FONDAPARINUX COMPARED WITH ENOXAPARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER HIP-FRACTURE SURGERY

BENGT I. ERIKSSON, M.D., KENNETH A. BAUER, M.D., MICHAEL R. LASSEN, M.D., AND ALEXANDER G.G. TURPIE, F.R.C.P., FOR THE STEERING COMMITTEE OF THE PENTASACCHARIDE IN HIP-FRACTURE SURGERY STUDY*

ABSTRACT

Background Surgery for hip fracture carries a high risk of venous thromboembolism, despite the use of current thromboprophylactic treatments. Fondaparinux, a synthetic pentasaccharide, is a new antithrombotic agent that may reduce this risk.

Methods In a double-blind study, we randomly assigned 1711 consecutive patients undergoing surgery for fracture of the upper third of the femur to receive subcutaneous doses of either 2.5 mg of fondaparinux once daily, initiated postoperatively, or 40 mg of enoxaparin once daily, initiated preoperatively, for at least five days. The primary efficacy outcome was venous thromboembolism up to postoperative day 11. Venous thromboembolism was defined as deep-vein thrombosis detected by mandatory bilateral venography, documented symptomatic deep-vein thrombosis, or documented symptomatic pulmonary embolism. The main safety outcomes were major bleeding and mortality from all causes. The duration of follow-up was six weeks.

Results The incidence of venous thromboembolism by day 11 was 8.3 percent (52 of 626 patients) in the fondaparinux group and 19.1 percent (119 of 624 patients) in the enoxaparin group ($P<0.001$). The reduction in risk with fondaparinux was 56.4 percent (95 percent confidence interval, 39.0 to 70.3 percent). There were no significant differences between the two groups in the incidence of death or clinically relevant bleeding.

Conclusions In patients undergoing surgery for hip fracture, fondaparinux was more effective than enoxaparin in preventing venous thromboembolism and was equally safe. (N Engl J Med 2001;345:1298-304.)

PATIENTS undergoing surgery for hip fracture are in the highest category of risk for postoperative venous thromboembolism.[1,2] Fatal pulmonary embolism occurs in 3.6 to 12.9 percent of patients who have not received prophylaxis against thromboembolism.[1] There are few data on thromboprophylaxis after surgery for hip fracture, and recommendations are based mainly on expert opinion.[1] Even with current methods of thromboprophylaxis, the incidence of venographically confirmed deep-vein thrombosis is 24 to 34 percent.[1,3-21]

Fondaparinux is a new synthetic pentasaccharide that causes selective inhibition of activated factor X (factor Xa).[22-25] A recent study of patients undergoing major orthopedic procedures suggested that a once-daily subcutaneous injection of fondaparinux reduces the risk of venous thromboembolism more than does low-molecular-weight heparin.[26]

We conducted a multicenter, randomized, double-blind trial to compare two types of thromboprophylaxis after hip-fracture surgery: a once-daily subcutaneous injection of fondaparinux, initiated postoperatively, and a once-daily subcutaneous injection of enoxaparin, initiated preoperatively.

METHODS

Patients

Patients were considered for inclusion if they were at least 18 years of age and were scheduled to undergo standard surgery for fracture of the upper third of the femur, including the femoral head and neck, within 48 hours after admission.

The main reasons for exclusion were multiple trauma affecting more than one organ system; an interval of more than 24 hours between the injury and hospital admission; pregnancy; active bleeding; a documented congenital or acquired bleeding disorder; current ulcerative or angiodysplastic gastrointestinal disease; a history of hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the previous three months; planned use of an indwelling intrathecal or epidural catheter for more than six hours after surgery; hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contrast medium; a contraindication to anticoagulant therapy; a current addictive disorder; a serum creatinine concentration above 2 mg per deciliter (177 μmol per liter) in a well-hydrated patient; and a platelet count below 100,000 per cubic millimeter. Patients who required anticoagulant therapy or received dextran or any type of anticoagulant or fibrinolytic therapy from admission to the time of first administration of the study drug or surgery were also excluded.

Study Design

Within 24 hours after admission and before surgery, patients were randomly assigned to treatment groups in blocks of four, with stratification according to center, with the use of a computer-generated randomization list. Patients were assigned to receive once-daily subcutaneous injections of either 2.5 mg of fondaparinux (Arixtra, Sanofi–Synthelabo, Paris, and NV Organon, Oss, the Netherlands) and a placebo or 40 mg of enoxaparin (Clexane/Lovenox, Aventis Pharmaceuticals, Bridgewater, N.J.) and a placebo. In the enoxaparin group, the first active dose was given 12 ± 2 hours preoperatively and the second 12 to 24 hours postoperatively, according to the recommendation of the manufactur-

From the Department of Orthopedics, Sahlgrenska University Hospital–Östra, Göteborg, Sweden (B.I.E.); the Department of Medicine, Veterans Affairs Boston Healthcare System and Beth Israel Deaconess Medical Center, Boston (K.A.B.); the Department of Orthopedics, Hillerød University, Hillerød, Denmark (M.R.L.); and the Department of Medicine, Hamilton Health Sciences Corporation–General Division, Hamilton, Ont., Canada (A.G.G.T.). Address reprint requests to Dr. Eriksson at the Orthopedics Department, Sahlgrenska University Hospital–Östra, S-41685 Göteborg, Sweden, or at b.eriksson@orthop.gu.se.

