ORIGINAL ARTICLE

Fondaparinux for the Treatment of Superficial-Vein Thrombosis in the Legs

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ABSTRACT

BACKGROUND

The efficacy and safety of anticoagulant treatment for patients with acute, symptomatic superficial-vein thrombosis in the legs, but without concomitant deep-vein thrombosis or symptomatic pulmonary embolism at presentation, have not been established.

METHODS

In a randomized, double-blind trial, we assigned 3002 patients to receive either fondaparinux, administered subcutaneously at a dose of 2.5 mg once daily, or placebo for 45 days. The primary efficacy outcome was a composite of death from any cause or symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis at day 47. The main safety outcome was major bleeding. The patients were followed until day 77.

RESULTS

The primary efficacy outcome occurred in 13 of 1502 patients (0.9%) in the fondaparinux group and 88 of 1500 patients (5.9%) in the placebo group (relative risk reduction with fondaparinux, 85%; 95% confidence interval [CI], 74 to 92; P<0.001). The incidence of each component of the primary efficacy outcome was significantly reduced in the fondaparinux group as compared with the placebo group, except for the outcome of death (0.1% in both groups). The rate of pulmonary embolism or deep-vein thrombosis was 85% lower in the fondaparinux group than in the placebo group (0.2% vs. 1.3%; 95% CI, 50 to 95; P<0.001). Similar risk reductions were observed at day 77. A total of 88 patients would need to be treated to prevent one instance of pulmonary embolism or deep-vein thrombosis. Major bleeding occurred in one patient in each group. The incidence of serious adverse events was 0.7% with fondaparinux and 1.1% with placebo.

CONCLUSIONS

Fondaparinux at a dose of 2.5 mg once a day for 45 days was effective in the treatment of patients with acute, symptomatic superficial-vein thrombosis of the legs and did not have serious side effects. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT00443053.)

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Superficial-vein thrombosis of the legs is a common condition,[1,2] with an estimated incidence that may exceed that of deep-vein thrombosis.[3,4] Patients with isolated superficial-vein thrombosis — that is, without concomitant deep-vein thrombosis or symptomatic pulmonary embolism at presentation — are at risk for subsequent symptomatic venous thromboembolic complications.[1-7] In a large, prospective, observational study, the 3-month risk of such complications was 8.3%, with a 3.3% risk of deep-vein thrombosis or pulmonary embolism.[8]

The treatment of this disease has not been adequately addressed in randomized trials. Accordingly, the recommendations in various guidelines are weak, and in practice, therapeutic strategies vary, ranging from no treatment to the use of antiinflammatory agents or anticoagulant drugs or surgery.[8-14] The few randomized studies that have been performed did not clarify the circumstances under which surgery is required or the value or optimal dose and duration of anticoagulant or antiinflammatory therapy.[6,15-19] The results of the two largest studies, evaluating low-molecular-weight heparin, suggest that high-dose (therapeutic) or intermediate-dose regimens do not provide substantial benefits over low-dose (prophylactic) regimens and that a treatment period of 12 days or of 30 days is too short, with most symptomatic thromboembolic complications occurring after the treatment period.[6,17] None of the published studies showed a clinically relevant benefit of any treatment as compared with placebo.[6,7] Thus, the aim of our study was to determine whether there is a well-defined treatment that could provide a benefit.

We conducted the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) trial to evaluate the efficacy and safety of fondaparinux, a specific factor Xa inhibitor, in reducing symptomatic venous thromboembolic complications or death from any cause in patients with acute, isolated superficial-vein thrombosis of the legs. For the active treatment, we selected the prophylactic dose of 2.5 mg of fondaparinux once daily, because this dose has been shown to be reasonably effective and to have an acceptable side-effect and adverse-event profile in a broad range of conditions.[20-23] Treatment was to be administered for 45 days.

METHODS

PATIENTS

Hospitalized or nonhospitalized patients 18 years of age or older, with acute, symptomatic lower-limb superficial-vein thrombosis at least 5 cm long, as confirmed by standardized compression ultrasonography, were eligible to undergo randomization. Patients were excluded if the interval between the onset of their symptoms and planned randomization was more than 3 weeks; if they had been treated for cancer within the previous 6 months; if they presented with symptomatic or asymptomatic deep-vein thrombosis, symptomatic documented pulmonary embolism, or superficial-vein thrombosis associated with sclerotherapy or placement of an intravenous catheter or located within 3 cm of the saphenofemoral junction; or if they had a documented history of superficial-vein thrombosis within the previous 3 months or deep-vein thrombosis or pulmonary embolism within the previous 6 months. Patients were also excluded from randomization if they had received an antithrombotic agent for more than 48 hours (other than aspirin at a dose ≤325 mg per day) or a nonsteroidal antiinflammatory drug for more than 72 hours as treatment for the current episode of superficial-vein thrombosis or if, in the investigator's opinion, they required ligation of the saphenofemoral junction or stripping of varicose veins. Other exclusion criteria were major surgery within the previous 3 months and conditions that could confer a predisposition to bleeding, including severe hepatic impairment, a creatinine clearance of less than 30 ml per minute, and a platelet count of less than 100,000 per cubic millimeter. Finally, women of childbearing age were excluded if they were pregnant or were not using a reliable contraceptive method.

