ORIGINAL INVESTIGATION

Duration of Prophylaxis Against Venous Thromboembolism With Fondaparinux After Hip Fracture Surgery

A Multicenter, Randomized, Placebo-Controlled, Double-blind Study

Bengt I. Eriksson, MD, PhD; Michael R. Lassen, MD; for the PENTasaccharide in HIp-FRActure Surgery Plus (PENTHIFRA Plus) Investigators

Background: The benefit of thromboprophylaxis for 1 month has never been evaluated in patients undergoing hip fracture surgery, a setting in the highest risk category for postoperative venous thromboembolism (VTE).

Methods: In a double-blind multicenter trial, 656 patients undergoing hip fracture surgery were randomly assigned to receive prophylaxis with a once-daily subcutaneous injection of either 2.5 mg of fondaparinux sodium or placebo for 19 to 23 days. Before randomization, all patients had received fondaparinux for 6 to 8 days. The primary efficacy outcome was VTE occurring during the double-blind period (deep vein thrombosis detected by mandatory bilateral venography or documented symptomatic deep vein thrombosis or pulmonary embolism). The main safety outcome was major bleeding.

Results: The primary efficacy outcome was assessed in 428 patients. Fondaparinux reduced the incidence of VTE compared with placebo from 35.0% (77/220) to 1.4% (3/208), with a relative reduction in risk of 95.9% (95% confidence interval, 87.2%-99.7%; $P<.001$). Similarly, the incidence of symptomatic VTE was significantly lower with fondaparinux (1/326; 0.3%) than with placebo (9/330; 2.7%). The relative reduction in risk was 88.8% ($P=.02$). Although there was a trend toward more major bleeding in the fondaparinux group than in the placebo group ($P=.06$), there were no differences between the 2 groups in the incidence of clinically relevant bleeding (leading to death, reoperation, or critical organ bleeding).

Conclusions: Extended prophylaxis with fondaparinux for 3 weeks after hip fracture surgery reduced the risk of VTE by 96% and was well tolerated.

Arch Intern Med. 2003;163:1337-1342

From Orthopedics Departments, Sahlgrenska University Hospital/Östra, Göteborg, Sweden (Dr Eriksson), and University Hospital of Copenhagen Hillerød, Hillerød, Denmark (Dr Lassen). All committees and investigators participating in the PENTHIFRA Plus Study are listed at the end of this article. Drs Eriksson and Lassen have served as consultants to Sanofi-Synthelabo and NV Organon.

PATIENTS UNDERGOING surgery for hip fracture are in the highest category of risk for postoperative venous thromboembolism (VTE).[1,2] Without prophylaxis, fatal pulmonary embolism is much more common after hip fracture surgery (3.6%-12.9%) than after elective hip replacement (0.1%-0.4%).[1] It has recently been reported that treatment with the new selective factor Xa inhibitor fondaparinux,[3,4] administered subcutaneously at the dose of 2.5 mg once daily for up to 11 days in patients undergoing surgery for hip fracture, reduced by 56.4% (from 19.1% to 8.3%) the rate of VTE ($P<.001$), with a similar safety profile to the low-molecular-weight heparin enoxaparin (the PENTasaccharide in HIp-FRActure [PENTHIFRA] Study).[5] However, as shown in elective hip replacement surgery,[6-8] the risk of VTE may persist longer than 11 days after surgery for hip fracture.[9] For instance, in the PENTHIFRA study, 22 of the 30 symptomatic venous thromboembolic events and 11 of the 15 fatal pulmonary embolism episodes occurred during follow-up between day 11 and day 49.[5] The benefit of thromboprophylaxis for up to 4 weeks after surgery has now been well established in elective hip replacement surgery[6-8] and more recently in abdominal surgery for cancer,[10] but no such data exist in surgery for hip fracture.

The aim of the present randomized, double-blind trial was therefore to evaluate the benefit-to-risk ratio of a 2.5-mg once-daily subcutaneous injection of fondaparinux sodium compared with placebo. Both treatments were administered for 3 weeks after an initial 1-week prophylaxis with fondaparinux for the prevention of VTE in patients undergoing surgery for hip fracture.