*Participants in the study are listed in the Appendix.

er. Since fondaparinux is a new compound, which differs from enoxaparin in its mechanism of action and pharmacokinetic properties, the starting time after surgery and the dose were determined during the early development of the drug[26]; the first dose of fondaparinux was administered 6±2 hours postoperatively and the second 12 hours or more after the first. However, if surgery was delayed until 24 to 48 hours after admission, administration of fondaparinux was initiated 12±2 hours before surgery. In both groups, omission of preoperative injections was recommended if spinal or epidural anesthesia or catheterization was planned, and any indwelling intrathecal or epidural catheter was to be removed at least two hours before the first postoperative injection.

Day 1 was defined as the day of surgery. Treatment was scheduled to continue until day 5 to day 9, and the primary efficacy outcome was assessed between day 5 and day 11. Patients were then followed up in person, by mail, or by telephone between day 35 and day 49. During follow-up, patients were instructed to report any symptoms or signs of venous thromboembolism or bleeding and any other clinical event occurring since the completion of treatment. Investigators could extend prophylaxis during follow-up with any currently available therapy, but only after venography had been performed. If venous thromboembolism occurred during the study, treatment was left to the discretion of the investigators.

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

Study medications were packaged in boxes of identical appearance, each containing 10 prefilled, single-dose syringes of active treatment and 10 prefilled, single-dose syringes of matching placebos. Each syringe contained either 2.5 mg of fondaparinux sodium in 0.25 ml of water for injectable preparations (a concentration of 10 mg per milliliter), 40 mg of enoxaparin sodium in 0.4 ml of water for injectable preparations (a concentration of 100 mg per milliliter), or placebo (0.25 or 0.4 ml of isotonic saline).

Throughout the treatment period, the use of intermittent pneumatic compression, dextran, and thrombolytic, anticoagulant, or antiplatelet agents was prohibited. Centers were advised to avoid giving patients aspirin or nonsteroidal antiinflammatory drugs whenever possible. The use of graduated compression stockings and physiotherapy was recommended.

Outcome Measures

The primary efficacy outcome was assessed by the rate of venous thromboembolism (defined as deep-vein thrombosis, pulmonary embolism, or both) up to day 11. Secondary efficacy outcomes were total, proximal, or distal deep-vein thrombosis or symptomatic venous thromboembolism up to day 11 and symptomatic venous thromboembolism up to day 49. Patients were examined for deep-vein thrombosis by systematic bilateral ascending venography of the legs[27] between day 5 and day 11, but no more than two days after the last dose of study drug, or earlier if thrombosis was clinically suspected. Symptomatic pulmonary embolism was confirmed by a lung scan indicating a high probability of pulmonary embolism, by pulmonary angiography,[28] by helical computed tomography, or at autopsy.

The primary safety outcome was the incidence of major bleeding, which included fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more. The bleeding index was calculated as the number of units of packed red cells or whole blood transfused plus the hemoglobin values before the bleeding episode minus the hemoglobin values after the episode (in grams per deciliter). Secondary safety outcomes were death, minor bleeding, a need for transfusion, thrombocytopenia, and any other adverse event. Minor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding.

Efficacy and safety outcomes were adjudicated by a central independent committee whose members were unaware of the treatment assignments and included review of all venograms and reports of bleeding and death.

Statistical Analysis

Assuming an incidence of venous thromboembolism by day 11 of 22 percent in the enoxaparin group[7] and a risk reduction of about 30 percent (i.e., an incidence of 15 percent in the fondaparinux group), 600 patients were needed per group to provide the study with a power of 85 percent. The target number of recruited patients was 1700, a number that allowed for failure to obtain primary efficacy data in approximately 30 percent of patients.

The analysis of the primary efficacy outcome included data on all patients who had received at least one dose of study medication, had undergone the appropriate surgery, and had had an adequate assessment for venous thromboembolism by day 11. The analysis of safety included data on patients who had received at least one dose of study medication.