STUDY DESIGN

This trial was an international, multicenter, randomized, double-blind, placebo-controlled study; the protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. With the use of a central telephone system and a computer-generated randomization list, consecutive patients were randomly assigned, in a 1:1 ratio, to fondaparinux at a dose of 2.5 mg or matching placebo, administered subcutaneously

once daily for 45 days. Randomization was performed in blocks of four without any stratification. The maximum interval allowed between the qualifying ultrasonographic study and randomization was 48 hours. The day of randomization was defined as day 1. Follow-up visits were scheduled at days 10±2, 30±2, 45±2, and 75±2. No routine ultrasonographic examinations were required during the follow-up period. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by an independent ethics committee, and written informed consent was obtained from all patients before they underwent randomization.

The study was funded by GlaxoSmithKline. A steering committee, including one nonvoting member representing the sponsor, was responsible for the design, conduct, and reporting of the study. Data were collected and analyzed by the study sponsor. The database of adjudicated outcomes was managed by an independent central adjudication committee. The members of the writing committee wrote the first draft of the manuscript and made the decision to submit the manuscript for publication. All the authors contributed to the writing of subsequent drafts of the manuscript, had full access to the data and analyses, and vouch for the accuracy and completeness of the report, as well as the fidelity of the study to the protocol and statistical analysis plan.

STUDY DRUGS

Fondaparinux and placebo were packaged in identical boxes containing visually identical, prefilled 0.5-ml single-dose syringes. Each patient received one box containing 45 single-dose syringes (1 per day for 45 days) of either 2.5 mg of fondaparinux sodium (Arixtra, GlaxoSmithKline) or placebo (sodium chloride). At the time of randomization, patients were provided with an injection diary. The investigators were encouraged to teach the patients to administer the study drugs themselves, but the final decision about self-administration was left to the investigator's discretion.

Patients were encouraged to use graduated compression stockings and were allowed to take acetaminophen or topical nonsteroidal antiinflammatory drugs as needed. The use of oral antiplatelet agents or aspirin at a low dose (≤325 mg per day) was discouraged. Concomitant treatment with dextran, thrombolytic agents, any other anticoagulant agent, more than one antiplatelet agent, aspirin at doses higher than 325 mg per day, glycoprotein IIb/IIIa inhibitors, oral nonsteroidal antiinflammatory drugs, or topical heparins or heparinoids was prohibited throughout the course of the study.

OUTCOME MEASURES

The primary efficacy outcome was the composite of death from any cause, symptomatic pulmonary embolism (confirmed by ventilation–perfusion scanning, helical computed tomography, pulmonary angiography, or autopsy), symptomatic deep-vein thrombosis (confirmed by ultrasonography or venography), or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis (confirmed by ultrasonography) up to day 47. (For definitions of recurrence and extension of superficial-vein thrombosis, see the Supplementary Appendix, available at NEJM.org.) Secondary efficacy outcomes were the composite primary efficacy outcome up to day 77 and the following outcomes up to day 47 and day 77: each component of the primary efficacy outcome, the composite of symptomatic pulmonary embolism or deep-vein thrombosis, and surgery for superficial-vein thrombosis.

Analyses of safety outcomes were performed with data obtained until day 47 or until 4 days after the last injection of the study drug (whichever was longer), with data obtained until 4 days after the last injection of the study treatment (on-treatment analysis), and with data obtained until day 77. The main safety outcome was major bleeding. Other safety outcomes were clinically relevant nonmajor, minor, and total (any) bleeding (definitions provided in the Supplementary Appendix) and arterial thromboembolic events. All other adverse events that occurred while the patient was receiving treatment were reported.

If a thromboembolic or bleeding complication occurred during the course of the study, management of the condition was left to the investigator's discretion. All symptomatic outcomes were reviewed by the central adjudication committee, whose members were unaware of the patients' group assignments. Patient safety was monitored by an independent data and safety monitoring committee.

STATISTICAL ANALYSIS

We estimated that with a sample of 1250 patients in each group, the study would have at least 98% power to detect a 50% reduction in the rate of the

primary efficacy outcome, assuming an incidence of the primary efficacy outcome of 8.0% in the placebo group,[6,8,17] at a two-sided 5% level of significance. As planned, the independent steering committee, whose members were unaware of the group assignments, monitored the overall event rate for the primary efficacy outcome. On November 5, 2008, on the basis of an observed rate of the primary efficacy outcome of 3.1%, the committee decided to increase the sample to 3000 patients in order to preserve at least 90% power to detect a 50% reduction in the rate of the primary efficacy outcome in the fondaparinux group.