METHODS

PATIENTS

Patients aged at least 18 years who were undergoing standard surgery for fracture of the

upper third of the femur, including femoral head and neck, were considered for inclusion if surgery was planned within 48 hours after admission. Patients were excluded if they presented with trauma affecting more than 1 organ system or if more than 24 hours had elapsed between the causative trauma and hospital admission. Other main exclusion criteria were active bleeding; documented congenital or acquired bleeding disorder; current ulceration or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmological surgery within the previous 3 months; difficulty in performing epidural or spinal anesthesia; planned indwelling intrathecal or epidural catheter for more than 6 hours after surgery; contraindication to anticoagulant therapy; pregnancy; hypersensitivity to contrast media; or serum creatinine concentration above 2.0 mg/dL (177 µmol/L) in a well-hydrated patient. Patients who required long-term anticoagulant treatment for a chronic comorbid condition or were receiving any type of anticoagulant or fibrinolytic therapy or dextran from admission to first study drug administration or surgery were also excluded.

STUDY DESIGN

This study was a prospective, placebo-controlled, double-blind, randomized trial. The day of surgery was defined as day 1. All eligible patients were given a once-daily, subcutaneous injection of 2.5 mg of fondaparinux sodium (Arixtra; Sanofi-Synthelabo, Paris, France, and NV Organon, Oss, the Netherlands) up to day 6 to 8 after surgery, according to the dosage regimen used in a prior clinical study.[5]

After this open-label period, patients were randomly assigned, according to a computer-generated randomization list balanced in blocks of equal numbers and stratified by center, to receive a once-daily, subcutaneous injection of either 2.5 mg of fondaparinux sodium or placebo for 19 to 23 additional days, for a total duration of treatment of 25 to 31 days. The first injection was to be given less than 2 hours after randomization. Patients were excluded from randomization if they experienced 1 of the following events during the open-label period: active and unusual clinically significant bleeding, confirmed symptomatic deep vein thrombosis or pulmonary embolism, or reoperation.

During the period of prophylaxis after the patients had been discharged from the hospital, competent patients, their caregivers, or district nurses administered the injections. Compliance was checked by reviewing records of injections and was defined as receipt of at least 19 doses of study drug in the absence of a premature study drug discontinuation owing to lack of efficacy or adverse event. In cases of suspected VTE, patients underwent appropriate diagnostic tests, and in the event that VTE was confirmed, the study treatment was discontinued and replaced by another treatment at the investigator's discretion.

The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by independent ethics committees, and written informed consent was obtained from all patients before randomization.

MEDICATIONS

For the open-label period, treatment kits containing 8 prefilled, single-dose syringes of fondaparinux were used. Each syringe contained 2.5 mg of fondaparinux sodium in 0.5 mL of water for injectable preparations, a concentration of 5 mg/mL. For the double-blind period, study medications were packaged in boxes containing 24 prefilled, single-dose syringes of either 2.5 mg of fondaparinux sodium or placebo (0.5 mL of isotonic sodium chloride solution). All syringes were of identical appearance.

Throughout the study, the use of aspirin and nonsteroidal anti-inflammatory drugs was discouraged. Other antiplatelet agents, intermittent pneumatic compression, dextran, and anticoagulant and thrombolytic agents were prohibited. The use of graduated elastic stockings was permitted, and early mobilization was strongly recommended.

OUTCOME MEASURES

Outcome measures were the incidence of efficacy and safety end points during the double-blind period. The primary efficacy outcome was VTE (defined as deep vein thrombosis, pulmonary embolism, or both). Secondary efficacy outcomes were total, proximal, and distal deep vein thrombosis, and symptomatic VTE. Patients were examined for deep vein thrombosis by systematic ascending bilateral contrast venography of the legs[11] between days 25 and 32, no more than 1 calendar day after the last study treatment administration or earlier if thrombosis was clinically suspected. Symptomatic pulmonary embolism was confirmed by high-probability lung scanning, pulmonary angiography,[12] spiral computed tomography, or at autopsy.