A two-tailed P value of less than 0.05 was considered to indicate statistical significance. The analysis of the primary efficacy outcome was performed with the use of a two-sided Fisher's exact test. Exact 95 percent confidence intervals for the absolute difference between fondaparinux and enoxaparin and the risk ratio were calculated. The treatment effect was also analyzed according to predefined categorical covariates with use of a logistic-regression model.

The study was supervised by a steering committee of 10 people, which included 6 representatives of the sponsor (Sanofi–Synthelabo and NV Organon). The committee designed the study, interpreted the data, and wrote the article. The final statistical analysis was performed by the sponsor. The central adjudication committee and the data-monitoring committee operated independently of the sponsor. One planned interim analysis was conducted when half the projected patient population had been enrolled, for reestimation of the sample size, since the rate of venous thromboembolism in patients undergoing hip-fracture surgery was uncertain. Simulations demonstrated that the predefined procedure did not inflate the type I error. No change in the sample size was found to be necessary, and the study continued as planned.

RESULTS

Study Population

Between November 1998 and October 1999, 1711 patients were enrolled in 99 centers in 21 countries (listed in the Appendix). Thirty-eight patients did not receive either study drug (Table 1). Two patients did not undergo the appropriate surgery, and primary efficacy had not been assessed by day 11 in 421 patients. Thus, 1250 patients (73.1 percent) were included in the primary efficacy analysis, a percentage in line with other large multicenter studies that used venography after orthopedic surgery.[29-31] The characteristics of patients excluded from the primary efficacy analysis did not differ from those of patients included in the analysis (data not shown).

Base-line characteristics did not differ significantly between the two groups of patients included in the analysis of safety (Table 2) or primary efficacy (data not shown). A total of 551 and 569 patients underwent surgery within 24 hours after admission in the fondaparinux and enoxaparin groups, respectively. Among the 626 patients in the fondaparinux group who were included in the primary efficacy analysis, fondaparinux was given preoperatively to 68 (10.9

TABLE 1. PATIENTS INCLUDED IN THE ANALYSES AND REASONS FOR EXCLUSION.

VARIABLE	FONDAPARINUX (N=849)	ENOXAPARIN (N=862)
	no. (%)	
Not treated	18 (2.1)	20 (2.3)
Inclusion criteria not met	13 (1.5)	13 (1.5)
Informed consent withdrawn	2 (0.2)	4 (0.5)
Technical problem	1 (0.1)	2 (0.2)
Death	2 (0.2)	1 (0.1)
Treated with at least one dose of study drug (able to be evaluated for safety)	831 (97.9)	842 (97.7)
Not able to be evaluated for primary efficacy	205 (24.1)	218 (25.3)
No surgery or inappropriate surgery	0	2 (0.2)
Inadequate venography*	205 (24.1)	216 (25.1)
Not done†	125 (14.7)	116 (13.5)
Not able to be evaluated	72 (8.5)	88 (10.2)
Outside specified interval‡	8 (0.9)	12 (1.4)
Able to be evaluated for primary efficacy	626 (73.7)	624 (72.4)

*Venography was considered adequate by the central adjudication committee if films were provided visualizing the whole deep-venous system of the legs, including the iliofemoral segment, with a minimum of two views in perpendicular directions.

†No venography was performed in the absence of pulmonary embolism up to day 11.

‡Patients were assessed before day 5 (and had no deep-vein thrombosis on venography), after day 11, or more than 48 hours after the last dose of the study drug was administered.

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	FONDAPARINUX (N=831)	ENOXAPARIN (N=842)
Age — yr	76.8±12.3	77.3±12.6
Sex — M/F	187/644	224/618
Weight — kg	64.3±13.1	64.2±13.8
Body-mass index†	23.8±4.0	23.6±4.3
Body-mass index ≥30 — no. (%)†	42 (5.4)	59 (7.6)
History of venous thromboembolism — no. (%)	29 (3.5)	32 (3.8)
Orthopedic surgery within previous 12 mo — no. (%)	33 (4.0)	26 (3.1)
Underlying cancer — no. (%)	79 (9.5)	74 (8.8)
Time from injury to surgery — hr	24.7±16.2	25.2±15.9
Time from admission to surgery — hr	20.9±15.4	21.2±16.5
Anticoagulant or antiplatelet agents given between trauma and first injection of study drug — no. (%)	144 (17.3)	134 (15.9)
Type of fracture — no. (%)‡		
Cervical only	400 (48.1)	388 (46.3)
Trochanteric§	373 (44.9)	368 (43.9)
Subtrochanteric	58 (7.0)	82 (9.8)
Type of surgery — no. (%)¶		
Total prosthesis	56 (6.7)	58 (6.9)
Half prosthesis	193 (23.2)	183 (21.8)
Osteosynthesis‖	582 (70.0)	600 (71.3)
Use of cement — no. (%)¶	176 (21.2)	183 (21.8)
Type of anesthesia — no. (%)¶		
General only	262 (31.5)	276 (32.8)
Regional only	554 (66.7)	548 (65.2)
Both	15 (1.8)	17 (2.0)
Duration of surgery — min	101±39	104±44

*Plus–minus values are means ±SD.

