Fondaparinux or Enoxaparin for the Initial Treatment of Symptomatic Deep Venous Thrombosis

A Randomized Trial

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Background: **The current standard initial therapies for deep venous thrombosis are low-molecular-weight heparin and unfractionated heparin. In a dose-ranging study of patients with symptomatic deep venous thrombosis, fondaparinux had efficacy and a safety profile similar to those of low-molecular-weight heparin (dalteparin).**

Objective: **To evaluate whether fondaparinux has efficacy and safety similar to those of enoxaparin in patients with deep venous thrombosis.**

Design: **Randomized, double-blind study.**

Setting: **154 centers worldwide.**

Patients: **2205 patients with acute symptomatic deep venous thrombosis.**

Intervention: **Fondaparinux, 7.5 mg (5.0 mg in patients weighing <50 kg and 10.0 mg in patients weighing >100 kg) subcutaneously once daily, or enoxaparin, 1 mg/kg of body weight, subcutaneously twice daily for at least 5 days and until vitamin K antagonists induced an international normalized ratio greater than 2.0.**

Measurements: **The primary efficacy outcome was the 3-month incidence of symptomatic recurrent venous thromboembolic complications. The main safety outcomes were major bleeding during initial treatment and death. An independent, blinded committee adjudicated all outcomes.**

Results: **43 (3.9%) of 1098 patients randomly assigned to fondaparinux had recurrent thromboembolic events compared with 45 (4.1%) of 1107 patients randomly assigned to enoxaparin (absolute difference, −0.15 percentage point [95% CI, −1.8 to 1.5 percentage points]). Major bleeding occurred in 1.1% of patients receiving fondaparinux and 1.2% of patients receiving enoxaparin. Mortality rates were 3.8% and 3.0%, respectively.**

Limitations: **Follow-up was incomplete in 0.4% of fondaparinux-treated patients and 1.0% of enoxaparin-treated patients.**

Conclusions: **Once-daily subcutaneous fondaparinux was at least as effective (not inferior) and safe as twice-daily, body weight–adjusted enoxaparin in the initial treatment of patients with symptomatic deep venous thrombosis.**

Ann Intern Med. 2004;140:867-873. **www.annals.org**

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See editorial comment on pp 925-926.

Low-molecular-weight heparin (LMWH) therapy has expanded the options for initial management of patients presenting with deep venous thrombosis (1, 2). Low-molecular-weight heparin treatment is simple and consists of once- or twice-daily subcutaneous injection of a dose adjusted only for body weight. Treating suitable patients at home, often with self-injection, is effective and safe and has become standard practice in many settings (2–4).

Clinically relevant aspects of LMWH treatment of venous thromboembolism remain uncertain, which may influence usage and recurrence or bleeding. First, LMWHs differ among themselves. Second, data on whether once- or twice-daily LMWH may be superior are conflicting (5, 6), suggesting that a once-daily regimen of enoxaparin may be less effective in patients with higher body mass index and patients with cancer (7). Third, since LMWHs are eliminated in the urine and plasma levels are higher in patients with even modest renal insufficiency (8), some clinicians administer lower dosages when the patient's creatinine clearance is less than 0.84 mL/s (9), despite few outcome data to guide such alterations. Finally, in addition to the clinical and economic circumstances, practical issues surround drug administration, including the patient's capacity to administer the desired dosage from a fixed-volume syringe or multidose vial; these issues can affect the feasibility of early discharge and home treatment.

Fondaparinux is a synthetic and selective inhibitor of factor Xa that has proven efficacy and safety for preventing venous thromboembolism in orthopedic surgery. Although laboratory observations and theory suggested that such a compound might not be effective for treating established thrombosis (10), a dose-ranging study of deep venous thrombosis treatment found that a once-daily subcutaneous injection of fondaparinux, 7.5 mg, may be effective and safe across a broad range of body weights (50 kg and 100 kg) (11). Pharmacokinetic analyses suggested that daily doses of 5 mg and 10 mg are appropriate for patients less than and more than that weight range, respectively. Moreover, the predictable and sustained anticoagulant effect of fondaparinux for 24 hours allows once-daily injection, and since fondaparinux does not cross-react with heparin-induced antibodies, platelet count monitoring may no longer be needed (12). This may further simplify treatment.