The primary safety outcome was major bleeding, including fatal bleeding, retroperitoneal, intracranial, or intraspinal bleeding, bleeding that involved any other critical organ, bleeding leading to reoperation, and overt bleeding with a bleeding index of 2 or more. Bleeding index was calculated as follows: number of units of packed red blood cells or whole blood transfused + (prebleeding – postbleeding hemoglobin values in grams per deciliter). Secondary safety outcomes were death, other bleeding, transfusion requirements, and any other adverse events. The blood platelet count was measured at baseline, at the end of the open-label period, and at the end of the double-blind period.

All efficacy outcomes 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

The trial was designed to demonstrate the superiority of fondaparinux over placebo when both were administered for 3 weeks after an initial administration of fondaparinux for 1 week. Assuming that the VTE incidence after 4 weeks of thromboprophylaxis with fondaparinux would be 11.5% (ie, 1.4 times higher than that observed at 10 days with fondaparinux in the same setting),[5] and that the risk reduction would be 50%, based on previous 4-week prophylaxis studies of similar design in total hip replacement with low-molecular-weight heparin,[13,14] the expected VTE incidence in the placebo group was 23%. Thus, with a power of 85%, 210 patients were needed per group. Estimating that 10% of patients would not enter the double-blind period and that 30% would not be evaluable for primary efficacy, the target number of recruited patients was 670 to reach 600 randomized patients, 300 per group.

The primary efficacy analysis included data on all randomized patients who had an adequate VTE assessment. Safety analyses included data on all randomized patients who had received at least 1 dose of the study medication. A 2-tailed P value of less than .05 was considered statistically significant for the primary efficacy end point. A 2-sided Fisher exact test was used for binary variables. Exact 95% confidence intervals for absolute difference and risk ratio between fondaparinux and placebo were calculated.

The study was supervised by a steering committee. The committee designed the study, interpreted the data, and wrote the article. The central adjudication committee and the data monitoring committee were independent from the sponsor.

RESULTS

STUDY POPULATION

Between June 2001 and February 2002, 737 patients were enrolled in 57 centers in 16 countries. Eighty-one patients were not randomized in the double-blind period because of, among other reasons, confirmed symptomatic venous thromboembolism in 5 cases and bleeding complications in 8. Thus, 656 patients met the selection criteria for randomization and were assigned to receive either fondaparinux or placebo. All randomized patients received at least 1 injection of the study drug (**Table 1**). By day 32, 428 patients (65.2%) had an adequate VTE assessment, a percentage close to that recently reported in another 4-week prophylaxis study,[10] and were included in the primary efficacy analysis.

The mean±SD duration of open-label fondaparinux prophylaxis was 7.0±0.8 days for patients randomized to fondaparinux and 7.0±0.9 days for those randomized to placebo. Baseline characteristics did not differ significantly between the 2 groups of patients analyzed for safety (**Table 2**) or for primary efficacy (data not shown). Prophylaxis with the study drug was discontinued in 86 patients during the double-blind period, and the 2 groups did not differ significantly with respect to reasons for discontinuation (**Table 3**). Moreover, the 2 groups did not differ in the number of treatment days or use of concomitant treatments during the double-blind period (**Table 4**). The mean±SD duration between surgery and hospital discharge was 13.9±8.1 and 13.1±6.5 days in fondaparinux- and placebo-treated patients, respectively. Treatment compliance was verified for 307 (94.2%) of 326 patients who were assigned to fondaparinux and 305 (92.4%) of 330 patients assigned to placebo.

Table 1. Patients Randomized and Included in Analyses*

Characteristic	Fondaparinux Sodium	Placebo
Randomized	326 (100.0)	330 (100.0)
Included in the safety analyses (treated with at least 1 dose of fondaparinux or only with placebo)	327†	329†
Not evaluable for primary efficacy	118 (36.2)	110 (33.3)
No venous thromboembolism assessment	67 (20.6)	69 (20.9)
Inadequate venous thromboembolism assessment	51 (15.6)	41 (12.4)
Included in the primary efficacy analysis	208 (63.8)	220 (66.7)

*Data are number (percentage) of patients.
†One patient randomized in the placebo group received by mistake 1 injection of fondaparinux. This patient was included in the fondaparinux group for the safety analyses.

