

FONDAPARINUX COMPARED WITH ENOXAPARIN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER ELECTIVE MAJOR KNEE SURGERY

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ABSTRACT

Background Despite thromboprophylaxis, major knee surgery carries a high risk of venous thromboembolism. Fondaparinux, the first of a new class of synthetic antithrombotic agents, may reduce this risk.

Methods In a double-blind study, we randomly assigned 1049 consecutive patients undergoing elective major knee surgery to receive subcutaneous doses of either 2.5 mg of fondaparinux once daily or 30 mg of enoxaparin twice daily, with both treatments initiated postoperatively. The primary efficacy outcome was venous thromboembolism up to postoperative day 11, defined as deep-vein thrombosis detected by mandatory bilateral venography, documented symptomatic deep-vein thrombosis, or documented symptomatic pulmonary embolism. The primary safety outcome was major bleeding.

Results The primary efficacy outcome was assessed in 724 patients. The fondaparinux group had a significantly lower incidence of venous thromboembolism by day 11 (12.5 percent [45 of 361 patients]) than the enoxaparin group (27.8 percent [101 of 363 patients]; reduction in risk, 55.2 percent; 95 percent confidence interval, 36.2 to 70.2; $P < 0.001$). Major bleeding (including overt bleeding with a bleeding index of 2 or more) occurred more frequently in the fondaparinux group ($P = 0.006$), but there were no significant differences between the two groups in the incidence of bleeding leading to death or reoperation or occurring in a critical organ.

Conclusions In patients undergoing elective major knee surgery, postoperative treatment with 2.5 mg of fondaparinux once daily was significantly more effective in preventing deep-vein thrombosis than 30 mg of enoxaparin twice daily. (N Engl J Med 2001;345:1305-10.)

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VENOUS thromboembolism is a frequent, life-threatening postoperative complication of total-knee-replacement surgery.^{1,2} Without thromboprophylaxis, the prevalence rate is 40 to 84 percent for venographically verified postoperative deep-vein thrombosis and 2 to 7 percent for pulmonary embolism.¹ Thromboprophylaxis that is effective in hip-replacement surgery, such as low-dose heparin, low-molecular-weight heparin, or warfarin, is less successful in knee-replacement surgery and reduces the prevalence of deep-vein thrombosis only to 31 to 47 percent.¹ For this reason, more effective antithrombotic prophylaxis is needed in knee-replacement surgery.

Fondaparinux is one of a new class of antithrombotic agents, the selective inhibitors of activated factor X (factor Xa).³⁻⁶ Fondaparinux is an entirely synthetic pentasaccharide that is structurally related to the antithrombin-binding site of heparin. In contrast to heparin, which interacts with many plasma components, the pentasaccharide selectively binds to antithrombin, causing it to rapidly inhibit factor Xa, a key enzyme in the coagulation pathway. Recent dose-ranging studies suggested that a once-daily subcutaneous injection of 2.5 mg of fondaparinux can prevent venous thromboembolism after hip-replacement⁷ or knee-replacement surgery (unpublished data).

This multicenter, randomized, double-blind trial was part of a program that also evaluated fondaparinux as prophylaxis against venous thromboembolism in patients undergoing surgery for hip fracture⁸ and elective hip replacement.^{9,10} The aim of the study was to compare the efficacy and safety of a once-daily subcutaneous injection of 2.5 mg of pentasaccharide with twice-daily subcutaneous injections of 30 mg of enoxaparin for the prevention of venous thromboembolism after elective major knee surgery.

METHODS**Patients**

Patients were considered for inclusion if they were at least 18 years of age and were undergoing elective major knee surgery — that is, surgery requiring resection of the distal end of the femur or proximal end of the tibia or revision of at least one component of a previously implanted total-knee prosthesis.

