receive either subcutaneous fondaparinux (2.5 mg once daily) starting postoperatively or approved enoxaparin regimens.

**Results:** Using the original end point of the fondaparinux studies, the incidence of venous thromboembolism was 13.7% (371 of 2,703 patients) in the enoxaparin group compared with 6.8% (182 of 2,682 patients) in the fondaparinux group, with a common odds reduction of 55.2% (p < 0.001; 95% confidence interval, 45.8% to 63.1%) in favor of fondaparinux. The respective incidences of efficacy end points with enoxaparin and fondaparinux were 3.3% and 1.7%, respectively, according to the ACCP definition, and 3.9% and 2.1%, respectively, according to the CPMP definition. The common odds reduction in favor of fondaparinux was 49.6% (p < 0.001) and 48.0% (p < 0.001), respectively.

**Conclusions:** Fondaparinux was consistently more effective than enoxaparin in preventing venous thromboembolism in patients undergoing major orthopedic surgery, irrespective of the established composite outcomes used.

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**Key words:** clinical trial; factor Xa inhibitors; fondaparinux; low-molecular-weight heparins; major orthopedic surgery; Org31540/SR90107; pentasaccharide; thromboprophylaxis; venography; venous thromboembolism

**Abbreviations:** ACCP = American College of Chest Physicians; CI = confidence interval; CPMP = Committee for Proprietary Medicinal Products

Thromboprophylaxis aims to prevent the occurrence of deep-vein thrombosis and its complication, pulmonary embolism. However, the most reliable primary efficacy end point for thromboprophylaxis trials is a matter of debate. Clinically symptomatic venous thromboembolic events are rare, necessitating the enrollment of a large number of patients into trials in order to be able to demonstrate significant differences between various thromboprophylactic strategies. Moreover, the diagnosis of venous thromboembolism based on clinical presentation is unreliable. Asymptomatic deep-vein thrombosis (ie, that detected by routine surveillance testing) has been proposed as a surrogate end point. It occurs more frequently than do symptomatic events. In patients undergoing total hip replacement...
without any thromboprophylaxis, the incidence of deep-vein thrombosis diagnosed by mandatory venography 7 to 14 days after surgery ranges from 45 to 57%,1 whereas in a cohort of 1,162 comparable patients, the 6-month cumulative incidence of symptomatic deep-vein thrombosis was 1.9%.3 In addition, asymptomatic deep-vein thrombosis can be diagnosed by objective methods, ascending bilateral venography being the reference standard.2,4 However, the clinical relevance of these asymptomatic events, particularly distal deep-vein thrombosis, has been questioned, as these conditions may resolve spontaneously without causing clinical symptoms.1 Thus, the American College of Chest Physicians (ACCP) Consensus on Antithrombotic Therapy,1 and the European Committee for Proprietary Medicinal Products5 (CPMP) have proposed various definitions of primary efficacy outcomes combining asymptomatic and symptomatic events (Table 1).

In four double-blind, randomized trials6–9 comparing fondaparinux, the first synthetic and selective factor Xa inhibitor, with the low-molecular-weight heparin enoxaparin in 7,344 patients undergoing major orthopedic surgery, the primary efficacy end point, predefined with regulatory bodies, was a composite of symptomatic and asymptomatic venous thromboembolic events (Table 1). Using this composite end point, fondaparinux showed a significantly superior efficacy over enoxaparin, with a reduction in relative risk of > 50% (p < 0.001).10 The composite end point used in the fondaparinux studies differed from those proposed by the ACCP Consensus Conference on Antithrombotic Therapy and the by CPMP, notably by taking into account asymptomatic distal deep-vein thromboses. We verified in the present study whether the superior efficacy of fondaparinux over enoxaparin was maintained when utilizing the composite efficacy end points proposed by the ACCP Consensus Conference on Antithrombotic Therapy and the European CPMP. Although these analyses were not predefined in the protocol of the fondaparinux studies, data from the fondaparinux phase III studies in major orthopedic surgery are particularly compelling to test the relevance of these different efficacy end points because of the large study population involved.

Materials and Methods

Study Design

The four multicenter studies were conducted as randomized, parallel-group, double-blind clinical trials.6–9 In all four studies, the day of surgery was defined as day 1. Treatment was scheduled to last up to days 5 to 9 after surgery. These studies were conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, and with good clinical practice and local regulations. The protocols were approved by independent ethics committees or institutional review boards, where applicable, and written informed consent was obtained from all patients before randomization.