Table 2. Baseline Characteristics of the Patients Randomized and Analyzed for Safety*

Characteristic	Fondaparinux Sodium (n = 327)	Placebo (n = 329)
Median (range) age, y	79 (23-94)	79 (28-96)
No. of men/women	92/235	98/231
Median (range) weight, kg	65 (39-115)	66 (41-127)
Median (range) BMI†	24 (15-38)	24 (15-41)
Patients with BMI†≥30	25 (7.8)	26 (8.0)
History of venous thromboembolism	13 (4.0)	12 (3.6)
Orthopedic surgery within the previous 12 mo	16 (4.9)	12 (3.6)
Type of fracture		
Cervical only	125 (38.2)	141 (42.9)
Trochanteric	174 (53.2)	166 (50.5)
Subtrochanteric	28 (8.6)	22 (6.7)
Type of surgery		
Total prosthesis	30 (9.2)	30 (9.1)
Half prosthesis	80 (24.5)	83 (25.2)
Osteosynthesis	217 (66.4)	216 (65.7)
Use of cement	78 (23.9)	83 (25.2)
Type of anesthesia		
General only	102 (31.2)	102 (31.0)
Regional only	221 (67.6)	222 (67.5)
Both	4 (1.2)	5 (1.5)
Median (range) duration of surgery, h:min	1:33 (0:27-5:35)	1:35 (0:27-4:15)

Abbreviation: BMI, body mass index.
*Unless otherwise indicated, data are number (percentage) of patients.
†BMI is calculated as the weight in kilograms divided by the square of height in meters.

INCIDENCE OF VTE

Fondaparinux significantly reduced the incidence of VTE compared with placebo, from 35.0% (77/220) to 1.4% (3/208), with a relative risk reduction of 95.9% (95% confidence interval, 87.2%-99.7%; $P<.001$) (**Table 5**). There was a significant reduction in the incidence of total, proximal, and distal-only deep vein thrombosis with fondaparinux compared with placebo ($P<.001$ for each comparison). The number of patients treated for a VTE event during the double-blind period, based on the local site assessment, was 12 (4.6%) of 261 in the fondaparinux group and 59 (22.3%) of 264 in the placebo group.

Similarly, fondaparinux significantly reduced the incidence of symptomatic VTE compared with placebo, from 2.7% (9/330) to 0.3% (1/326), with a relative risk reduction of 88.8% (95% confidence interval, 67.7%-100%; $P=.02$) (Table 5). Symptomatic pulmonary embolism occurred in 3 placebo-treated patients (1 episode being fatal), but in no fondaparinux-treated patients.

SAFETY OUTCOMES

There was no fatal bleeding or bleeding in a critical organ in either treatment group. Bleeding was associated with a need for reoperation in 2 patients in each group. One of these episodes in each group led to the discontinuation of study treatment. In the fondaparinux group, 6 episodes of overt bleeding were associated with a bleeding index of 2 or more, all occurring at the surgical site, 5 occurring before the third day after randomization, and 1 before the ninth day. Only 1 of these 6 episodes led to the permanent discontinuation of study treatment, and none was associated with wound infection. The total primary safety outcome was therefore 8 adjudicated major bleeding episodes in the fondaparinux group (2.4%), compared with 2 in the pla-

Table 3. Reasons for Discontinuing Prophylaxis During the Double-blind Period*

Reason	Fondaparinux Sodium (n = 326)	Placebo (n = 330)
Venous thromboembolism	2 (0.6)	12 (3.6)
Adverse event	20 (6.1)	14 (4.2)
Informed consent withdrawn	12 (3.7)	16 (4.8)
Other reason	6 (1.8)	4 (1.2)
Total	**40** (12.3)	**46** (13.9)

*Data are number (percentage) of patients.