Therefore, we designed this randomized, double-blind study of 2205 symptomatic patients to determine whether

Context

Are selective inhibitors of factor Xa "as good as" low-molecular-weight heparin in treating deep venous thrombosis?

Contribution

In this large, multicenter, double-blind trial, patients with symptomatic deep venous thrombosis were randomly assigned to receive either fondaparinux (a selective inhibitor of factor Xa) or enoxaparin given subcutaneously for at least 5 days plus an oral vitamin K antagonist for 3 months. In both groups, about 1% of the patients experienced major bleeding during initial treatment and about 4% had recurrent thromboembolic events within 3 months.

Implications

Fondaparinux and enoxaparin have similar safety and efficacy for initial treatment of symptomatic deep venous thrombosis.

–The Editors

the efficacy and safety of a once-daily subcutaneous fixed-dose regimen of fondaparinux are similar to those of the standard therapy of a twice-daily, subcutaneous, body weight–adjusted regimen of enoxaparin. Early discharge was encouraged in both treatment groups. The large sample size allowed outcome assessment in patients with a broad range of body weights and renal function.

METHODS

Patients

Consecutive patients (>18 years of age) who presented with acute symptomatic deep venous thrombosis involving the popliteal, femoral, or iliac veins or the trifurcation of the calf veins and who required antithrombotic therapy were eligible for the study. Diagnostic criteria for deep venous thrombosis were a noncompressible vein found on ultrasonography or an intraluminal filling defect found on venography (11, 13).

Patients were ineligible for the study if they had symptomatic pulmonary embolism; received therapeutic doses of anticoagulants or oral anticoagulant therapy for more than 24 hours; required thrombolysis, thrombectomy, or a vena cava filter; had contraindication to anticoagulant therapy (for example, active bleeding, thrombocytopenia [platelet count $< 100 \times 10^9$ cells/L]); had elevated serum creatinine levels (>177 μmol/L [>2 mg/dL]); had contraindication to contrast medium; had uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg); were pregnant; or had a life expectancy of less than 3 months.

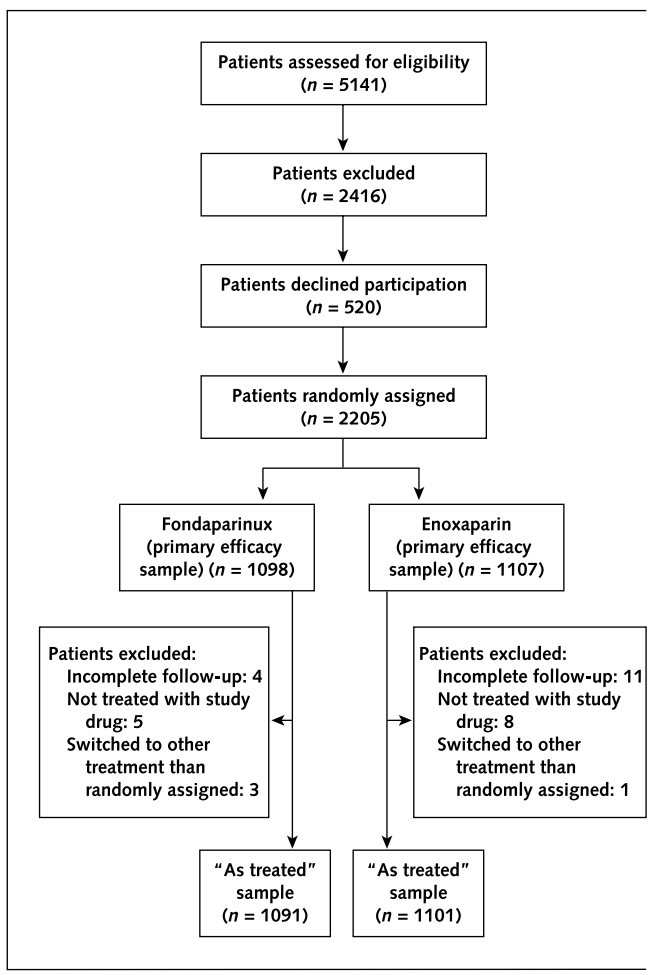
After giving informed consent, patients were randomly assigned by a computerized interactive voice response system that recorded information about patients before treatment assignment. Randomization was stratified by center in balanced blocks of 4 patients. The respective institutional review boards approved the study protocol, and an independent data safety monitoring board monitored the study.