Patient Population

Patients who were at least 18 years of age were considered for inclusion if they were scheduled for elective major hip surgery,8,9 elective major knee surgery,7 or standard surgery for a fracture of the upper third of the femur.9 Exclusion criteria were described previously.6–9

Table 1—Definitions of the Three Composite Primary Efficacy End Points*

<table>
<thead>
<tr>
<th>End Points</th>
<th>Fondaparinux Studies†</th>
<th>ACCP Consensus Conference</th>
<th>European CPMP‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DVT</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Any proximal DVT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Documented symptomatic DVT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Documented asymptomatic proximal DVT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Documented asymptomatic PE</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*DVT = deep-vein thrombosis; PE = pulmonary embolism.  
†The composite end point included any one of the following events.  
‡Primary efficacy end points defined for noninferiority trials.
Randomization of the Patients, Medications, and Dosing Schedule

In all studies, patients were randomly assigned to receive subcutaneously either fondaparinux (2.5 mg once daily) [Arixtra; Sanofi-Synthelabo; Paris, France; and NV Organon; Oss, the Netherlands] or enoxaparin (Clexane/Klexane/Lovenox; Aventis Pharma; Bridgewater, NJ) in a double-blind manner. In all four studies, the protocol required that the first injection of fondaparinux be administered at a mean (± SD) 6 ± 2 h postoperatively. Enoxaparin was administered according to the dosage regimens recommended for use by health authorities and the manufacturer (ie, 30 mg twice daily starting 12 to 24 h postoperatively in two of the trials,7,8 and 40 mg once daily starting 12 h before surgery, followed by a second injection 12 to 24 h postoperatively in the two other trials6,9). Throughout the treatment period, therapy with intermittent pneumatic compression, dextran, and thrombolytic or anticoagulant agents was prohibited. Centers were instructed to avoid the use of aspirin or nonsteroidal antiinflammatory drugs whenever possible. Other antiplatelet agents were prohibited. The use of graduated compression stockings was allowed, and physiotherapy was recommended.

Outcome Measures

The primary efficacy end point was venous thromboembolism (defined as deep-vein thrombosis, pulmonary embolism, or both) up to day 11. Patients were systematically examined for deep-vein thrombosis by mandatory ascending bilateral contrast venography of the lower limbs,11 which is the standard recommended method for the evaluation of new antithrombotic drugs in patients undergoing major orthopedic procedures.2,4 Venography was performed between days 5 and 11, but no more than 2 days after the last study drug injection, or earlier if thrombosis was clinically suspected. Symptomatic pulmonary embolism was confirmed by lung scanning, pulmonary angiography,12 or helical CT scanning, or, in the event of death, at autopsy. During the treatment period, the investigator performed daily assessments for signs and symptoms of venous thromboembolism. Efficacy outcomes, including a review of all venograms, and the safety outcomes bleeding and death were adjudicated by a central independent committee, the members of which were unaware of the patients’ treatment assignment.

Statistical Analysis

To determine the effect of using the composite end points suggested by the ACCP Consensus Conference on Antithrombotic Therapy1 and the European CPMP,5 post hoc analyses were performed using data from the database of the four thromboprophylaxis studies in orthopedic surgery.6-9 The efficacy end point established by the ACCP Consensus Conference on Antithrombotic Therapy comprises any proximal deep-vein thrombosis, symptomatic proven deep-vein thrombosis, or pulmonary embolism, or fatal pulmonary embolism, and that established by the European CPMP comprises any proximal deep-vein thrombosis, symptomatic proven pulmonary embolism, or death from any cause. The primary efficacy outcome analysis included data on all patients who had received at least one dose of study medication, had undergone the appropriate surgery, and had undergone an adequate venous thromboembolism assessment by day 11. Before pooling all the efficacy data, the homogeneity among the four studies was tested using the Zelen exact test.