Table 4. Treatments Received During the Double-blind Period by Patients Assessed for the Primary Efficacy Outcome*

Characteristic	Fondaparinux Sodium (n = 208)	Placebo (n = 220)
Study Treatment		
Median (range) No. of treatment days up to the qualifying examination for venous thromboembolism	21 (3-24)	21 (4-24)
Concomitant Treatment		
Patients receiving prohibited therapy (dextran, anticoagulant, or antiplatelet agents other than aspirin)	6 (2.9)	5 (2.3)
Patients receiving discouraged therapy (nonsteroidal anti-inflammatory agents or aspirin)	42 (20.2)	34 (15.5)
Patients receiving graduated compression stockings	92 (44.2)	107 (48.6)

*Unless otherwise indicated, data are number (percentage) of patients.

cebo group (0.6%) (P=.06) (**Table 6**). No episode of thrombocytopenia occurred. Finally, there were no differences between the 2 groups in the overall incidence of adverse events and in overall mortality.

COMMENT

This study shows that, in patients undergoing surgery for hip fracture, the incidence of VTE was dramatically reduced by 96% when 2.5 mg of fondaparinux sodium once daily was compared with placebo during 3 weeks of administration after an initial 1-week prophylaxis with fondaparinux. Furthermore, an additional 3 weeks of fondaparinux prophylaxis significantly reduced by 94% the incidence of proximal deep vein thrombosis (ie, those more prone to embolize),[15-17] and by 89% the incidence of symptomatic VTE. Fondaparinux was compared with placebo because, in constrast to other surgical settings,[6-8,10,13,14,18-21] no reliable data on the incidence of late-onset VTE after a 7-day highly effective thromboprophylaxis were available, and no antithrombotic strategy administered for 1 month for the prevention of VTE had been adequately tested in patients undergoing surgery for hip fracture.[1,22-27] The incidence of events observed 1 month after surgery in our placebo group after an initial 7-day period of open-label treatment with fondaparinux (35%) was close to that reported in the placebo group of another study with a similar duration of prophylaxis after an initial 7-day period of open-label treatment with enoxaparin in hip-replacement surgery (39%).[13] This confirms that the very high risk of VTE associated with surgery for hip fracture persists longer than 11 days. Fondaparinux administered for 4 weeks reduced this 35% incidence to a very low absolute incidence of 1.4%.

Table 5. Incidence of Venous Thromboembolic Events

Event	Fondaparinux Sodium*	Placebo*	Fondaparinux Minus Placebo, % Difference (Exact 95% CI)	*P* Value†	Relative Reduction in Risk, % (95% CI)‡
Venous thromboembolism (primary outcome)	3/208 (1.4) (0.3 to 4.2)	77/220 (35.0) (28.7 to 41.7)	−33.6 (−41.4 to −26.5)	<.001	−95.9 (−99.7 to −87.2)
Any deep vein thrombosis§	3/208 (1.4) (0.3 to 4.2)	74/218 (33.9) (27.7 to 40.6)	−32.5 (−40.4 to −25.4)	<.001	−95.8 (−99.7 to −86.8)
Any proximal deep vein thrombosis‖	2/221 (0.9) (0.1 to 3.2)	35/222 (15.8) (11.2 to 21.2)	−14.9 (−22.1 to −9.4)	<.001	−94.3 (−99.9 to −75.5)
Distal deep vein thrombosis only¶	1/207 (0.5) (0.0 to 2.7)	42/211 (19.9) (14.7 to 25.9)	−19.4 (−27.0 to −13.5)	<.001	−97.6 (−100.0 to −84.9)
Symptomatic venous thromboembolism#	1/326 (0.3) (0.0 to 1.7)	9/330 (2.7) (1.3 to 5.1)	−2.4 (−6.5 to 0.1)	.02	−88.8 (−100.0 to −67.7)
Deep vein thrombosis	1/326 (0.3)	6/330 (1.8)			
Nonfatal pulmonary embolism	0/326 (0.0)	2/330 (0.6)			
Fatal pulmonary embolism	0/326 (0.0)	1/330 (0.3)			