†The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 57 patients in the fondaparinux group and 61 in the enoxaparin group.

‡Data were missing for three patients in the enoxaparin group.

§This injury was not associated with any subtrochanteric fracture.

¶The number of patients who were treated and underwent surgery was 831 in the fondaparinux group and 841 in the enoxaparin group.

‖This category included nailing, screwing, plate, and any type of combined surgery.

percent) because surgery was delayed until 24 to 48 hours after admission; enoxaparin was given postoperatively, rather than preoperatively, to 464 of 624 patients assigned to that drug (74.4 percent) because of very early surgery after admission or planned regional anesthesia. The median time between surgery and the assessment of primary efficacy was eight days in both groups; most patients were assessed between day 5 and day 11 as planned. The two groups did not differ significantly with regard to the last day of active treatment or the use of concomitant treatments up to day 11 (Table 3).

Overall, 829 patients treated with fondaparinux and 840 patients treated with enoxaparin returned for the follow-up visit on day 49. The duration of follow-up was similar between the two groups. During follow-up of patients who did not receive treatment for an acute thromboembolic event, 58.5 percent of patients treated with fondaparinux and 55.8 percent of patients treated with enoxaparin received prolonged thromboprophylaxis, primarily with a preparation of heparin or a vitamin K antagonist, after the study treatment.

Incidence of Venous Thromboembolism

The incidence of venous thromboembolism by day 11 was 8.3 percent in the fondaparinux group (52 of 626 patients) and 19.1 percent in the enoxaparin group (119 of 624 patients). This was a decrease of 10.8 percentage points, or a relative reduction in risk of 56.4 percent (95 percent confidence interval, 39.0 to 70.3 percent; $P<0.001$) (Table 4). A similar result was found in sensitivity analyses when patients who had had no primary efficacy assessment by day 11 were included in the primary efficacy analysis (data not shown). The incidence of total, proximal, and distal-only deep-vein thrombosis was significantly lower in the fondaparinux group ($P<0.001$ for all three comparisons). The incidence of symptomatic venous thromboembolism was low (6.5 percent), with no difference between the two groups.

The superior efficacy of fondaparinux over enoxaparin was found when patients were grouped ac-

TABLE 3. TREATMENTS RECEIVED DURING THE STUDY PERIOD BY PATIENTS ASSESSED FOR THE PRIMARY EFFICACY OUTCOME.

STUDY TREATMENT	FONDAPARINUX (N=626)	ENOXAPARIN (N=624)
No. of active injections up to the qualifying examination for venous thromboembolism		
Median	7	7
Range	1–11	2–10
Last day of active treatment — no. (%)		
<Day 5	11 (1.8)	4 (0.6)
Day 5 to day 9	585 (93.5)	589 (94.4)
>Day 9	30 (4.8)	31 (5.0)
CONCOMITANT TREATMENT		
Patients receiving prohibited therapy (dextran or anticoagulant or antiplatelet agents other than aspirin) — no. (%)	23 (3.7)	21 (3.4)
Patients receiving discouraged therapy (nonsteroidal antiinflammatory agents or aspirin) — no. (%)	141 (22.5)	126 (20.2)
Patients receiving graduated compression stockings — no. (%)	312 (49.8)	295 (47.3)

cording to age, sex, body-mass index (the weight in kilograms divided by the square of the height in meters [<30 vs. ≥30]), type of anesthesia (general, regional, or both), type of hip fracture (cervical, trochanteric, or subtrochanteric), type of surgery (implantation of half prosthesis, implantation of total prosthesis, or osteosynthesis), the use or nonuse of cement, or whether or not the patient had had previous venous thromboembolism (data not shown). The number of patients treated by participating physicians for a venous thromboembolic event by day 11 was significantly lower in the fondaparinux group (6.1 percent [43 of 702]) than in the enoxaparin group (11.7 percent [84 of 716], P<0.001).

By day 49, the incidence of symptomatic venous thromboembolism was similar in the fondaparinux group (2.0 percent [17 of 831 patients]) and the enoxaparin group (1.5 percent [13 of 840 patients]). Fatal pulmonary embolism occurred in 8 of 831 patients in the fondaparinux group and 7 of 840 patients in the enoxaparin group; nonfatal pulmonary embolism occurred in 3 of 831 patients and 4 of 840 patients, respectively.