Efficacy analyses were performed on data from the intention-to-treat population, which included all the patients who had undergone randomization. Patients for whom a primary efficacy assessment was lacking (i.e., those with no events and no information on their status with respect to efficacy at day 45±2) were assumed not to have had any event. Safety analyses were performed on data from the as-treated population, which comprised all patients who had undergone randomization and who had received at least one dose of the study drug.

A two-sided Fisher's exact test at the 5% significance level was performed for efficacy evaluations, and the resulting P values are reported. Absolute differences and relative risks, with 95% confidence intervals, are also reported. Time-to-event outcomes estimated by means of the Kaplan–Meier method were compared with the use of the log-rank test. A prespecified sensitivity analysis was performed in which patients with missing data on the primary efficacy outcome were excluded. Zelen's exact test was used to verify the consistency of the treatment effect across 16 prespecified sets of subgroups and 1 set of subgroups that was defined post hoc.[24]

RESULTS

STUDY POPULATIONS AND TREATMENTS

Between March 2007 and May 2009, a total of 3002 patients were enrolled at 171 centers in 17 countries (see the Supplementary Appendix) — 1502 in the fondaparinux group and 1500 in the placebo group. Of the 3002 patients who underwent randomization, 18 patients in the fondaparinux group (1.2%) and 22 in the placebo group (1.5%) did not have a primary efficacy assessment (Table 1 in the Supplementary Appendix). Overall, 1481 patients in the fondaparinux group (98.6%) and 1467 in the placebo group (97.8%) completed the follow-up visit at day 75±2 (Table 2 in the Supplementary Appendix). Of the 3002 patients who underwent randomization, 4 patients in the fondaparinux group and 11 in the placebo group received no study drug (as a result of the patient's decision, in each case), and 1 patient who was randomly assigned to the placebo group received at least one dose of fondaparinux in error; thus, 1499 patients in the fondaparinux group (99.8%) and 1488 in placebo group (99.2%) were included in the safety analyses.

The demographic and clinical characteristics of the patients, the medications and interventions the patients received before their entry into the study (Table 1, and Table 3 in the Supplementary Appendix), the duration of treatment, and the adherence to treatment, as calculated with the use of a formula that was based on the number of syringes used and the number returned unused (Table 2), were well balanced between the two groups. In addition, the treatments other than the study drugs that patients received during the course of the study were well balanced between the two groups, with two exceptions: patients in the placebo group received anticoagulant drugs or oral nonsteroidal antiinflammatory drugs more frequently than did patients in the fondaparinux group (Table 2).

EFFICACY OUTCOMES

The primary efficacy outcome occurred in 13 of 1502 patients (0.9%) in the fondaparinux group and 88 of 1500 patients (5.9%) in the placebo group (relative risk with fondaparinux, 0.15; 95% confidence interval [CI], 0.08 to 0.26; P<0.001; number needed to treat, 20) (Table 3). This result was confirmed in the sensitivity analysis in which patients with a missing primary efficacy assessment were excluded (data not shown). The incidence of each component of the primary efficacy outcome was significantly reduced in the fondaparinux group as compared with the placebo group (including the incidence of pulmonary embolism [number needed to treat to prevent one pulmonary embolism was 300]), except for the incidence of death, which did not differ significantly between the two groups. The risk of the composite of deep-vein thrombosis or pulmonary embolism was reduced by 85% with fondaparinux as compared with placebo (0.2% [3 of 1502 patients] vs. 1.3% [20 of 1500 patients]; P<0.001; number needed to treat, 88). All the efficacy results were main-