We assessed 5141 patients for eligibility: 2205 patients were randomly assigned to study groups, 2416 patients were excluded, and 520 patients declined to participate (**Figure**). The most common reasons for exclusion were the use of therapeutic anticoagulation for more than 24 hours, thrombolytic therapy, or vena cava filter (580 patients); contraindication to anticoagulant therapy (395 patients); symptomatic pulmonary embolism (387 patients); and a life expectancy of less than 3 months (228 patients).

Treatment Regimens

The patients allocated to fondaparinux (Arixtra, NV Organon, Oss, the Netherlands, and Sanofi-Synthélabo, Paris, France) received a once-daily subcutaneous injection of 5.0 mg if they weighed less than 50 kg, 7.5 mg if they weighed between 50 and 100 kg, or 10.0 mg if they weighed more than 100 kg. They also received twice-daily subcutaneous injections of placebo that appeared identical to enoxaparin.

Figure. **Flow of patients through the study.**



The patients allocated to enoxaparin (Lovenox, Clexane, Aventis Pharmaceuticals, Bridgewater, New Jersey) received a twice-daily subcutaneous dose of 1 mg/kg of body weight and a once-daily subcutaneous injection of placebo that appeared identical to fondaparinux.

Although home treatment with the study drug was allowed, the treating physician made this decision and the drug had to be administered by a home care service.

In both groups, vitamin K antagonist therapy was started as soon as possible but within 72 hours of initiation of fondaparinux or enoxaparin therapy. The investigator chose the type of vitamin K antagonist therapy according to local hospital practice. The same type of vitamin K antagonist was recommended for all patients in a particular center. During initial treatment, prothrombin times were measured at least every other day and the dose of vitamin K antagonist was adjusted to maintain the international normalized ratio between 2.0 and 3.0. Double-blind, initial treatment was continued for at least 5 days and until the international normalized ratio was greater than 2.0 for 2 consecutive days. Treatment with vitamin K antagonists was continued for 3 months, and the international normalized ratio was determined at least once per month.

Surveillance and Follow-up

All patients were contacted daily during initial treatment and at 1 and 3 months. At each contact, patients were evaluated for symptomatic recurrence of deep venous thrombosis or pulmonary embolism and bleeding and were informed about the symptoms and signs of these conditions. They were instructed to report to the study center on an emergency basis if any of these conditions occurred. If recurrent deep venous thrombosis or pulmonary embolism was suspected, the protocol required objective testing for confirmation.

Outcome Assessment

The primary efficacy outcome was the incidence of symptomatic recurrent venous thromboembolism during the 3-month study period. Symptomatic recurrent venous thromboembolism was defined as objectively documented recurrent deep venous thrombosis or pulmonary embolism or death in which pulmonary embolism was a contributing cause or could not be excluded. Without objective test results to adequately confirm or exclude recurrent venous thromboembolism, this diagnosis was accepted if the physician managed the patient with therapeutic doses of LMWH for more than 2 days, thrombolysis, a vena cava filter, or thrombectomy (3, 13).

The criteria for the objective diagnosis of recurrent deep venous thrombosis were a new noncompressible venous segment or a substantial increase ($\geq$4 mm) in diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography (14, 15) or a new intraluminal filling defect found on venography.

The criteria for the objective diagnosis of pulmonary embolism were an intraluminal filling defect on spiral computed tomography or pulmonary angiography, cut-off of a vessel of more than 2.5 mm in diameter on pulmonary angiography, perfusion defect of at least 75% of a segment with corresponding normal ventilation (high-probability lung scan), nondiagnostic lung scan associated with new deep venous thrombosis documented by ultrasonography or venography, or pulmonary embolism confirmed by autopsy.

The main safety outcomes were major bleeding during the initial treatment period and 3-month mortality. Bleeding was defined as major if it was clinically overt and associated with a decrease in the hemoglobin level of 20 g/L or more, led to transfusion of 2 or more units of red blood cells or whole blood cells, was retroperitoneal or intracranial, occurred in a critical organ, or contributed to death. Bleeding episodes that were clinically relevant but not major (for example, epistaxis that required intervention or spontaneous macroscopic hematuria) were an additional safety outcome. The cause of death was classified as due to pulmonary embolism, bleeding, cancer, or other established diagnoses or was classified as unexplained. A central adjudication committee whose members were unaware of treatment assignment reviewed and classified all suspected outcome events.