Abbreviation: CI, confidence interval.
*Data are number of patients with events/total number of patients assessed for this event (percentage) (95% CI).
†Values were calculated using the Fisher exact test.
‡The reduction in risk is in the fondaparinux group as compared with the placebo group.
§Venography could not be evaluated in 2 patients with pulmonary embolism in the placebo group. Patients were considered able to be evaluated when proximal and distal deep veins in both legs were visualized. However, if deep vein thrombosis was seen in any 1 of the veins visualized, the patient was considered to have reached the end point even if the venous system was not visualized entirely.
‖The number of patients with available data for this variable was higher than 428 because visualization of proximal and distal deep veins in both legs was no longer a prerequisite. A patient was considered able to be evaluated for proximal deep vein thrombosis when the proximal deep veins in both legs were visualized, regardless of whether the distal veins were entirely visualized.
¶Patients with distal deep vein thrombois but not evaluable for proximal deep vein thrombosis were not counted.
#Data refer to randomized patients. Symptomatic events are included in the other categories; for instance, in the fondaparinux group, the case of symptomatic deep vein thrombosis is included in the "any deep vein thrombosis" category.

Table 6. Safety Outcomes*

Safety Outcome	Fondaparinux Sodium (n = 327)	Placebo (n = 329)
Primary		
Fatal bleeding	0	0
Bleeding in critical organ	0	0
Bleeding leading to reoperation	2 (0.6)	2 (0.6)
Overt bleeding with a bleeding index ≥2†	6 (1.8)	0
At the surgical site	6	
Associated with subsequent wound infection	0	
Leading to permanent study treatment discontinuation	1	
Secondary		
Minor bleeding	5 (1.5)	2 (0.6)
Transfusion	29 (8.9)	20 (6.1)
Death from any cause	6 (1.8)	8 (2.4)‡

*Data are number (percentage) of patients.

†The bleeding index was calculated as follows: number of units of packed red blood cells or whole blood transfused + (prebleeding − postbleeding hemoglobin values in grams per deciliter).

‡After the end of the study, ie, day 32, two deaths were recorded, both in the placebo group, of which one resulted on day 33 from an episode of pulmonary embolism. Overall, there were 2 episodes of fatal pulmonary embolism in the placebo group, 1 during the double-blind period and 1 after the end of the study, compared with none in the fondaparinux group.

The clinical relevance of reducing the incidence of asymptomatic deep vein thrombosis detected by screening venography has been regularly questioned because of the difficulty of demonstrating in a single study an associated reduction in symptomatic VTEs. However, meta-analyses of trials on prophylaxis of similar duration with low-molecular-weight heparin in elective joint replacement surgery have shown that a 50% to 60% reduction in venographically detected deep vein thrombosis and proximal deep vein thrombosis compared with placebo was associated with a reduction in symptomatic VTE of the same magnitude.[6-8] In the present study in hip fracture surgery, the 96% reduction in venographically detected deep vein thrombosis was associated with an 89% reduction in symptomatic events, indicating that asymptomatic thrombosis detected by screening venography is a valid surrogate end point for symptomatic events. This high relative reduction in the risk of VTE is consistent with the reduction we observed in phase 3 clinical studies comparing fondaparinux with low-molecular-weight heparin.[5,28] Hip fracture surgery is associated with high mortality and VTE rates, and studies suggest that fatal VTE is one of the most important factors contributing to mortality.[1,9,29,30] Our study was not powered to detect mortality differences. However, the significant reduction in symptomatic events observed with fondaparinux is consistent with an important clinical benefit.

The advanced age and frailty of patients experiencing hip fracture and the high frequency of intercurrent illnesses result in a particularly high risk of general complications related to major surgical procedures in this population.[31,32] However, fondaparinux reduced the risk of VTE without increasing the risk of clinically relevant bleeding. Although the number of patients experiencing bleeding associated with a bleeding index of 2 or more was higher in the fondaparinux than in the placebo group, the clinical relevance of such bleeding events is questionable: they were not associated with wound infection, they did not result in reoperation, and they led to permanent cessation of study treatment in only 1 patient. Finally, there was no other safety concern compared with placebo, despite the fragile nature of these patients.