TABLE 4. INCIDENCE OF VENOUS THROMBOEMBOLIC EVENTS BY DAY 11.*

EVENT	FONDAPARINUX		ENOXAPARIN		DIFFERENCE†	P VALUE‡	REDUCTION IN RISK§
	no. with events/ total no.	percent (95% CI)	no. with events/ total no.	percent (95% CI)	percent (95% CI)		percent (95% CI)
Venous thromboembolism (primary outcome)	52/626	8.3 (6.3 to 10.8)	119/624	19.1 (16.1 to 22.4)	−10.8 (−15.3 to −6.6)	<0.001	56.4 (39.0 to 70.3)
Any deep-vein thrombosis¶	49/624	7.9 (5.9 to 10.2)	117/623	18.8 (15.8 to 22.1)	−10.9 (−15.4 to −6.8)	<0.001	58.2 (41.0 to 71.8)
Any proximal deep-vein thrombosis‖	6/650	0.9 (0.3 to 2.0)	28/646	4.3 (2.9 to 6.2)	−3.4 (−6.1 to −1.3)	<0.001	78.7 (41.2 to 96.0)
Distal deep-vein thrombosis only‖	42/627	6.7 (4.9 to 8.9)	94/626	15.0 (12.3 to 18.1)	−8.3 (−12.5 to −4.5)	<0.001	55.4 (34.4 to 71.3)
Symptomatic venous thromboembolism**	4/831	0.5 (0.1 to 1.2)	4/840	0.5 (0.1 to 1.2)	0.0 (−1.1 to 1.6)	1.00	
Symptomatic deep-vein thrombosis	1/831	0.1	1/840	0.1			
Nonfatal pulmonary embolism	1/831	0.1	1/840	0.1			
Fatal pulmonary embolism	2/831	0.2	2/840	0.2			

*CI denotes confidence interval.

†Differences shown are the rates in the fondaparinux group minus the rates in the enoxaparin group.

‡Values were calculated with the use of Fisher's exact test.

§The reduction in risk is in the fondaparinux group as compared with the enoxaparin group.

¶Venography could not be evaluated in three patients with pulmonary embolism, two in the fondaparinux group and one in the enoxaparin 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 one of the veins visualized, the patient was considered to have reached the end point, even if the venous system was not visualized entirely.

‖The numbers of patients with available data for these variables were higher than 1250, since visualization of proximal and distal deep veins in both legs was no longer a prerequisite. For instance, a patient was considered able to be evaluated for proximal deep-vein thrombosis when the proximal deep veins in both legs were visualized, irrespective of whether or not the distal veins were entirely visualized.

**Data refer to patients who received at least one dose of study treatment and who underwent the appropriate surgery. 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 category "any deep-vein thrombosis."

Safety Outcomes

Major bleeding occurred by day 11 in 18 of 831 patients treated with fondaparinux and 19 of 842 patients treated with enoxaparin (P=1.00) (Table 5). Most of these episodes occurred at the surgical site (14 of 18 patients in the fondaparinux group and 14 of 19 patients in the enoxaparin group). Minor bleeding occurred more often in the fondaparinux group (P=0.02). By day 49, three patients in the fondaparinux group and six patients in the enoxaparin group underwent reoperation because of bleeding. Transfusion requirements and the incidence of other adverse events during treatment or follow-up did not differ significantly between groups. The platelet count was lower than 100,000 per cubic millimeter in 40 of 822 patients in the fondaparinux group (4.9 percent) and 44 of 831 patients in the enoxaparin group (5.3 percent). No episode of decreased platelet count was reported as a serious adverse event in either group. The incidence of wound infection was low and was the same in both groups (0.7 percent [6 of 831 in the fondaparinux group and 6 of 842 in the enoxaparin group]). By day 49, 38 patients in the fondaparinux group (4.6 percent) and 42 in the enoxaparin group (5.0 percent) had died.

DISCUSSION

This large study demonstrates that fondaparinux is significantly more effective than enoxaparin in preventing postoperative venous thromboembolism after surgery for hip fracture. The 19.1 percent incidence of venous thromboembolism in the enoxaparin group by day 11 is consistent with the results of previous studies of enoxaparin after hip-fracture surgery.[7-10] By contrast, 8.3 percent of patients given fondaparinux had postoperative venous thromboembolism. Moreover, proximal deep-vein thrombosis, which is prone to embolize, occurred in 6 of 650 patients in the fondaparinux group and 28 of 646 patients in the enoxaparin group (P<0.001).[32-34] Three other large studies in patients undergoing elective knee[35] or hip-replacement[36,37] surgery also showed the superiority of fondaparinux over enoxaparin in preventing venous thromboembolism. The efficacy of fondaparinux may be attributed to its ability to inhibit factor Xa rapidly and selectively, its predictable linear pharmacokinetics, and its relatively long half-life, which permits the drug to achieve an antithrombotic effect for 24 hours.