Platelet counts were measured at baseline, day 4, and the end of initial treatment. Antiplatelet antibody levels were measured at baseline, at the end of initial treatment, and if heparin-induced thrombocytopenia was suspected because a platelet count, confirmed by retesting, was less than 100×10^9 cells/L or decreased more than 40% from baseline (16).

Statistical Analysis

We hypothesized that fondaparinux would be as effective as enoxaparin. Studies in patients with deep venous thrombosis who received no or inadequate treatment reported incidences of recurrence of approximately 20% (95% CI, 8% to 22%) (17–19). This incidence is 5% in patients who received current standard treatment (2); thus, an absolute risk reduction is approximately 15%. To maintain at least half of the lower limit of the 95% CI, we selected a conservative noninferiority margin of 3.5% for the absolute difference of the venous thromboembolism rates between the 2 treatment groups. From these assumptions, we calculated that a study with 1100 patients per treatment group would provide 95% power, with a 1-sided, type I error of 0.025 for rejecting the hypothesis that the rate of recurrence with fondaparinux would be 3.5% higher than with enoxaparin.

The primary efficacy analysis was based on the incidence of symptomatic recurrent venous thromboembolism during the 3-month study period. Analyses of bleeding events included events during initial treatment and 3, 4, or 9 days in patients with creatinine clearance more than 0.84 mL/s, between 0.5 and 0.84 mL/s, and below 0.5 mL/s, respectively (20).

Table 1. **Demographic and Baseline Characteristics of Randomly Assigned Patients***

Characteristic	Fondaparinux Group (*n* = 1098)	Enoxaparin Group (*n* = 1107)
Age, *y*	61.1 ± 16.7	61.5 ± 16.5
Men/women, *n/n*	581/517	578/529
Body weight, *kg*	79.4 ± 17.4	80.1 ± 17.2
<50 kg, *n (%)*	31 (2.8)	24 (2.2)
50–100 kg, *n (%)*	948 (86.3)	974 (88.0)
>100 kg, *n (%)*	119 (10.8)	109 (9.8)
Creatinine clearance, *n (%)*†		
<0.5 mL/s	25 (2.3)	19 (1.7)
0.5–0.84 mL/s	471 (43.6)	513 (46.8)
>0.84 mL/s	584 (54.1)	563 (51.4)
Time between first symptoms and first active study drug, *d*	6.9 ± 8.7	7.4 ± 9.7
Diagnostic method, *n (%)*‡		
Ultrasonography	1045 (95.2)	1042 (94.1)
Venography	39 (3.6)	48 (4.3)
Location of deep venous thrombosis, *n (%)*		
Femoral or Iliac	601 (54.7)	595 (53.7)
Popliteal or trifucation	493 (44.9)	505 (45.6)
Bilateral	5 (0.5)	12 (1.1)
Risk factors, *n (%)*		
Previous venous thromboembolism	273 (24.9)	280 (25.3)
Active cancer§	126 (11.5)	111 (10.0)
Active cancer or history of cancer	202 (18.4)	186 (16.8)
Surgery or trauma (<3 mo)	251 (22.9)	251 (22.7)
Estrogen use	126 (11.5)	140 (12.6)
Known prothrombotic state	58 (5.3)	63 (5.7)
≥2 of the above	293 (26.7)	283 (25.6)

* Values expressed with a plus/minus sign are means ± SD.
† Creatinine clearance was missing in 18 patients in the fondaparinux group and 12 patients in the enoxaparin group.
‡ Some patients had more than 1 confirmatory diagnostic test.
§ Active cancer was defined as cancer treated within the last 6 mo or not cured.

Efficacy analyses were based on all randomly assigned patients, whereas safety analyses were based on all patients who received at least 1 dose of study medication. The 95% CIs for the absolute difference in outcome rates between treatment groups were calculated by using the normal approximation. All analyses were performed by using SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

Sanofi-Synthélabo and NV Organon sponsored the study and monitored all study patients on site. The steering committee had the final responsibility for the study protocol, case report forms, statistical analysis plan, progress of the study, and analysis, as well as the reporting of the data, whatever the outcome of the study. The sponsors had an opportunity to comment on the manuscripts before submission, but the final version was the sole responsibility of the authors. In addition, the steering committee had full access to the data files of the study.