Patients were excluded if surgery in the contralateral knee was performed at the same time or within two weeks after enrollment. Women were excluded if they were pregnant or not using effective contraception. Other main reasons for exclusion were active bleeding; a documented congenital or acquired bleeding disorder; current ulcerative or angiodysplastic gastrointestinal disease; hemorrhagic stroke or brain, spinal, or ophthalmologic surgery within the previous three months; insertion of an indwelling intrathecal or epidural catheter during the treatment period; unusual difficulty in administering epidural or spinal anesthesia (e.g., more than two attempts); hypersensitivity to heparin, low-molecular-weight heparins, porcine products, or iodinated contrast medium; a contraindication to anticoagulant therapy; a current addictive disorder; a

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*Participants in the study are listed in the Appendix.

serum creatinine concentration above 2 mg per deciliter (177 μ mol per liter) in a well-hydrated patient; and a platelet count below 100,000 per cubic millimeter. Finally, patients who required anticoagulant therapy were also excluded. The use within one week before randomization of dextran or any type of anticoagulant, fibrinolytic, or antiplatelet agent was discouraged.

Study Design

Immediately after surgery, patients were randomly assigned (in a ratio of 1:1 in blocks of four, stratified according to center), through a central computer-derived randomization scheme to receive subcutaneous doses of either 2.5 mg of fondaparinux (Arixtra, NV Organon, Oss, the Netherlands, and Sanofi-Synthelabo, Paris) once daily and a placebo once daily or 30 mg of enoxaparin (Clexane/Lovenox, Aventis Pharmaceuticals, Bridgewater, N.J.) twice daily. In the enoxaparin group, the first dose was given between 12 and 24 hours after surgery, according to the recommendation of the manufacturer. 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 drug⁷; the first postoperative injection was administered 6 ± 2 hours after surgery and the second injection 12 hours or more after the first.

The day of surgery was defined as day 1. 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 investigator.

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

Medications

Study medications were packaged in boxes of identical appearance, each containing 19 prefilled, single-dose syringes: 10 syringes of fondaparinux and 9 syringes of placebo for each patient assigned to fondaparinux, or 18 syringes of enoxaparin and 1 syringe of placebo for each patient assigned to enoxaparin. Each syringe contained 2.5 mg of fondaparinux sodium in 0.25 ml of water for injectable preparations (a concentration of 10 mg per milliliter), 30 mg of enoxaparin sodium in 0.3 ml of water for injectable preparations (a concentration of 100 mg per milliliter), or placebo (0.25 or 0.3 ml of isotonic saline). Each syringe was loaded inside an opaque autoinjector (Autoject, Owen Mumford, Woodstock, United Kingdom) to maintain blinding.

Throughout the treatment period, the use of intermittent pneumatic compression, dextran, and any other anticoagulant, thrombolytic, or antiplatelet agent 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 legs¹¹ between day 5 and day 11, but no more than two days after the last injection 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, pulmonary angiography,¹² or 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, other bleeding, a need for transfusion, thrombocytopenia, and any other adverse event.

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

Statistical Analysis

Assuming an incidence of venous thromboembolism by day 11 of 34 percent in the enoxaparin group and a risk reduction of about 30 percent (i.e., an incidence of 24 percent in the fondaparinux group), 319 patients were needed in each group (for a total of 638 patients) to provide the study with a power of 85 percent. The target number of recruited patients was 912, a number that allowed for failure to obtain primary efficacy data in up to 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 the use of a logistic-regression model.

The study was supervised by a steering committee of 11 people, which included 7 representatives of the sponsors (NV Organon and Sanofi-Synthelabo). 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 by an independent statistical center when half the projected patient population had been enrolled, for reestimation of the sample size, since the rate of venous thromboembolism in patients undergoing knee 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 Populations

Between December 1998 and January 2000, 1049 patients were enrolled in 64 centers in North America. Fifteen patients did not receive any study drug, leaving 1034 available for the safety analysis (Table 1); primary efficacy had not been assessed by day 11 in 310 patients. Thus, 724 patients (69.0 percent) were included in the primary efficacy analysis, a percentage in line with other large multicenter trials that used venography after orthopedic surgery.¹³⁻¹⁶ The characteristics of patients excluded from the primary