Table 1. Baseline Characteristics of the Study Patients.*

Characteristic	Fondaparinux (N=1502)	Placebo (N=1500)	P Value†
Age — yr	57.1±13.3	56.9±13.6	0.69
Female sex — no. (%)	974 (64.8)	944 (62.9)	0.29
Body-mass index‡			
Mean	29.2±5.2	29.0±5.4	0.32
≥30 — no. (%)	574 (38.2)	536 (35.7)	0.16
Medical conditions — no. (%)			
Varicose veins	1331 (88.6)	1329 (88.6)	1.00
Previous superficial-vein thrombosis	178 (11.9)	178 (11.9)	1.00
Previous deep-vein thrombosis or pulmonary embolism	105 (7.0)	104 (6.9)	1.00
Cardiovascular disease§	71 (4.7)	66 (4.4)	0.73
Heart failure or respiratory failure			
Chronic	71 (4.7)	88 (5.9)	0.17
Acute¶	5 (0.3)	1 (0.1)	0.22
Known thrombophilia	20 (1.3)	18 (1.2)	0.87
Autoimmune disease	12 (0.8)	14 (0.9)	0.70
Acute infectious disease¶	11 (0.7)	8 (0.5)	0.65
History of cancer	32 (2.1)	29 (1.9)	0.80
Current hospitalization	10 (0.7)	11 (0.7)	0.83
Trauma¶	10 (0.7)	16 (1.1)	0.25
Treatment at inclusion — no. (%)			
Graduated compression stockings	1131 (75.3)	1147 (76.5)	0.47
Analgesic agents	391 (26.0)	401 (26.7)	0.68
Topical nonsteroidal antiinflammatory drugs	598 (39.8)	608 (40.5)	0.71
Topical anticoagulant drugs	57 (3.8)	50 (3.3)	0.55
Oral nonsteroidal antiinflammatory drugs or COX-2 inhibitors	54 (3.6)	65 (4.3)	0.31
Oral or parenteral anticoagulant drugs	67 (4.5)	58 (3.9)	0.46
Aspirin or other antiplatelet agents	347 (23.1)	364 (24.3)	0.47
Glucocorticoids	34 (2.3)	25 (1.7)	0.29
Oral contraceptive or hormone-replacement therapy	43 (2.9)	40 (2.7)	0.82

* Plus–minus values are means ±SD.
† The P values were calculated with the use of Student's t-test for continuous variables and Fisher's exact test for categorical variables.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Cardiovascular disease includes myocardial infarction, ischemic stroke, and peripheral arterial occlusive disorder.
¶ Data are shown for patients in whom the condition was present at baseline or had occurred within the previous 4 weeks.

tained at day 77 (Fig. 1 and Table 3). The treatment effect was consistent across all the subgroups we examined (Fig. 2). Finally, more patients in the placebo group than in the fondaparinux group underwent surgery for superficial-vein thrombosis (Table 3), including ligation of the saphenofemoral junction, which by day 77 had been performed in 52 patients in the placebo group (3.5%), as compared with 8 in the fondaparinux group (0.5%).

SAFETY OUTCOMES

By day 47, major bleeding had occurred in one patient (0.1%) in each group (P=1.00). The rates of clinically relevant nonmajor, minor, and total

Table 2. Treatment Received during the Study.*

Treatment	Fondaparinux (N=1502)	Placebo (N=1500)
Study treatment		
Receipt of at least one injection of study drug — no. (%)	1499 (99.8)	1488 (99.2)
Mean days of treatment	43.6±7.3	41.2±11.0
Duration of treatment — no./total no. (%)		
≤10 days	35/1499 (2.3)	95/1488 (6.4)
11–30 days	26/1499 (1.7)	66/1488 (4.4)
31–45 days	1161/1499 (77.5)	1091/1488 (73.3)
>45 days	277/1499 (18.5)	236/1488 (15.9)
Self-administered treatment — no. (%)	1360/1499 (90.7)	1364/1488 (91.7)
Adherence to treatment		
Patients who adhered — no. (%)†	1434 (95.5)	1329 (88.6)
Mean adherence — %‡	98.3±8.9	98.4±8.7
Other treatments		
Graduated compression stockings — no. (%)	1247 (83.0)	1247 (83.1)
Analgesic agents — no. (%)	416 (27.7)	428 (28.5)
Topical nonsteroidal antiinflammatory drugs — no. (%)	623 (41.5)	627 (41.8)
Topical anticoagulant drugs — no. (%)	59 (3.9)	50 (3.3)
Oral nonsteroidal antiinflammatory drugs or COX-2 inhibitors — no. (%)	32 (2.1)	56 (3.7)
Oral or parenteral anticoagulant treatment — no. (%)§	17 (1.1)	96 (6.4)
High (therapeutic) dose	10 (0.7)	62 (4.1)
Intermediate dose	1 (0.1)	6 (0.4)
Low (prophylactic) dose	6 (0.4)	44 (2.9)
Unknown dose	2 (0.1)	3 (0.2)
Aspirin or other antiplatelet agents — no. (%)	322 (21.4)	339 (22.6)

* Plus–minus values are means ±SD.
† Patients were considered not to have adhered to treatment if they received less than 80% of the scheduled study drug (i.e., <36 injections) or if the last day of treatment was before day 40. This included patients who discontinued treatment owing to an adverse event or a lack of efficacy.
‡ Mean adherence was calculated with the use of the following formula: [(number of syringes dispensed − number of syringes returned − number of syringes lost or not returned and not used) ÷ total number of days of treatment] × 100.
§ Patients could have received more than one anticoagulant treatment; different treatments might have been dispensed with the use of different dosage regimens (therapeutic, intermediate, or prophylactic).

bleeding and arterial thromboembolic complications did not differ significantly between the two groups (Table 4). Safety results were similar in on-treatment analyses and in analyses at day 77 (Table 4 in the Supplementary Appendix). There were no clinically relevant between-group differences in the incidence of any other adverse events (Table 5 and Table 6 in the Supplementary Appendix). The only serious adverse event that was reported in more than one patient in either study group was coronary artery disease, which was reported in two patients in the placebo group (0.1%). No episodes of thrombocytopenia were reported in the fondaparinux group.