RESULTS

Patients and Baseline Characteristics

Between April 2000 and July 2001, a total of 2205 patients were randomly allocated to receive fondaparinux (*n* = 1098) or enoxaparin (*n* = 1107) in the 154 participating centers. The baseline characteristics of the patients in the 2 treatment groups were similar (**Table 1**). Follow-up was incomplete in 4 (0.4%) patients receiving fondaparinux and 11 (1.0%) patients receiving enoxaparin. Reasons for incomplete follow-up included withdrawal of consent and too-early discharge from follow-up.

Treatment

Table 2 shows data on initial treatment, hospitalization, and vitamin K antagonist therapy. The duration of initial treatment was similar in both groups. The proportion of patients who received initial treatment partially or entirely out of the hospital was similar in both groups. In both groups, more than 95% of patients had an international normalized ratio of 2.0 or greater at the end of initial treatment. The intensity of treatment with vitamin K antagonists was similar in both groups.

Recurrent Venous Thromboembolism

Among the 1098 patients receiving fondaparinux, 114 had 1 or more episodes of clinically suspected recurrent venous thromboembolism, which were confirmed in 43 (3.9%) patients (**Table 3**). Among the 1107 patients receiving enoxaparin, 116 had 1 or more episodes of clinically suspected recurrent venous thromboembolism, which were confirmed in 45 (4.1%) patients (absolute difference, −0.15 percentage point [CI, −1.8 to 1.5 percentage points]). The upper limit of this CI indicates that noninferiority was demonstrated. **Table 3** details the type of recurrence. Of the 88 patients with confirmed recurrent venous thromboembolism, 82 patients underwent objective

Table 2. **Treatment Characteristics***

Characteristic	Fondaparinux Group (*n* = 1091)†	Enoxaparin Group (*n* = 1101)†
Patients receiving anticoagulant therapy in the 24 h before randomization, *n (%)*		
Unfractionated heparin or LMWH	567 (52.0)	595 (54.0)
Vitamin K antagonists	92 (8.4)	113 (10.3)
Mean duration of initial treatment ± SD, *d*	7.0 ± 2.2	7.1 ± 2.2
Initiation of vitamin K antagonist therapy, *n (%)*		
Day of randomization (including previous 24 h)	609 (55.8)	618 (56.1)
Day 1	313 (28.7)	334 (30.3)
Day 2 or 3	142 (13.0)	124 (11.3)
Day 4 or later	27 (2.5)	25 (2.3)
Patients treated out of the hospital, *n (%)*		
Entirely	88 (8.1%)	91 (8.3)
≥3 d	253 (23.2)	277 (25.2)
2 d	0 (0.0)	4 (0.4)
1 d	3 (0.3)	3 (0.3)
Patients with INR > 2.0 at end of initial treatment, *n (%)*	1052 (96.4)	1059 (96.2)
Patients with INR ≥ 2.0 during > 70% of the follow-up, *n (%)*	714 (65.4)	765 (69.5)

* INR = international normalized ratio; LMWH = low-molecular-weight heparin.
† Patients are considered according to the treatment they actually received (a total of 13 randomly assigned patients were not treated).

Table 3. **Clinical Outcomes during the Study**

Outcomes	Fondaparinux Group	Enoxaparin Group	Difference (95% CI)*
Randomly assigned patients, *n*	1098	1107	
Recurrent venous thromboembolism, *n (%)*			
During entire study	43 (3.9)	45 (4.1)	−0.15 (−1.8 to 1.5)
Type of recurrence, *n*			
Fatal pulmonary embolism	5	5	
Nonfatal pulmonary embolism	20	12	
Deep venous thrombosis only	18	28	
As-treated patients, *n*	1091	1101	
Major bleeding, *n (%)*			
During initial treatment	12 (1.1)	13 (1.2)	−0.1 (−1.0 to 0.8)
During entire study	28 (2.6)	26 (2.4)	0.2 (−1.1 to 1.5)
Clinically relevant nonmajor bleeding only, *n (%)*			
During initial treatment	28 (2.6)	33 (3.0)	−0.4 (−1.8 to 0.9)
During entire study	60 (5.5)	63 (5.7)	−0.2 (−2.1 to 1.7)
Mortality, *n (%)*			
During entire study	41 (3.8)	33 (3.0)	0.8 (−0.8 to 2.3)

*Differences are expressed as percentage points.

testing to confirm the diagnosis. Of the remaining 6 patients, 1 patient receiving fondaparinux was treated for recurrent pulmonary embolism without objective testing and 5 patients died, in whom pulmonary embolism could not be ruled out (1 patient receiving fondaparinux and 4 patients receiving enoxaparin).