Results

A total of 7,344 patients were randomized in 375 centers worldwide, with 3,668 patients being assigned to receive fondaparinux and 3,676 patients being assigned to receive enoxaparin. Among these patients, 5,385 (73.3%) were available for the analysis of efficacy. Using the original primary efficacy end point, the overall incidence of venous thromboembolism up to day 11 was lower in the fondaparinux group than in the enoxaparin group (6.8% [182 of 2,682 patients] vs 13.7% [371 of 2,703 patients], respectively) with a highly significant common odds reduction of 55.2% in favor of fondaparinux (95% confidence interval [CI], 45.8 to 63.1%; p < 0.001).10 The incidence of the composite efficacy end point as proposed by the ACCP Consensus Conference on Antithrombotic therapy was 1.7% with fondaparinux and 3.3% with enoxaparin (Fig 1). The common odds reduction in favor of fondaparinux was 49.6% (95% CI, 27.3 to 65.5%; p < 0.001). Using the definition suggested by the CPMP, the incidence of the composite efficacy end point was 2.1% with fondaparinux and 3.9% with enoxaparin, with a common odds reduction in favor of fondaparinux of 48.0% (95% CI, 27.3 to 63.2%; p < 0.001). Therapy with fondaparinux was superior to enoxaparin in major knee and hip fracture surgery (p < 0.05), regardless of the efficacy end point. After elective hip replacement surgery, fondaparinux also significantly (p < 0.001) reduced the incidence of venous thromboembolism using the original primary efficacy end point. However, in this setting, the trend in favor of fondaparinux was not significant using the ACCP consensus conference and European CPMP criteria.

The results of each efficacy end point included in the definitions of the different composite primary efficacy end points are shown in Table 2. The incidences of total, proximal only, and distal only deep-vein thromboses were lower in the fondaparinux group (6.5%, 1.3%, and 5.2%, respectively) than in the enoxaparin group (13.5%, 2.9%, and 10.8%, respectively). Interestingly, in knee surgery patients > 95% of proximal thromboses were associated with distal deep-vein thrombosis, whereas in hip surgery patients 65% were associated with distal deep-vein thrombosis (Table 3). Likewise, while only 12.6% of deep-vein thromboses (19 of 151 thromboses) were located in the leg not operated on after major knee surgery, 39.2% of those (102 of 260 thromboses) were in the contralateral leg after hip replacement surgery (Table 4). Overall, therapy with fondaparinux provided a
significant and comparable benefit over enoxaparin, irrespective of the legs examined. Finally, the incidence of other symptomatic outcomes was low and did not differ between the two groups.

**Table 2—Incidence of Each Efficacy End Point up to Day 11 Included in the Definitions of the Three Different Composite Primary Efficacy End Points**

<table>
<thead>
<tr>
<th>Event</th>
<th>Fondaparinux</th>
<th>Enoxaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any DVT detected by mandatory bilateral venography†</td>
<td>174/2,677 (6.5)</td>
<td>363/2,698 (13.5)</td>
</tr>
<tr>
<td>Any proximal DVT</td>
<td>35/2,756 (1.3)</td>
<td>81/2,775 (2.9)</td>
</tr>
<tr>
<td>Documented symptomatic DVT</td>
<td>12/3,603 (0.3)</td>
<td>6/3,608 (0.2)</td>
</tr>
<tr>
<td>Documented symptomatic proximal DVT</td>
<td>9/3,603 (0.2)</td>
<td>4/3,608 (0.1)</td>
</tr>
<tr>
<td>Documented symptomatic PE</td>
<td>11/3,603 (0.3)</td>
<td>10/3,608 (0.3)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>2/3,603 (0.1)</td>
<td>3/3,608 (0.1)</td>
</tr>
<tr>
<td>Death from any cause including fatal PE</td>
<td>15/3,616 (0.4)</td>
<td>21/3,621 (0.6)</td>
</tr>
</tbody>
</table>

*Values given as the No. of patients with events/the total No. of patients assessed for this event (%). See Table 1 for abbreviations not used in the text.
†Overall, there were 18 symptomatic DVTs (13 proximal and 5 distal only).

**Figure 1.** Common odds reduction in the incidence of venous thromboembolism up to day 11 according to the definition of the primary efficacy outcome. n = total number of patients assessed for the event.