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

| VARIABLE | FONDAPARINUX ONCE DAILY (N=526) | ENOXAPARIN TWICE DAILY (N=523) |
|---|---------------------------------------|--------------------------------------|
| | no. (%) | |
| Not treated | 9 (1.7) | 6 (1.1) |
| Inclusion criteria not met | 3 (0.6) | 2 (0.4) |
| Informed consent withdrawn | 1 (0.2) | 1 (0.2) |
| Other | 5 (1.0) | 3 (0.6) |
| Treated with at least one dose of study drug (able to be evaluated for safety) | 517 (98.3) | 517 (98.9) |
| Not able to be evaluated for primary efficacy | 156 (29.7) | 154 (29.4) |
| No surgery or inappropriate surgery | 0 | 0 |
| Inadequate venography* | 156 (29.7) | 154 (29.4) |
| Not done† | 79 (15.0) | 78 (14.9) |
| Not able to be evaluated | 75 (14.3) | 76 (14.5) |
| Outside specified interval‡ | 2 (0.4) | 0 |
| Able to be evaluated for primary efficacy | 361 (68.6) | 363 (69.4) |

*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 by venography before day 5 (and without deep-vein thrombosis on venogram and without pulmonary embolism up to day 11).

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). Among patients analyzed for primary efficacy, the median time between surgery and the qualifying examination for venous thromboembolism was seven days in both groups; most patients underwent this examination between day 5 and day 11, as planned. The two groups did not differ with regard to the last day of active treatment or the use of concomitant treatments up to day 11 (Table 3).

Overall, 514 patients treated with fondaparinux and 511 patients treated with enoxaparin returned for the follow-up visit on day 49. The duration of follow-up was similar in the two groups. During follow-up of patients who were not treated for an acute thromboembolic event, 19.1 percent of patients assigned to fondaparinux (86 of 450) and 20.2 percent of patients assigned to enoxaparin (82 of 406) received prolonged thromboprophylaxis, primarily with a preparation of heparin or a vitamin K antagonist.

Incidence of Venous Thromboembolism

The incidence of venous thromboembolism by day 11 was 27.8 percent (101 of 363 patients) in the enoxaparin group and 12.5 percent (45 of 361 pa-

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

| CHARACTERISTIC | FONDAPARINUX ONCE DAILY (N=517) | ENOXAPARIN TWICE DAILY (N=517) |
|---|---------------------------------------|--------------------------------------|
| Age — yr | 67.5±10.7 | 67.5±10.2 |
| Sex — M/F | 204/313 | 223/294 |
| Weight — kg | 89.0±20.0 | 88.4±19.6 |
| Body-mass index† | 31.5±6.5 | 30.9±6.2 |
| Body-mass index ≥30 — no. (%)† | 274 (53.3) | 275 (53.3) |
| History of venous thromboembolism — no. (%) | 23 (4.4) | 28 (5.4) |
| Orthopedic surgery within the previous 12 mo — no. (%) | 87 (16.8) | 77 (14.9) |
| Type of surgery — no. (%) | | |
| Primary | 478 (92.5) | 479 (92.6) |
| Revision | 39 (7.5) | 38 (7.4) |
| Use of cement — no. (%) | 482 (93.2) | 484 (93.6) |
| Type of anesthesia — no. (%) | | |
| General only | 386 (74.7) | 369 (71.4) |
| Regional only | 126 (24.4) | 142 (27.5) |
| Both | 5 (1.0) | 6 (1.2) |
| Duration of surgery — min | 127±39 | 128±42 |

*Plus-minus values are means ±SD.

†Body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for three patients in the fondaparinux group and one in the enoxaparin group.