Bleeding Complications

Major bleeding during initial treatment occurred in 12 (1.1%) patients receiving fondaparinux and 13 (1.2%) patients receiving enoxaparin (absolute difference, −0.1 percentage point [CI, −1.0 to 0.8 percentage points]). Bleeding contributed to death in 2 patients in the fondaparinux group. One patient, who was 78 years of age, died at day 6 with retroperitoneal hemorrhage and a supratherapeutic international normalized ratio (6.5 on day 5). The second patient, who was 66 years of age, died on day 8 with metastatic hepatic tumors and an international normalized ratio of 4 at day 6.

Major or clinically relevant nonmajor bleeding during initial treatment occurred in 40 (3.7%) patients receiving fondaparinux and 46 (4.2%) patients receiving enoxaparin (absolute difference, −0.5 percentage point [CI, −2.1 to 1.1 percentage points]). Bleeding rates during vitamin K antagonist treatment were low and similar in the treatment groups (**Table 3**).

Mortality

During the entire 3-month study period, 41 (3.8%) patients who received fondaparinux and 33 (3.0%) patients who received enoxaparin died (absolute difference, 0.8 percentage point [CI, −0.8 to 2.3 percentage points]). In the fondaparinux group, the causes of death were pulmonary embolism, including unexplained death ($n = 5$); bleeding ($n = 5$); cancer ($n = 24$); and other ($n = 7$). In the enoxaparin group, the causes of death were pulmonary embolism, including unexplained death ($n = 5$); cancer ($n = 19$); and other ($n = 9$). Two of the 5 fatal bleeding episodes in the fondaparinux group occurred during initial treatment, and the other 3 episodes occurred during long-term treatment with vitamin K antagonists.

Additional Observations

Table 4 shows the incidence of recurrent venous thromboembolism and major bleeding for the various body weight categories.

Major bleeding occurred in 2 (8.0%) of the 25 patients who received fondaparinux and 1 (5.6%) of the 18 patients who received enoxaparin and had a creatinine clearance less than 0.5 mL/s. Both major and clinically relevant nonmajor bleeding occurred in 16% and 11% of patients who received fondaparinux and enoxaparin, respectively.

The incidence of recurrent venous thromboembolism in patients who received initial treatment partially or entirely out of the hospital was 2.0% in the 345 patients who received fondaparinux and 4.3% in the 374 patients who received enoxaparin (absolute difference, −2.3 percentage points [CI, −4.8 to 0.3 percentage points]). Major bleeding during initial treatment in these patients occurred in 1.5% and 0.8% of the patients receiving fondaparinux and enoxaparin, respectively (absolute difference, 0.7 percentage point [CI, −0.9 to 2.2 percentage points]).

Thrombocytopenia occurred in 7 (0.6%) patients in each treatment group. None of these patients had associated thromboembolism, and none had antiplatelet antibodies induced.

DISCUSSION

Our study had 3 main goals. First, we wanted to demonstrate whether once-daily subcutaneous fondaparinux as initial therapy for symptomatic, confirmed deep venous thrombosis has efficacy (was not inferior) and safety similar to those of twice-daily subcutaneous enoxaparin, a standard and widely used LMWH regimen. We have demonstrated the noninferiority of fondaparinux. The 3-month

Table 4. **Incidence of Recurrent Venous Thromboembolism (during the 3-Month Study Period) and Major Bleeding (during the Initial Treatment Period) for the Various Body Weight Categories***

Treatment	Recurrent Venous Thromboembolism			Major Bleeding		
	Body Weight < 50 kg	Body Weight, 50–100 kg	Body Weight > 100 kg	Body Weight < 50 kg	Body Weight, 50–100 kg	Body Weight > 100 kg
	← n/n (%) →					
Fondaparinux	1/31 (3.2)	37/948 (3.9)	5/119 (4.2)	1/31 (3.2)	11/942 (1.2)	0/118
Enoxaparin	3/24 (12.5)	39/974 (4.0)	3/109 (2.8)	0/24	12/967 (1.2)	1/110 (0.9)

* Data are presented as patients/total patients.

rates for recurrence, 3.9% with fondaparinux and 4.1% with enoxaparin, are within previously reported experience with LMWH treatment for deep venous thrombosis, as were the bleeding rates (2–4). Thrombocytopenia was rare and was not associated with heparin-related antibodies.