We believe that our study population is representative of patients undergoing surgery for hip fracture in clinical practice and that these beneficial results can be reproduced in a routine setting for the following reasons: (1) In contrast to some previous trials investigating optimal prophylaxis duration in hip replacement surgery,[18-20] we did not perform systematic venography at the time of hospital discharge; thus, patients with asymptomatic deep vein thrombosis 7 days after surgery were not excluded, and the natural history of the disease was not altered.[33] (2) The very low absolute number of venous thromboembolic events observed in the fondaparinux group indicates that no particular subgroup at lower risk for VTE can be identified; thus, all patients with hip fracture surgery, and not only high-risk targeted patients, should benefit from this 1-month treatment with fondaparinux. And (3) fondaparinux administration necessitates no monitoring of anticoagulant activity or dose adjustment, and a high level of compliance (94%) was achieved.

In conclusion, extended prophylaxis with fondaparinux for 3 weeks after hip fracture surgery reduced the risk of VTE by 96% and was well tolerated.

Members of the PENTHIFRA Plus Study Group

Steering Committee: B. Eriksson, M. R. Lassen. *Adjudication Committee:* M. Gent (Chair) and members of the Hamilton Research Center group. *Data Monitoring Committee:* A. Planes, M. Samama. *Participating centers: Argentina (18 patients, 2 centers):* J. M. Ceresetto, D. Roubicek; *Australia (77 patients, 9 centers):* T. Brighton, J. Eikelboom, A. Gallus, S. Graves, B. Halliday, K. Narayan, H. Salem, P. Stalley, S. Williams; *Belgium (35 patients, 4 centers):* P. Broos, P. Putz, L. Renson, D. Uyttendaele; *Czech Republic (181 patients, 7 centers):* G. Berlinger, I. Kofranec, K. Koudela, M. Krbec, Z. Krska, M. Sir, T. Trc; *Denmark (23 patients, 3 centers):* L. Borris, M. R. Lassen, S. Mejdahl; *Finland (15 patients, 2 centers):* P. Jokipii, U. Vaatainen; *France (33 patients, 5 centers):* J. P. Delagoutte, M. Delecroix, S. Passot, J. Puget, F. Vogt; *Greece (26 patients, 2 centers):* J. Pournaras, M. Tyllianakis; *Italy (37 patients, 5 centers):* G. Agnelli, B. Borghi, G. Fraschini, F. Piovella, A. Venco; *Poland (56 patients, 3 centers):* P. J. Bilinski, K. Modrzewski, T. Niedzwiedzki; *Portugal (36 patients, 3 centers):* L. Almeida, A. Meireles, J. Morais Neves; *Spain (30 patients, 2 centers):* M. Monreal, L. Peidro; *Sweden (27 patients, 2 centers):* B. I. Eriksson, J. Milbrink; *Switzerland (31 patients, 2 centers):* M. Heinzelmann, P. Hoffmeyer; *the Netherlands (23 patients, 5 centers):* G. H. R. Albers, R. K. Marti, J. J. J. Van der List, J. Van der Meer, M. Van Marwijk Kooy; *United Kingdom (8 patients, 1 center):* A. T. Cohen.

Accepted for publication October 22, 2002.

This study was supported by a grant from Sanofi-Synthelabo, Paris, France, and NV Organon, Oss, the Netherlands.

This work was presented in part at the 22nd World Congress of the Société Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT), San Diego, Calif, August 23-30, 2002.

Corresponding author and reprints: Bengt I. Eriksson, MD, PhD, Orthopedics Department, Sahlgrenska University Hospital/Östra, S-41685 Göteborg, Sweden (e-mail: b.eriksson@orthop.gu.se).