DISCUSSION

In this study, we investigated the effect of anticoagulant therapy as compared with placebo on symptomatic outcomes in patients with isolated superficial-vein thrombosis. Treatment with fondaparinux at a dose of 2.5 mg once daily for 45 days, as compared with placebo, resulted in an absolute risk reduction of 5 percentage points — which

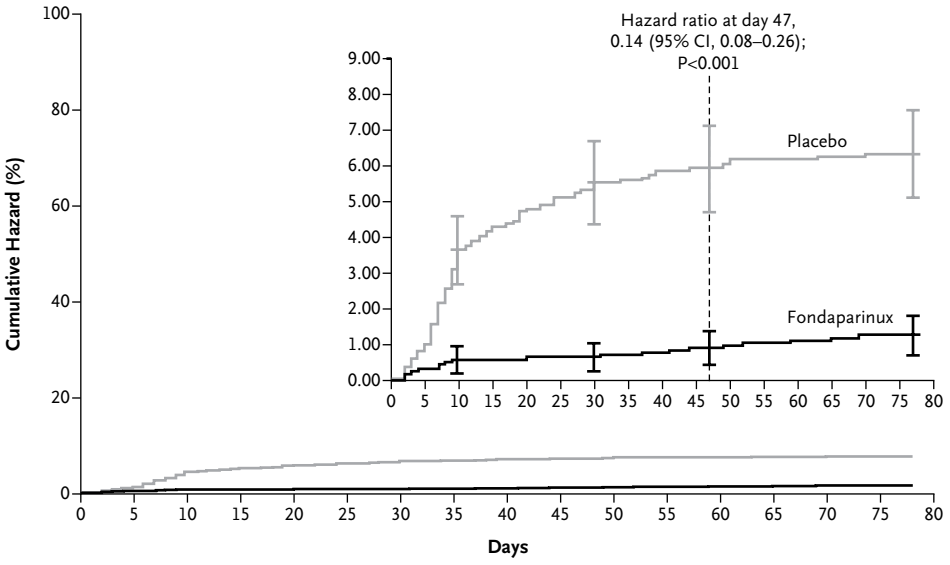
Table 3. Efficacy Outcomes.

Efficacy Outcome	Fondaparinux (N=1502)	Placebo (N=1500)	Absolute Risk Reduction with Fondaparinux	Relative Risk with Fondaparinux	P Value*
	no. with event (%)		*percentage points (95% CI)*	*% (95% CI)*	
By Day 47					
Primary composite outcome†	13 (0.9)	88 (5.9)	−5.0 (−6.3 to −3.7)	0.15 (0.08 to 0.26)	<0.001
Death‡	2 (0.1)	1 (0.1)	0.1 (−0.2 to 0.3)	1.99 (0.18 to 21.87)	1.00
Pulmonary embolism§	0	5 (0.3)	−0.3 (−0.6 to 0.0)	Not calculated	0.03
Deep-vein thrombosis¶	3 (0.2)	18 (1.2)	−1.0 (−1.6 to −0.4)	0.17 (0.05 to 0.56)	<0.001
Extension of superficial-vein thrombosis to the saphenofemoral junction	4 (0.3)	51 (3.4)	−3.1 (−4.1 to −2.2)	0.08 (0.03 to 0.22)	<0.001
Recurrence of superficial-vein thrombosis	5 (0.3)	24 (1.6)	−1.3 (−2.0 to −0.6)	0.21 (0.08 to 0.54)	<0.001
Deep-vein thrombosis or pulmonary embolism	3 (0.2)	20 (1.3)	−1.1 (−1.8 to −0.5)	0.15 (0.05 to 0.50)	<0.001
Surgery for superficial-vein thrombosis	11 (0.7)	57 (3.8)	−3.1 (−4.1 to −2.0)	0.19 (0.10 to 0.37)	<0.001
By Day 77					
Composite outcome†	18 (1.2)	94 (6.3)	−5.1 (−6.4 to −3.7)	0.19 (0.12 to 0.32)	<0.001
Death‡	2 (0.1)	1 (0.1)	0.1 (−0.2 to 0.3)	1.99 (0.18 to 21.87)	1.00
Pulmonary embolism§	0	6 (0.4)	−0.4 (−0.7 to −0.1)	Not calculated	0.02
Deep-vein thrombosis	4 (0.3)	19 (1.3)	−1.0 (−1.6 to −0.4)	0.21 (0.07 to 0.62)	0.001
Extension of superficial-vein thrombosis to the saphenofemoral junction	5 (0.3)	54 (3.6)	−3.3 (−4.3 to −2.3)	0.09 (0.04 to 0.23)	<0.001
Recurrence of superficial-vein thrombosis	8 (0.5)	26 (1.7)	−1.2 (−2.0 to −0.4)	0.31 (0.14 to 0.68)	0.002
Deep-vein thrombosis or pulmonary embolism	4 (0.3)	22 (1.5)	−1.2 (−1.9 to −0.5)	0.18 (0.06 to 0.53)	<0.001
Surgery for superficial-vein thrombosis	15 (1.0)	61 (4.1)	−3.1 (−4.2 to −1.9)	0.25 (0.14 to 0.43)	<0.001