The fondaparinux regimen with prefilled syringes, in which the 7.5-mg dose suited 85% of patients, is feasible for outpatient therapy. Approximately one third of the study patients received treatment partially or entirely outside of the hospital.

Our second goal was to evaluate this experience. The incidence of clinical outcomes in patients who received some or all of their initial treatment at home was low and similar in each group. Home treatment with self-administered LMWH is increasingly used but is subject to dosing errors by physicians or patients when body weight, dosage, or dose intervals are uncertain and when patients have limited capability to titrate prefilled syringes or withdraw dosages from multidose vials. Simple regimens, such as that of fondaparinux, may minimize these problems.

Finally, we aimed to use the broad study entry criteria and large sample size of this study to describe the influence of body weight and renal clearance on the clinical outcomes. Subgroup analyses should be interpreted with care, but it seems that both treatments had similar efficacy and safety independent of body weight. Patients with calculated creatinine clearance less than 0.5 mL/s had an increased risk for major and other clinically important bleeding regardless of which treatment they received.

The study was randomized and double-blind and used central adjudication for all clinical outcome events. Injections were supervised, vitamin K antagonists were administered optimally, and a broad range of patients was included. Therefore, we believe that our findings are both valid and applicable for most patients with symptomatic deep venous thrombosis.

Major bleeding is a concern with any anticoagulant, and the appropriate responses are important to consider. The clinical effectiveness of protamine sulfate in patients treated with LMWH remains uncertain, and fondaparinux does not have a specific antidote. A recent study revealed that a bolus injection of 90 μg/kg of recombinant factor VIIa restored, at peak concentrations, thrombin generation and normalize the prothrombin time and activated partial thromboplastin time in volunteers given 10 mg of fondaparinux subcutaneously (21). In emergency situations, clinicians have this option. In our study, this was never needed.

This study adds to the growing body of evidence that inhibitors of activated factor X are effective, safe, and easy-to-use antithrombotics. We conclude that fondaparinux given subcutaneously once daily is at least as effective and safe as enoxaparin for initially treating symptomatic deep venous thrombosis.

From the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; Swedish Medical Center, University of Washington School of Medicine, Seattle, Washington; Hospital de Bellevue, University Jean Monnet, Saint-Etienne, France; Flinders Medical Centre, Bedford Park, Australia; Hamilton Civic Hospitals Research Centre, Hamilton, Ontario, Canada; Instituto di Clinica Medica, Policlinico San Matteo, University of Pavia, Pavia, Italy; University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; University Hospital of Maastricht, Maastricht, the Netherlands; Sanofi-Synthélabo, Paris, France; and NV Organon, Oss, the Netherlands.

Grant Support: By Sanofi-Synthélabo and NV Organon.

Potential Financial Conflicts of Interest: *Employment:* A.E.M. Segers (NV Organon); R. Cariou (Sanofi-Synthélabo); O. Leeuwenkamp (Organon); A.W.A. Lensing (NV Organon). *Consultancies:* H.R. Büller (Sanofi-Synthélabo, NV Organon); B.L. Davidson (Sanofi-Synthélabo, NV Organon, Bristol-Myers Squibb, Aventis); A. Gallus (Sanofi-Synthélabo, NV Organon); M.H. Prins (Sanofi-Synthélabo, NV Organon); G. Raskob (Sanofi-Synthélabo, NV Organon). *Honoraria:* H.R. Büller (Sanofi-Synthélabo, NV Organon); B.L. Davidson (Sanofi-Synthélabo, NV Organon); H. Decousus (Sanofi-Synthélabo, NV Organon); A. Gallus (Sanofi-Synthélabo, NV Organon); F. Piovella (Sanofi-Synthélabo, NV Organon); G. Raskob (Sanofi-Synthélabo, NV Organon). *Stock ownership or options (other than mutual funds):* R. Cariou (Sanofi-Synthélabo). *Grants received:* H.R. Büller (Sanofi-Synthélabo, NV Organon); H. Decousus (Sanofi-Synthélabo); G. Raskob (Sanofi-Synthélabo, NV Organon). *Grants pending:* H. Decousus (Sanofi-Synthélabo, NV Organon).

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Appendix: The Matisse Investigators

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