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

| STUDY TREATMENT | FONDAPARINUX ONCE DAILY (N=361) | ENOXAPARIN TWICE DAILY (N=363) |
|--|---------------------------------------|--------------------------------------|
| No. of active injections up to the qualifying examination for venous thromboem- bolism | | |
| Median | 5 | 8 |
| Range | 2–9 | 2–16 |
| Last day of active treatment — no. (%) | | |
| <Day 5 | 8 (2.2) | 2 (0.6) |
| Day 5 to day 9 | 351 (97.2) | 360 (99.2) |
| >Day 9 | 2 (0.6) | 1 (0.3) |
| CONCOMITANT TREATMENT | | |
| Patients receiving prohibited therapy (anti- coagulant or antiplatelet agents other than aspirin or thrombolytic therapy) — no. (%) | 4 (1.1) | 11 (3.0) |
| Patients receiving discouraged therapy (nonsteroidal antiinflammatory agents or aspirin) — no. (%) | 44 (12.2) | 60 (16.5) |
| Patients receiving graduated compression stockings — no. (%) | 298 (82.5) | 294 (81.0) |

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

| EVENT | FONDAPARINUX ONCE DAILY | | ENOXAPARIN TWICE DAILY | | DIFFERENCE† | P VALUE‡ | REDUCTION IN RISKS percent (95% CI) |
|--|-------------------------------|--------------------|-------------------------------|---------------------|-----------------------|----------|--|
| | no. with events/ total no. | percent (95% CI) | no. with events/ total no. | percent (95% CI) | | | |
| Venous thromboembolism (primary outcome) | 45/361 | 12.5 (9.2 to 16.3) | 101/363 | 27.8 (23.3 to 32.7) | -15.3 (-22.3 to -9.3) | <0.001 | 55.2 (36.2 to 70.2) |
| Any deep-vein thrombosis¶ | 45/361 | 12.5 (9.2 to 16.3) | 98/361 | 27.1 (22.6 to 32.0) | -14.6 (-21.4 to -8.4) | <0.001 | 54.1 (34.5 to 69.6) |
| Any proximal deep-vein thrombosis | 9/368 | 2.4 (1.1 to 4.6) | 20/372 | 5.4 (3.3 to 8.2) | -3.0 (-7.6 to 0.4) | 0.06 | 54.5 (-17.8 to 87.5) |
| Distal deep-vein thrombosis only | 35/372 | 9.4 (6.6 to 12.8) | 78/366 | 21.3 (17.2 to 25.9) | -11.9 (-18.3 to -6.2) | <0.001 | 55.9 (33.0 to 72.9) |
| Symptomatic venous thromboembolism** | 3/517 | 0.6 (0.1 to 1.7) | 7/517 | 1.4 (0.5 to 2.8) | -0.8 (-3.3 to 1.1) | 0.34 | |
| Symptomatic deep-vein thrombosis | 3/517 | 0.6 | 4/517 | 0.8 | | | |
| Nonfatal pulmonary embolism | 1/517 | 0.2 | 4/517 | 0.8 | | | |
| Fatal pulmonary embolism | 0/517 | | 0/517 | | | | |

*CI denotes confidence interval.

†Differences are the rate in the fondaparinux group minus the rate in the enoxaparin group.

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

§The reduction in risk is in favor of fondaparinux. The minus sign indicates an increase in risk.

¶In two patients with pulmonary embolism, venography could not be evaluated. Patients were considered able to be evaluated when the proximal and distal deep veins in both legs were visualized. However, if deep-vein thrombosis was seen in any one of the veins, the patient was considered to have reached the end point, even if the venous system was not visualized entirely.

||More than 724 patients were able to be evaluated for these events, 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.

**A patient could have more than one event. 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 three cases of symptomatic deep-vein thrombosis are included in the category "any deep-vein thrombosis."

tients) in the fondaparinux group (reduction in risk, 55.2 percent; 95 percent confidence interval, 36.2 to 70.2 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). As compared with enoxaparin, fondaparinux reduced the incidence of proximal deep-vein thrombosis by 54.5 percent ($P = 0.06$) and distal deep-vein thrombosis by 55.9 percent ($P < 0.001$). The incidence of symptomatic venous thromboembolism was low and did not differ significantly between the two groups (Table 4). Overall, the superiority of fondaparinux over enoxaparin with respect to primary efficacy was consistent according 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 surgery (primary or revision), use or nonuse of cement, and whether or not patients 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 (15.1 percent [67 of 443]) than in the enoxaparin group (25.1 percent [111 of 442], $P < 0.001$).