* P values were calculated with the use of Fisher's exact test.
† Some patients had more than one event.
‡ There were two deaths from cancer in the fondaparinux group and one death from acute heart failure in the placebo group.
§ No instance of pulmonary embolism was fatal.
¶ There were 11 cases of proximal deep-vein thrombosis: 1 in the fondaparinux group and 10 in the placebo group.

was equivalent to an 85% reduction in the risk of symptomatic thromboembolic complications or death — without increasing the incidence of bleeding. The number needed to treat to prevent one event of the primary efficacy outcome was 20, whereas the number needed to treat to prevent deep-vein thromboembolism or a pulmonary embolism was 88. The study was placebo-controlled, since no standard treatment has been established in this clinical setting.[7,9] This design was considered to be ethical, since all the patients benefited from close clinical monitoring, with adequate diagnostic procedures performed in the event of new or persistent symptoms, and since an independent data and safety monitoring committee carefully oversaw the study outcomes.

The patients in our study are representative of those encountered in routine practice[1,2,8]: almost all were outpatients, and there was a clear predominance of women and a substantial proportion of obese patients, most presenting with varicose veins and superficial-vein thrombosis involving the great saphenous vein. The rate of symptomatic thromboembolic complications in the placebo group at day 47 (5.9%; 95% CI, 4.7 to 7.2) was in the low range of the expected rate of thromboembolic events, possibly because very-high-risk patients (e.g., those with active cancer or a recent history of venous thromboembolism and those in whom the thrombus was located within 3 cm of the saphenofemoral junction) were not enrolled in this placebo-controlled trial. However, this rate and the corresponding rate at day 77 (6.3%; 95% CI, 5.1 to 7.6) are consistent with that observed at 3 months in a prospective observational study in which a similar composite outcome was evaluated



No. at Risk	Day 10±2	Day 30±2	Day 45±2	Day 75±2
Placebo	1437	1399	1388	1330
Fondaparinux	1483	1477	1468	1410

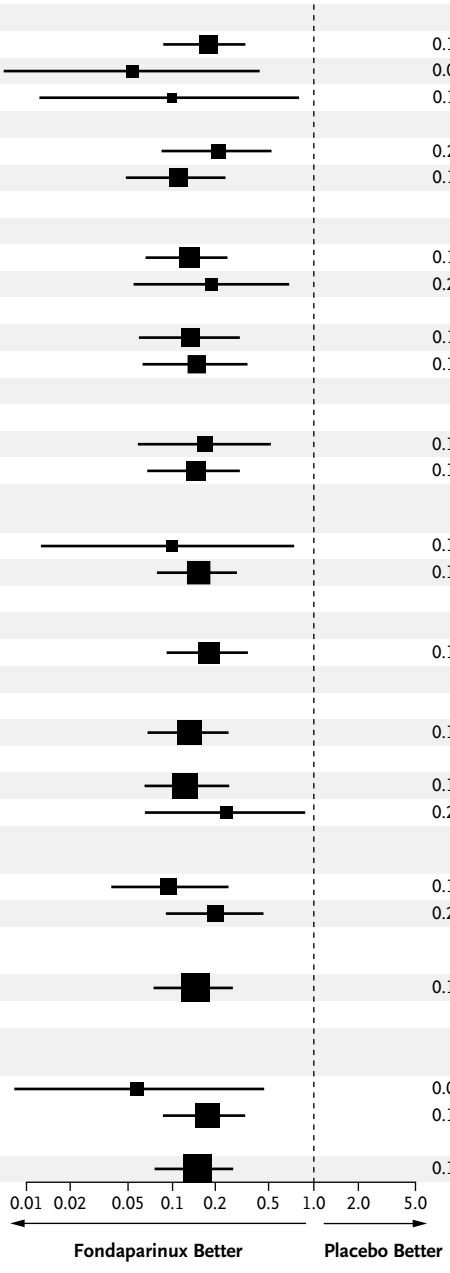
Figure 1. Kaplan–Meier Estimates of the Probability of the Primary Efficacy Outcome, According to Study Group.
The primary efficacy outcome was a composite of death from any cause, symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis. Data from patients who were lost to follow-up were censored at the time of the last contact. I bars indicate 95% confidence intervals.