Physicians have been uncertain about effective and safe thromboprophylaxis after hip-fracture surgery.[1,2] Warfarin is moderately effective,[1,15-19] and aspirin is not recommended in patients undergoing such surgery.[1,20,38,39] Promising results have been reported in small studies of 40 mg of enoxaparin administered once daily, with treatment initiated preoperatively.[7-10] In our study, because of planned regional anesthesia, early surgery after admission, or both, only 25.6 percent of patients received the preoperative injection of enoxaparin. This indicates the difficulty of administering low-molecular-weight heparin preoperatively in emergency situations.

In our study, symptomatic events were rare during the treatment period, with a 0.2 percent incidence of fatal pulmonary embolism — similar to that reported in the large Pulmonary Embolism Prevention trial.[20] However, the incidence of symptomatic events in our study should be interpreted with caution. Early detection by venographic screening and prolonged prophylaxis in nearly 60 percent of our patients probably prevented symptomatic venous thromboembolism. The incidence of fatal pulmonary embolism by day 49 was nevertheless nearly 1.0 percent in both groups. The duration of treatment may have been too short for some patients who were still at risk for venous thromboembolism when treatment was discontinued.

Our study demonstrates that prophylactic fondaparinux is more effective than enoxaparin in preventing venous thromboembolism in patients undergoing hip-fracture surgery and does not increase the risk of clinically relevant bleeding.

TABLE 5. SAFETY OUTCOMES.

OUTCOME	FONDAPARINUX (N=831)	ENOXAPARIN (N=842)
Treatment period (up to day 11)		
Primary safety outcomes — no. (%)		
Fatal bleeding	0	1 (0.1)
Bleeding in critical organ	0	0
Bleeding leading to reoperation	3 (0.4)	2 (0.2)
Bleeding index ≥2*	15 (1.8)	16 (1.9)
Secondary safety outcomes		
Minor bleeding — no. (%)	34 (4.1)	18 (2.1)†
Transfusions — no. (%)	421 (50.7)	422 (50.1)
Mean (±SD) no. of units transfused among patients receiving transfusions for volume replacement	2.7±1.5	2.8±1.8
Death from any cause — no. (%)	11 (1.3)	16 (1.9)
Study period (up to day 49)		
Death from any cause — no. (%)	38 (4.6)	42 (5.0)

*The bleeding index was calculated as the number of units of packed red cells or whole blood transfused plus the hemoglobin values before the bleeding episode minus the hemoglobin values after the episode (in grams per deciliter).

†P=0.02 for the comparison with fondaparinux.

Supported by NV Organon and Sanofi–Synthelabo. All authors have served as consultants to NV Organon and Sanofi–Synthelabo.

Presented in abstract form at the 42nd Annual Meeting of the American Society of Hematology, San Francisco, December 1–5, 2000 (Blood 2000; 9:490A, A2110).

APPENDIX

The members of the Pentasaccharide in Hip-Fracture Surgery Study Group were as follows: **Steering Committee** — A.G.G. Turpie (chair),