By day 49, the incidence of symptomatic venous thromboembolism did not differ significantly between the fondaparinux group (1.0 percent [5 of 517 patients]) and the enoxaparin group (1.9 percent [10 of 517 patients]). Fatal pulmonary embolism occurred in one patient in each group; nonfatal pulmonary embolism occurred in two patients in the fondaparinux group and four in the enoxaparin group.

Safety Outcomes

There were no instances of fatal bleeding or bleeding in a critical organ in either treatment group; bleeding requiring reoperation occurred in two patients in the fondaparinux group and one in the enoxaparin group. In all three patients, drainage of a knee effusion was performed. In the fondaparinux group, nine episodes of overt bleeding were associated with a bleeding index of 2 or more; seven occurred at the surgical site, and only three led to discontinuation of study treatment. The total for the primary safety outcome was therefore 11 major bleeding episodes in the fondaparinux group and 1 in the enoxaparin group ($P = 0.006$) (Table 5). The incidence of minor bleeding, a need for transfusion, and other adverse events during treatment or follow-up did not differ significantly between the two groups. Platelet counts lower than 100,000 per cubic millimeter were measured in 14 patients (2.7 percent) in the fondaparinux group as compared with 19 (3.7 percent) in the enoxaparin group ($P = 0.27$). No episode of a decreased platelet count was reported as a serious adverse event in either group. By day 49, two patients in the fon-

TABLE 5. SAFETY OUTCOMES.

| OUTCOME | FONDAPARINUX ONCE DAILY (N=517) | ENOXAPARIN TWICE DAILY (N=517) |
|--|---------------------------------------|--------------------------------------|
| Treatment period (up to day 11) | | |
| Primary safety outcomes — no. (%) | | |
| Fatal bleeding | 0 | 0 |
| Bleeding in critical organ | 0 | 0 |
| Bleeding leading to reoperation | 2 (0.4) | 1 (0.2)* |
| Bleeding index ≥ 2 † | 9 (1.7)‡ | 0 |
| Secondary safety outcomes | | |
| Other bleeding — no. (%) | 14 (2.7) | 19 (3.7) |
| Postoperative transfusions — no. (%) | 222 (42.9) | 197 (38.1) |
| Mean (\pm SD) no. of units transfused for volume replacement | 1.9 \pm 1.1 | 1.8 \pm 0.9 |
| Death from any cause — no. (%) | 1 (0.2) | 2 (0.4) |
| Study period (up to day 49) | | |
| Death from any cause — no. (%) | 2 (0.4) | 3 (0.6) |

*Enoxaparin was permanently discontinued in this case.

†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).

‡Fondaparinux was permanently discontinued in three of these patients.

daparinux group (0.4 percent) and three in the enoxaparin group (0.6 percent) had died from causes unrelated to the treatment.

DISCUSSION

This study demonstrates that fondaparinux is significantly more effective than enoxaparin in preventing venous thromboembolism after elective major knee surgery. Deep-vein thrombosis has been more difficult to prevent with anticoagulation therapy after knee surgery than after total hip replacement, even with low-molecular-weight heparin, the most effective thromboprophylactic therapy to date.¹ The 27.8 percent incidence of venous thromboembolic events in the enoxaparin group by day 11 is consistent with the incidence of 19.0 to 25.0 percent in other trials of enoxaparin after knee surgery.¹⁶⁻¹⁹ In our study, the reduction to 12.5 percent in the fondaparinux group is consistent with the results of three other large studies in patients undergoing surgery for hip fracture⁸ or elective hip replacement.^{9,10} The superior efficacy of fondaparinux may be related to its ability to initiate selective inhibition of factor Xa, its predictable linear pharmacokinetics, the choice of dose, and the starting time after surgery.