(8.3%; 95% CI, 6.0 to 10.6),[8] confirming that superficial-vein thrombosis is not a benign disease.

The relative reduction of 85% in the risk of symptomatic events that we observed with 2.5 mg of fondaparinux daily as compared with placebo is consistent with the reduction in the risk of venous thromboembolic complications that has been observed in studies evaluating anticoagulant agents as compared with placebo or no therapy for prophylaxis[25-28] or treatment[29] of venous thromboembolism. This benefit was evident within the first days after treatment was initiated (Fig. 1), supporting the adequacy of the prophylactic dose of 2.5 mg of fondaparinux and in accord with the substantial efficacy data already available with respect to a dose of 2.5 mg of fondaparinux in various clinical settings.[20-23] We chose a 45-day duration of treatment with the specific objective of avoiding the "catch-up" phenomenon observed with shorter (up to 30-day) courses of low-molecular-weight heparin.[6,17] This objective was met, since the efficacy of fondaparinux efficacy was maintained through day 77.

As compared with placebo, fondaparinux also significantly reduced, by the same magnitude, the risk of each thromboembolic component of the primary efficacy outcome and was associated with a clinically important and statistically significant reduction of 85% in the risk of the composite outcome of symptomatic deep-vein thrombosis or pulmonary embolism at day 47. The number needed to treat to prevent one episode of pulmonary embolism with fondaparinux as compared with placebo in the patients with superficial-vein thrombosis in our study (300) is similar to the number needed to treat with low-molecular-weight heparin as compared with placebo or no treatment in trials of thromboprophylaxis in acutely ill medical patients (345).[28] Fondaparinux also reduced the risk of symptomatic recurrence of superficial-vein thrombosis and, more important, its extension to the saphenofemoral junction — a finding that is clinically relevant because such extension is considered to increase the risk of deep-vein thrombosis and pulmonary embolism, thereby prompting escalation of therapy (e.g., to full-dose anticoagulation or surgery).[1,2,6,8,10,11,14] In our study, fondaparinux reduced by 81% the rate

Subgroup	Fondaparinux	Placebo	Hazard Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<65 yr	11/1031 (1.1)	61/1033 (5.9)	0.18 (0.10–0.35)
65–75 yr	1/375 (0.3)	17/353 (4.8)	0.06 (0.01–0.41)
>75 yr	1/114 (0.9)	10/114 (8.8)	0.10 (0.01–0.77)
Sex			
Male	6/528 (1.1)	29/556 (5.2)	0.22 (0.09–0.52)
Female	7/974 (0.7)	59/944 (6.3)	0.12 (0.05–0.25)
Weight			
<50 kg	0/2 (0.0)	0/1 (0.0)	ND
50–100 kg	10/1313 (0.8)	73/1315 (5.6)	0.14 (0.07–0.27)
>100 kg	3/183 (1.6)	15/181 (8.3)	0.20 (0.06–0.67)
Body-mass index			
<30	7/922 (0.8)	52/961 (5.4)	0.14 (0.06–0.31)
≥30	6/574 (1.0)	36/536 (6.2)	0.16 (0.07–0.37)
Creatinine clearance			
<50 ml/min	0/68 (0.0)	7/64 (10.9)	ND
50–80 ml/min	4/412 (1.0)	24/438 (5.5)	0.18 (0.06–0.51)
>80 ml/min	9/1007 (0.9)	57/984 (5.8)	0.15 (0.08–0.31)
History of deep-vein thrombosis or pulmonary embolism			
Yes	1/105 (1.0)	10/104 (9.6)	0.10 (0.01–0.76)
No	12/1397 (0.9)	78/1396 (5.6)	0.15 (0.08–0.28)
History of superficial-vein thrombosis			
Yes	0/178 (0.0)	15/178 (8.4)	ND
No	13/1324 (1.0)	73/1322 (5.5)	0.18 (0.10–0.32)
History of cancer			
Yes	1/32 (3.1)	0/29 (0.0)	ND
No	12/1470 (0.8)	88/1471 (6.0)	0.14 (0.08–0.25)
Varicose veins at inclusion			
Yes	10/1331 (0.8)	76/1329 (5.7)	0.13 (0.07–0.25)
No	3/171 (1.8)	12/171 (7.0)	0.25 (0.07–0.87)
Superficial-vein thrombosis location relative to the knee			
Above	5/710 (0.7)	49/694 (7.1)	0.10 (0.04–0.25)
Below only	8/791 (1.0)	39/806 (4.8)	0.21 (0.10–0.44)
Superficial-vein thrombosis involving great saphenous vein			
Yes	13/1399 (0.9)	87/1382 (6.3)	0.15 (0.08–0.26)
No	0/103 (0.0)	1/118 (0.8)	ND
Distance of thrombus from saphenofemoral junction			
<10 cm	1/117 (0.9)	17/119 (14.3)	0.06 (0.01–0.44)
≥10 cm	11/1235 (0.9)	62/1235 (5.0)	0.18 (0.09–0.34)
Overall	13/1502 (0.9)	88/1500 (5.9)	0.15 (0.08–0.26)



of surgery, primarily ligation of the saphenofemoral junction, for superficial-vein thrombosis — a prespecified secondary outcome. In addition, more patients in the placebo group than in the fondaparinux group required therapeutic doses of anticoagulant therapy.