K.A. Bauer, J. Bouthier, R.G. Cariou, J.F.M. Egberts, B.I. Eriksson, J.A. Hoek, M.R. Lassen, A.W.A. Lensing, H. Magnani; **Data Monitoring Committee** — D. Bergqvist, G.D. Paiement, A. Planes; **Central Independent Adjudication Committee** — M. Gent (chair), J.S. Ginsberg, J. Hirsh, C. Kearon, M.N. Levine, J.G. Thomson, A.G.G. Turpie, J. Weitz; **Independent Statistical Center** — A. Leizorovicz, Lyons, France; **Sponsor, Sanofi–Synthelabo Recherche, France** — *Study Management:* R.G. Cariou; *Monitoring Coordination:* M. Blanchard, A. Denys, A. Pelizza, M.C. Pujol; *Statistical Analysis:* M. Fournier; *Data Management:* D. Marin, C. Thetiot; *Local Monitors and Clinical Research Associates:* Argentina: C. Falcon, M. Rodriguez; Australia: N. Chapman, S. Tjia; Belgium: K. Handelberg, F. Cilli; Czech Republic: J. Nedvedova; France: S. Fontecave, M.J. Casellas, V. Vajou; Germany: M. Decker; Greece: N. Nikitas, V. Konstanta; Hungary: D. Pasztor, O. Fister; Italy: F. Ciffo; Poland: A. Lukasik; Portugal: P. Rebelo; Spain: G. Estrada, S. Guttierez; Sweden: U. Tael, A. Klebbe, A. Svard; Switzerland: S. Pilot, A Kullin; the Netherlands: L. Muller, L. Willemsen; United Kingdom: C. Philips; South Africa: C. Toerien; **Investigators** — Argentina (46 patients, 6 centers): G. Cardinali, J.M. Ceresetto, H.N. Hendler, L. Palmer, E.D. Ruberto, F.S. Silberman; Australia/New Zealand (222 patients, 9 centers): R. Baker, T. Brighton, J. Cade, B. Chong, A. Gallus, M. Holt, B. Richard, D. Zavataro, H.N. Salem, S. Williams; Austria (15 patients, 1 center): V. Vecsei; Belgium (80 patients, 8 centers): P. Broos, F. Burny, J. Colinet, G. De Brouckere, P. Haentjens, E. Spyropoulos, D. Uyttendaele, F. Van Elst; Czech Republic (212 patients, 7 centers): G. Berlinger, I. Kofranek, K. Koudela, Z. Krska, M. Sir, T. Trc, O. Vlach; Denmark (147 patients, 6 centers): L. Borris, E. Horlyck, M.R. Lassen, S. Mejdahl, J.O. Storm, C. Torholm; Finland (26 patients, 1 center): U. Vaatainen; France (109 patients, 9 centers): J. Barre, J.P. Clarac, J.P. Delagoutte, M. Delecroix, P. Mismetti, L. Pidhorz, J. Puget, P. Simon, J. Tabutin; Germany (53 patients, 3 centers): P. Rommens, M. Schurmann, M. Winkler; Greece (70 patients, 3 centers): J. Pournaras, N. Tiliakos, M. Tyllianakis; Hungary (68 patients, 3 centers): Z. Magyari, E. Santha, K. Szepesi; Italy (67 patients, 4 centers): O. Bruchi, G. Caroli, L. Tessari, V. Zaffarana, F. Poivella; Norway (50 patients, 2 centers): O. Dahl, H. Luhr, E. Mohr; Poland (50 patients, 4 centers): A. Gorecki, K. Kwiatkowski, K. Modrzewski, T. Niedzwiecki; Portugal (65 patients, 6 centers): N.J. Canha, J. Carvalho de Oliveira, J. De Morais Neves, A. Figueiredo, E. Mendes, A. Rodrigues Gomes; South Africa (26 patients, 4 centers): L. Bloem, C. Lombard, W. Prinsloo, R.B. Snowdowne; Spain (78 patients, 5 centers): F. Gomar, M. Monreal, A. Navarro, R. Ramon, C. Resines; Sweden (108 patients, 4 centers): B.I. Eriksson, P. Hansson, B. Malmqvist, J. Milbrink; Switzerland (67 patients, 2 centers): P. Hoffmeyer, P.F. Leyvraz; the Netherlands (100 patients, 10 centers): G.H.R. Albers, D.A. Dartee, W. De Graaf, W.F.M. Fievez, M. Iprenburg, R.K. Marti, J. Van Der Meer, P. Van de Sar, M. Van Marwijk Kooij, A.D. Verburg; United Kingdom (52 patients, 2 centers): A.T. Cohen.

REFERENCES

1. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. 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. Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ. Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. J Orthop Trauma 1995;9:1-7.

4. Hartman JT, Pugh JL, Smith RD, Robertson WW Jr, Yost RP, Janssen HF. Cyclic sequential compression of the lower limbs in prevention of deep venous thrombosis. J Bone Joint Surg Am 1982;64:1059-62.

5. Moskovitz PA, Ellenberg SS, Feffer HL, et al. Low-dose heparin for prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. J Bone Joint Surg Am 1978;60:1065-70.

6. Monreal M, Lafoz E, Navarro A, et al. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. J Trauma 1989;29:873-5.

7. Borris LC, Lassen MR, Poulsen KA, Jensen HP. Thromboembolic complications after hip fracture — prophylaxis with low molecular weight- vs. unfractionated heparin. Thromb Haemost 1995;73:1104. abstract.

8. Barsotti J, Gruel Y, Rosset P, et al. Comparative double-blind study of two dosage regimens of low-molecular weight heparin in elderly patients with a fracture of the neck of the femur. J Orthop Trauma 1990;4:371-5.

9. The TIFDED Study Group. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. Haemostasis 1999;29:310-7.

10. Jorgensen PS, Strandberg C, Wille-Jorgensen P, et al. Early preoperative thromboprophylaxis with Klexane in hip fracture surgery: a placebo-controlled study. Clin Appl Thromb Hemost 1998;4:140-2.

11. Agnelli G, Cosmi B, Di Filippo P, et al. A randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. Thromb Haemost 1992;67:203-8.