The low incidence of symptomatic events in our study should be interpreted with caution, as it is likely to be lower than would be observed in typical clin-

ical situations. As in other trials of thromboprophylaxis, most of our asymptomatic patients with positive venograms had been receiving an anticoagulant at a therapeutic dose. Moreover, about 20 percent of our patients were receiving prophylaxis after the study treatment period ended. Both of these factors may have prevented symptomatic venous thrombosis.

Major bleeding was significantly more frequent in the fondaparinux group (11 patients, including 9 with a bleeding index of 2 or more) than in the enoxaparin group (1 patient). Administration of fondaparinux was continued in six of the nine patients with a bleeding index of 2 or more. Nevertheless, the two groups did not differ significantly with respect to fatal bleeding, bleeding in critical organs, or bleeding leading to reoperation.

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; 9:491A, A2111).

APPENDIX

The members of the Pentasaccharide in Major Knee 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, L. Snow-Adami; **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, NV Organon, the Netherlands** — *Study Management*: L. Snow-Adami, E. Wargha; *Statistical Analysis*: R. Vijayaraghavan, W.F. Sommer; *Clinical Documentation*: E. Osifchin; **Investigators, United States (861 patients)** — N. Abramson, Jacksonville, Fla.; J. Albrigo, Alexandria, Va.; J. Barnett, Orlando, Fla.; K. Beer, Toledo, Ohio; B. Bierbaum, Boston; W. Bose, West Mobile, Ala.; D. Bramlet, St. Petersburg, Fla.; F. Burke, Lexington, Ky.; D. Butler, Sacramento, Calif.; V. Cabanas and M. Swank, Cincinnati; F. Cannon, Ocala, Fla.; J. Caraveo, Temple, Tex.; C. Chalian, Pomona, Calif.; C. Christensen, J. Muntz, and S. Siff, Houston; P. Comp, Oklahoma City; D. Covall, Decatur, Ga.; R. Ennis, Hollywood, Fla.; G.S. Gill, Lubbock, Tex.; D. Green, Chicago; D. Gremillion, Nashville; N. Halbridge, Fountain Valley, Calif.; W. Hefley, R. Laverder, and R.B. Sorrells, Little Rock, Ark.; M. Hollman, Orlando, Fla.; W. Hopkinson, Maywood, Ill.; C. Hummer, Upland, Pa.; F. Ivey, Galveston, Tex.; A. Jahnke, Fort Gordon, Ga.; G. Johnson, Minneapolis; G. Kantor, Palm Beach Gardens, Fla.; H. Kim, San Francisco; W. Kim, Fountain Valley, Calif.; M. Koren, South Jacksonville, Fla.; W. Lanzer, Seattle; D. Lawlor, Olathe, Kans.; L. Levy, La Mesa, Calif.; A. Lombardi, Columbus, Ohio; P. Lunseth, Tampa, Fla.; D. MacDonald, East Lansing, Mich.; M. Mancao, Pensacola, Fla.; G. Mayfield, Honolulu; J. Ohar, St. Louis; P. Peters, Dallas; K. Plancher, Stamford, Conn.; P. Richin, Decatur, Ga.; D. Riff, Anaheim, Calif.; M. Ritter, Mooresville, Ind.; L. Rocamora, Winston-Salem, N.C.; W. Shelton, Jackson, Miss.; B. Spetzler, Salem, Va.; E. Strauss, Great Neck, N.Y.; J. Tozzi, Neptune, N.J.; C. Walker, Whittier, Calif.; L. Walker, San Bernardino, Calif.; M. Ward, Covina, Calif.; C. Williamson, South Daytona, Fla.; and I. Ziv, Buffalo, N.Y.; **Investigators, Canada (188 patients)** — D. Anderson and M. Gross, Halifax, N.S.; R. Bhargava, Oshawa, Ont.; J. Brandwein and J. Gollish, Toronto; L. Desjardins, Ste. Foy, Que.; M. Mant, Edmonton, Alta.; W. Pisesky, Kelowna, B.C.; B. Pressnail, Barrie, Ont.; M. Rodger, Ottawa, Ont.; S. Solymoss, Montreal; T. Sparling, Burnaby, B.C.; and J. Wilson, North York, Ont.

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