A potential limitation of our study is the difficulty in applying the data to clinical practice, because a complete ultrasonographic examination was performed in every patient with a suspected superficial-vein thrombosis — first, to confirm the condition, and second, to rule out the presence of deep-vein thrombosis. However, performing a complete ultrasonographic examination may help physicians avoid treating patients who do not have thrombosis and allow the appropriate

Figure 2 (facing page). Rates of the Primary Efficacy Outcome at Day 47 in Prespecified Subgroups.

The primary efficacy outcome was a composite of death from any cause, symptomatic pulmonary embolism, symptomatic deep-vein thrombosis, or symptomatic extension to the saphenofemoral junction or symptomatic recurrence of superficial-vein thrombosis. The size of each square is in proportion to the number of patients in the comparison. The analysis of subgroups according to the distance of thrombus from the saphenofemoral junction included only subjects who had a thrombosis involving the great saphenous vein. No adjustment for multiple comparisons was made, since subgroup analyses were performed for exploratory purposes only. None of the P values for interaction were less than 0.10 (data not shown). Results for 12 of the 16 prespecified subgroups are presented; the treatment effect was also consistent within each of the 4 other prespecified subgroups (defined according to country and status with respect to receipt of graduated compression stockings, use of nonsteroidal anti-inflammatory drugs, and use of aspirin or other antiplatelet agents at baseline), as well as the subgroup defined post hoc (defined according to whether the index superficial-vein thrombosis was in a varicose vein on ultrasonographic examination). The body-mass index is the weight in kilograms divided by the square of the height in meters. ND denotes not determined.

Table 4. Safety Outcomes up to Day 47.

Safety Outcome	Fondaparinux (N=1499)	Placebo (N=1488)
	no. with event (%)	
Bleeding		
Major*	1 (0.1)	1 (0.1)
Fatal	0	0
Symptomatic in a critical organ†	1 (0.1)	0
Causing 2 g/dl fall in hemoglobin or necessitating transfusion of ≥2 units of packed red cells or whole blood‡	0	1 (0.1)
Clinically relevant nonmajor	5 (0.3)	8 (0.5)
Minor	9 (0.6)	6 (0.4)
Any	15 (1.0)	14 (0.9)
Arterial thromboembolic complication§	0	3 (0.2)
Any adverse event	195 (13.0)	199 (13.4)
Drug-related	56 (3.7)	49 (3.3)
Nonfatal serious	10 (0.7)	16 (1.1)
Leading to discontinuation of study treatment	18 (1.2)	29 (1.9)
Leading to withdrawal from study	2 (0.1)	1 (0.1)

* P=1.00 with the use of Fisher's exact test.
† One patient in the fondaparinux group had retinal bleeding that resolved after the discontinuation of study treatment; there were no functional consequences that affected vision.
‡ One patient in the placebo group had epistaxis that necessitated medical intervention but that resolved without further consequences.
§ There were two cases of acute coronary syndrome and one of ischemic stroke — all in the placebo group.

care of patients who present with concomitant deep-vein thrombosis.[8] Our results were obtained without the use of repeat systematic compression ultrasonography — in contrast to clinical practice in certain countries.[8] The 45-day regimen of subcutaneous injections could also be questioned from a practical standpoint. However, the feasibility of such treatment was confirmed by the high degree of patient adherence; more than 90% of patients injected themselves with the study drug. The effect of the 45-day fondaparinux regimen on the quality of life was not formally assessed in our study. However, the significantly reduced risk of symptomatic complications and of recourse to surgery or therapeutic doses of anticoagulant agents that we observed with fondaparinux therapy is likely to be associated with an improved quality of life. Finally, the cost-effectiveness of a 45-day regimen of fondaparinux remains to be evaluated, taking into account the clinical events that may be prevented with treatment and factors that potentially vary across countries, such as the direct cost of fondaparinux and the clinical management (including diagnostic and therapeutic procedures) that is currently proposed in routine practice when fondaparinux is not used.

In conclusion, patients with isolated, symptomatic superficial-vein thrombosis in the legs are at substantial risk for symptomatic thromboembolic complications. Fondaparinux administered at a dose of 2.5 mg once daily for 45 days is effective and widely applicable for the treatment of such patients.

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