12. Bergqvist D, Kettunen K, Fredin H, et al. Thromboprophylaxis in patients with hip fractures: a prospective, randomized, comparative study between ORG 10172 and dextran 70. Surgery 1991;109:617-22.

13. Gent M, Hirsh J, Ginsberg JS, et al. Low-molecular-weight heparinoid Orgaran is more effective than aspirin in the prevention of venous thromboembolism after surgery for hip fracture. Circulation 1996;93:80-4.

14. Gerhart TN, Yett HS, Robertson LK, Lee MA, Smith M, Salzman EW. Low-molecular-weight heparinoid compared with warfarin for prophylaxis of deep-vein thrombosis in patients who are operated on for fracture of the hip: a prospective, randomized trial. J Bone Joint Surg Am 1991;73:494-502.

15. Borgström S, Greitz T, van der Linden W, et al. Anticoagulant prophylaxis of venous thrombosis in patients with fractured neck of the femur: a controlled clinical trial using venous phlebography. Acta Chir Scand 1965;129:500-8.

16. Hamilton JW, Crawford JS, Gardiner JH, Wiley AM. Venous thrombosis in patients with fracture of the upper end of the femur: a phlebographic study of the effect of prophylactic anticoagulation. J Bone Joint Surg Br 1970;52:268-89.

17. Powers PJ, Gent M, Jay RM, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med 1989; 149:771-4.

18. Bronge A, Dahlgren S, Lindquist B. Prophylaxis against thrombosis in femoral neck fractures — a comparison between dextran 70 and dicumarol. Acta Chir Scand 1971;137:29-35.

19. Bergquist E, Bergqvist D, Bronge A, Dahlgren S, Lindquist B. An evaluation of early thrombosis prophylaxis following fracture of the femoral neck: a comparison between dextran and dicoumarol. Acta Chir Scand 1972;138:689-93.

20. 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; 355:1295-302.

21. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. BMJ 1994;308:235-46.

22. Petitou M, Lormeau J-C, Choay J. Chemical synthesis of glycosaminoglycans: new approaches to antithrombotic drugs. Nature 1991;350: Suppl:30-3.

23. van Boeckel CAA, Petitou M. The unique antithrombin III binding domain of heparin: a lead to new synthetic antithrombotics. Angew Chem Int Ed Engl 1993;32:1671-90.

24. Lormeau JC, Herault JP. The effect of the synthetic pentasaccharide SR 90107/ORG31540 on thrombin generation ex vivo is uniquely due to ATIII-mediated neutralization of factor Xa. Thromb Haemost 1995;74: 1474-7.

25. Walenga JM, Bara L, Petitou M, Samama MM, Fareed J, Choay J. The inhibition of the generation of thrombin and the antithrombotic effect of a pentasaccharide with sole anti-factor Xa activity. Thromb Res 1988;51: 23-33.

26. Turpie AGG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 2001;344:619-25.

27. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Arch Surg 1972;104:134-44.

28. 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;263:2753-9.

29. Eriksson BI, Ekman S, Kälebo P, Zachrisson B, Bach D, Close P. Prevention of deep-vein thrombosis after total hip replacement: direct thrombin inhibition with recombinant hirudin, CGP 39393. Lancet 1996;347:635-9.

30. Eriksson BI, Wille-Jørgensen P, Kälebo P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. N Engl J Med 1997; 337:1329-35.

31. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind randomized comparison. Arch Intern Med 2000;160:2199-207.

32. Havig Ö. Deep vein thrombosis and pulmonary embolism: an autopsy study with multiple regression analysis of possible risk factors. Acta Chir Scand Suppl 1977;478:1-20.

33. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? Ann Intern Med 1981;94:439-44.

34. Eriksson BI, Kälebo P, Anthmyr BA, Wadenvik H, Tengborn L, Ris-

berg 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;73:484-93.
35. Bauer K. The PENTAMAKS Study: comparison of the first synthetic factor Xa inhibitor with low molecular weight heparin in the prevention of venous thromboembolism (VTE) after elective major knee surgery. Blood 2000;96:491a. abstract.
36. Lassen MR. The EPHESUS Study: comparison of the first synthetic factor Xa inhibitor with low molecular weight heparin (LMWH) in the prevention of venous thromboembolism (VTE) after elective hip replacement surgery. Blood 2000;96:490a. abstract.
37. Turpie G. The PENTATHLON 2000 Study: comparison of the first synthetic factor Xa inhibitor with low molecular weight heparin in the prevention of venous thromboembolism (VTE) after elective hip replacement surgery. Blood 2000;96:491a. abstract.
38. Sors H, Meyer G. Place of aspirin in prophylaxis of venous thromboembolism. Lancet 2000;355:1288-9.
39. Cohen A, Quinlan D. PEP trial. Lancet 2000;356:247.