**Discussion**

Illustrating the silent nature of deep-vein thrombosis and in accordance with observations in other clinical trials of thromboprophylaxis in a surgical setting, there were considerably fewer symptomatic thrombotic events than asymptomatic thrombotic events in the pooled fondaparinux trials presented. The difference in symptomatic events between patients treated with fondaparinux and those treated with enoxaparin was not significant, but the trials were not designed and powered to detect such a difference. In addition, as in all trials using a screening test after the treatment period, two therapeutic interventions are likely to have prevented the subsequent occurrence of symptomatic events. First, based on the local site assessment, >95% of patients with positive venography findings at screening received anticoagulant therapy in therapeutic doses. By day 11, fewer patients were being treated for a venous thromboembolic event in the fondaparinux group (5.5%) than in the enoxaparin group (9.7%; p < 0.0001). Second, about 40% of the remaining patients who were free of venous thromboembolic...
events at day 11 received prolonged prophylaxis with heparins or warfarin after the study treatment period. It is important to note that the primary efficacy end point was assessed at the end of the study treatment period (ie, up to day 11 after surgery) since, when our trials were designed, only short-term prophylaxis after total hip replacement was recommended by international guidelines for thromboprophylaxis, and by health authorities in both Europe and North America. Since asymptomatic deep-vein thromboses may resolve spontaneously, the incorporation of this event in the composite primary efficacy end point in thromboprophylaxis trials has been questioned. However, even asymptomatic deep-vein thrombosis carries a substantial risk of pulmonary embolism, and no simple parameter allows the prediction of this potential evolution. Thus, thromboprophylaxis is recommended for all patients undergoing major orthopedic surgery. As indicated above, it is interesting to note that the investigators of the fondaparinux studies considered asymptomatic deep-venous thrombosis to be clinically important since they treated > 95% of patients with positive venography findings, including those with isolated distal vein thromboses, with therapeutic doses of anticoagulants. Moreover, in several meta-analyses of data from trials performed in various clinical settings, including major orthopedic surgery, the reduction in asymptomatic venographically proven deep-vein thrombosis with anticoagulant therapy, compared with no treatment or placebo, was associated with a parallel reduction in symptomatic pulmonary embolism. Composite end points combining asymptomatic proximal and distal deep-vein thromboses and symptomatic venous thromboembolic events therefore have been used for the registration of low-molecular-weight heparins over the past years, as well as, more recently, hirudin and fondaparinux.

As reported previously, the majority of asymptomatic deep-vein thromboses occurring in the fondaparinux studies were distal, particularly in knee surgery patients. The fact that the majority of deep-vein thromboses in knee surgery involved both distal and proximal veins, whereas they were more frequently located in proximal veins only in hip surgery, suggests that in knee surgery thrombus formation occurs distally and further extends proximally,

Table 3—Incidence of Proximal and Distal Deep-Vein Thrombosis up to Day 11

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Fondaparinux Group</th>
<th>Enoxaparin Group</th>
<th>Total</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture (1,711 randomized patients, 194 DVTs)</td>
<td>7/8 (87.5)</td>
<td>19/19 (100)</td>
<td>26/27 (96.3) [81.0−99.9]</td>
<td></td>
</tr>
<tr>
<td>Elective hip replacement (8,9)</td>
<td>9/15 (60.0)</td>
<td>21/31 (67.7)</td>
<td>30/46 (65.2) [49.8−78.7]</td>
<td></td>
</tr>
<tr>
<td>Hip fracture (6)</td>
<td>2/4 (50.0)</td>
<td>17/26 (65.4)</td>
<td>19/30 (63.3) [43.9−80.1]</td>
<td></td>
</tr>
</tbody>
</table>

*Values given as proximal plus distal DVT/any proximal DVT (%) [95% CI].
†Pooled data from the two double-blind, randomized fondaparinux trials in elective hip replacement surgery.

Table 4—Incidence of Deep-Vein Thrombosis up to Day 11 in the Lower Extremities Operated On and Not Operated On

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fondaparinux Group</th>
<th>Enoxaparin Group</th>
<th>Total</th>
<th>p Value</th>
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<td></td>
</tr>
</tbody>
</table>