REFERENCES

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism: Sixth ACCP Consensus Conference on antithrombotic therapy. *Chest.* 2001;119 (suppl):132S-175S.
2. Nicolaides AN. Prevention of venous thromboembolism—international consensus statement: guidelines compiled in accordance with the scientific evidence. *Int Angiol.* 2001;20:1-37.
3. Herbert JM, Petitou M, Lormeau JC, et al. SR 90107/Org 31540, a novel antifactor Xa antithrombotic agent. *Cardiovasc Drug Rev.* 1997;15:1-26.
4. Turpie AGG, Gallus AS, Hoek JA, for the Pentasaccharide Investigators. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med.* 2001;344:619-625.
5. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG, for the Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med.* 2001;345:1298-1304.
6. Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low-molecular-weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty: a meta-analysis. *Thromb Haemost.* 2001;85: 940-941.
7. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. *Lancet.* 2001;358:9-15.
8. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med.* 2001;135:858-869.
9. Frostick SP. Death after joint replacement. *Haemostasis.* 2000;30(suppl 2):84-87.
10. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med.* 2002; 346:975-980.
11. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. *Arch Surg.* 1972;104:134-144.
12. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA.* 1990;263:2753-2759.
13. Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. *N Engl J Med.* 1996;335:696-700.
14. Lassen MR, Borris LC, Anderson BS, et al. Efficacy and safety of prolonged thromboprophylaxis with a low-molecular-weight heparin (dalteparin) after total hip arthroplasty: the Danish Prolonged Prophylaxis (DaPP) Study. *Thromb Res.* 1998; 89:281-287.
15. Havig Ö. Deep vein thrombosis and pulmonary embolism: an autopsy study with multiple regression analysis of possible risk factors. *Acta Chir Scand Suppl.* 1977; 478:1-120.
16. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? *Ann Intern Med.* 1981;94:439-444.
17. Eriksson BI, Kälebo P, Anthmyr BA, Wadenvik H, Tengborn L, Risberg B. Prevention of deep-vein thrombosis and pulmonary embolism after total hip replacement: comparison of low-molecular-weight heparin and unfractionated heparin. *J Bone Joint Surg Am.* 1991;73:484-493.
18. Planès A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet.* 1996;348:224-228.
19. Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery: results of a double-blind, prospective, placebo-controlled study with dalteparin (Fragmin®). *Thromb Haemost.* 1997; 77:26-31.
20. Hull RD, Pineo GF, Francis C, et al, for the North American Fragmin Trial Investigators. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients. *Arch Intern Med.* 2000;160:2208-2215.
21. Comp PC, Spiro TE, Friedman RJ, et al, for the Enoxaparin Clinical Trial Group. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. *J Bone Joint Surg Am.* 2001;83:336-345.
22. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet.* 2000;355:1295-1302.
23. Cohen A, Quinlan D. PEP trial correspondence [letter]. *Lancet.* 2000;356:247.
24. Sors H, Meyer G. Place of aspirin in prophylaxis of venous thromboembolism. *Lancet.* 2000;355:1288-1289.
25. Cimminiello C. PEP trial correspondence [letter]. *Lancet.* 2000;356:247-248.
26. Mahé I, Bergmann JF, Mahé E, Caulin C. PEP trial correspondence [letter]. *Lancet.* 2000;356:248.
27. Thomas DP. PEP trial correspondence [letter]. *Lancet.* 2000;356:249.
28. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies. Fondaparinux versus enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized studies. *Arch Intern Med.* 2002;162:1833-1840.
29. Perez JV, Warwick DJ, Case CP, Bannister GC. Death after proximal femoral fracture: an autopsy study. *Injury.* 1995;26:237-240.
30. Todd CJ, Freeman CJ, Camilleri-Ferrante C, et al. Differences in mortality after fracture of hip: the East Anglian Audit. *BMJ.* 1995;310:904-908.
31. Zuckerman JD. Hip fracture. *N Engl J Med.* 1996;334:1519-1525.
32. Prior GA. Mini-symposium: the difficult neck of femur fracture. *Curr Orthopaedics.* 2000;14:86-92.
33. ten Cate JW, Prins MH. Major orthopaedic surgery and post-discharge DVT. *Lancet.* 1996;348:209-210.