*Values given as the No. of patients with events/total No. of patients assessed for this event (%). Denominators have different values as venography was not evaluable in both legs in all patients. See Table 1 for abbreviations not used in the text.
†Pooled data from the two double-blind, randomized fondaparinux trials in elective hip replacement surgery.
whereas in hip surgery thrombus formation initiates more frequently in proximal veins. Distal deep-vein thromboses were included in the definition of the composite primary efficacy end point used in the fondaparinux studies since this was recommended at that time by health authorities. The ACCP Consensus Conference on Antithrombotic Therapy and the European CPMP (for noninferiority trials) now takes into account only proximal deep-vein thromboses (ie, those usually considered as posing a greater risk for pulmonary embolism due to their location in the vicinity of major venous trunks). However, although distal only deep-vein thrombi are often small and nonocclusive, and dissolve spontaneously, they are not risk-free. A total of 22% of those occurring postoperatively in untreated patients were shown to progress to more proximal venous segments, an event that is associated with a high risk of pulmonary embolism. Pulmonary perfusion defects on systematic lung scanning were present with a rate as high as 30% in patients with distal deep-vein thrombosis only. Furthermore, in unselected autopsies, pulmonary embolism and fatal pulmonary embolism were associated with isolated calf deep-vein thrombosis in 22.8% and 23.1% of the cases, respectively. It was also shown that patients with distal-vein thrombosis are exposed to a high 30% rate of recurrent deep-vein thrombosis or pulmonary embolism in the following 3 months if they are not adequately treated. The European CPMP includes distal deep-vein thrombosis in its definition of the primary efficacy end point for superiority trials and exploratory therapeutic studies. Importantly, we show here that the superiority of therapy with fondaparinux over that with enoxaparin is confirmed for each separate end point (ie, proximal and distal deep-vein thrombosis) and when the European CPMP and the ACCP Consensus on Antithrombotic Therapy composite end points are used.

Venography is invasive and not easy to perform, but it still remains the standard recommended screening method for asymptomatic deep-vein thrombosis in patients who are undergoing major orthopedic procedures, because it is both accurate and reliable. Leg scanning with labeled fibrinogen is no longer used since the product was taken off the market owing to the risk of viral contamination. Impedance plethysmography, duplex ultrasonography, and color Doppler ultrasound have only moderate sensitivity and a positive predictive value when used in asymptomatic medical or high-risk surgical patients. MRI awaits reproducible proof of its accuracy in asymptomatic patients receiving thromboprophylaxis. The consistency of bilateral venography in detecting deep-vein thrombosis has been well-illustrated by the fondaparinux studies in patients undergoing total hip replacement. Using 2.5 mg fondaparinux, the predicted incidence of deep-vein thrombosis in the phase II dose-finding study was 4.1%, and the actual incidences in the two phase III studies were 4.1% and 6.1%. The relatively high incidence of bilateral and unsuspected contralateral deep-vein thrombosis following orthopedic surgery, especially hip surgery, calls into question the reliance on unilateral objective diagnostic criteria as the basis for making decisions regarding antithrombotic therapy. Bilateral contrast venography not only provides a more accurate assessment of the actual incidence of deep-vein thrombosis than unilateral contrast venography, but permits the reduction of sample size in prophylaxis studies, particularly in hip surgery. Although a drawback of venography is the failure to obtain evaluable venography in all patients, thereby diminishing the statistical power of the test, this could not have biased our findings as the studies were double-blind, there was no difference in the rate of evaluable venography between the two groups, and venograms were interpreted by an adjudication committee that was blinded to treatment assignment.

In the definition of the composite efficacy end point, we and the ACCP Consensus Conference on Antithrombotic Therapy considered death to be related to venous thromboembolism only, whereas the European CPMP took into account all-cause death. Death related to venous thromboembolism has the advantage of being more closely related to the event that must be directly prevented by thromboprophylaxis, but, besides the difficulty of obtaining examinations by autopsy, it may be difficult to ascertain whether pulmonary embolism was the direct cause of death. In contrast, all-cause death is a nonspecific outcome in studies on thromboprophylactic treatments, but it is not subject to misclassification. Interestingly, the reduction in venographically proven deep-vein thrombosis with the use of anticoagulants has been shown to be associated with a reduction in the overall mortality rate.

**CONCLUSION**

We have shown in the present study that therapy with fondaparinux was significantly more effective than enoxaparin in preventing venous thromboembolism in patients undergoing major orthopedic surgery, whichever definition of the primary efficacy composite end point was used (ie, the original definition in the fondaparinux studies or the composite outcome proposed by the ACCP Consensus Conference on Antithrombotic Therapy or the European CPMP for thromboprophylaxis trials). A statistically
significant superiority of fondaparinux over enoxaparin, regardless of the efficacy composite endpoint, was demonstrated in patients undergoing major knee and hip fracture surgery. In hip replacement surgery, statistical significance was reached only when the original efficacy endpoint of the fondaparinux studies was used.

Overall, as the incidence of clinically relevant bleeding (leading to death or reoperation, or occurring in a critical organ) did not differ between the two study groups, fondaparinux may have a better benefit-risk ratio than enoxaparin in the prevention of venous thromboembolism after major orthopedic surgery.

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