

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

OCTOBER 30, 2003

VOL. 349 NO. 18

Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism

The Matisse Investigators*

ABSTRACT

BACKGROUND

The standard initial treatment of hemodynamically stable patients with pulmonary embolism is intravenous unfractionated heparin, requiring laboratory monitoring and hospitalization.

METHODS

We conducted a randomized, open-label trial involving 2213 patients with acute symptomatic pulmonary embolism to compare the efficacy and safety of the synthetic anti-thrombotic agent fondaparinux with those of unfractionated heparin and to document noninferiority in terms of efficacy. Patients received either fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing less than 50, 50 to 100, or more than 100 kg, respectively) subcutaneously once daily or a continuous intravenous infusion of unfractionated heparin (ratio of the activated partial-thromboplastin time to a control value, 1.5 to 2.5), both given for at least five days and until the use of vitamin K antagonists resulted in an international normalized ratio above 2.0. The primary efficacy outcome was the three-month incidence of the composite end point of symptomatic, recurrent pulmonary embolism (nonfatal or fatal) and new or recurrent deep-vein thrombosis.

RESULTS

Forty-two of the 1103 patients randomly assigned to receive fondaparinux (3.8 percent) had recurrent thromboembolic events, as compared with 56 of the 1110 patients randomly assigned to receive unfractionated heparin (5.0 percent), for an absolute difference of -1.2 percent in favor of fondaparinux (95 percent confidence interval, -3.0 to 0.5). Major bleeding occurred in 1.3 percent of the patients treated with fondaparinux and 1.1 percent of those treated with unfractionated heparin. Mortality rates at three months were similar in the two groups. Of the patients in the fondaparinux group, 14.5 percent received the drug in part on an outpatient basis.

CONCLUSIONS

Once-daily, subcutaneous administration of fondaparinux without monitoring is at least as effective and is as safe as adjusted-dose, intravenous administration of unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

The writing committee of the Matisse Study (H.R. Büller, B.L. Davidson, H. Decousus, A. Gallus, M. Gent, F. Piovela, M.H. Prins, G. Raskob, A.E.M. van den Berg-Segers, R. Cariou, O. Leeuwenkamp, and A.W.A. Lensing) takes responsibility for the content of this article. Address reprint requests to Dr. Büller at the Academic Medical Center, Department of Vascular Medicine, F4-211, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at m.rm.veendorp@amc.uva.nl.

*The institutions and investigators participating in the study are listed in the Appendix.

N Engl J Med 2003;349:1695-702.

Copyright © 2003 Massachusetts Medical Society.

PULMONARY EMBOLISM IS A FREQUENT and often life-threatening event that contributes to 5 to 10 percent of deaths among hospitalized patients.¹ The goals of antithrombotic therapy for this disease are to minimize early morbidity and mortality and to prevent recurrence without provoking excessive bleeding. In hemodynamically stable patients, unfractionated heparin is effective and remains the reference therapy for initial anticoagulation.¹⁻⁴ Because unfractionated heparin requires continuous intravenous infusion with regular laboratory monitoring and dose titration, patients remain hospitalized even when their clinical condition permits discharge. A less complex and resource-intensive but equally efficacious and safe treatment, allowing earlier discharge, would be desirable.

Low-molecular-weight heparins have replaced unfractionated heparin for the treatment of most patients with deep-vein thrombosis,³ but in patients with symptomatic acute pulmonary embolism they have been less extensively evaluated.⁵⁻⁷ As a result, use of low-molecular-weight heparins for this indication varies, and in many countries they have not been approved by regulatory authorities for the initial treatment of patients with pulmonary embolism.

Fondaparinux is a synthetic antithrombotic agent with specific anti-factor Xa activity. Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring.⁸ In a dose-ranging trial involving patients with symptomatic proximal deep-vein thrombosis, 7.5 mg of fondaparinux appeared to have efficacy and safety similar to those of a low-molecular-weight heparin (dalteparin).⁹

Given the practical advantages of a simple fondaparinux regimen, this study was designed to determine whether fixed-dose, once-daily, subcutaneous administration of fondaparinux is at least as effective as unfractionated heparin for the initial treatment of symptomatic pulmonary embolism. This randomized trial, with blinded adjudication of outcome events, was conducted on an open-label basis, permitting early discharge in the fondaparinux group.

METHODS

PATIENTS

Consecutive patients 18 years of age or older who presented with acute symptomatic pulmonary embolism and who required antithrombotic therapy

were potentially eligible for the study. Diagnostic criteria were an intraluminal filling defect on spiral computed tomography (CT) or pulmonary angiography, a high-probability ventilation-perfusion lung scan, or a nondiagnostic lung scan with documentation of deep-vein thrombosis either by compression ultrasonography or by venography.⁵

Patients were ineligible for the study if they had received therapeutic doses of low-molecular-weight heparin or oral anticoagulants for more than 24 hours; if they required thrombolysis, embolectomy, or a vena cava filter; or if anticoagulant therapy was contraindicated — for example, because of active bleeding or thrombocytopenia (a platelet count below 100,000 per cubic millimeter). Patients were also ineligible if they had a serum creatinine level above 2.0 mg per deciliter (177 μ mol per liter) or uncontrolled hypertension (systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg); if they were pregnant; or if a physician had estimated the life expectancy to be less than three months.

After written informed consent had been obtained, randomization was performed at a central location with the use of a computerized, interactive voice-response system that recorded information about the patient before his or her treatment assignment. The protocol was approved by the institutional review board at each of the study centers. The study was monitored by an independent data and safety monitoring board. The data were collected and held by the two sponsors, NV Organon and Sanofi-Synthélabo. The statistical-analysis plan was approved by the steering committee, which also checked the final analysis.

TREATMENT REGIMENS

The patients assigned to fondaparinux (Arixtra, NV Organon and Sanofi-Synthélabo) received a single daily subcutaneous injection of 5.0 mg (if their body weight was less than 50 kg), 7.5 mg (if their body weight was 50 to 100 kg), or 10.0 mg (if their body weight was greater than 100 kg). The patients assigned to unfractionated heparin received an initial intravenous bolus of at least 5000 IU, followed by at least 1250 IU per hour, administered as a continuous intravenous infusion. The infusion dose was adjusted to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times a control value.^{10,11} The activated partial-thromboplastin time was measured approximately six hours after the start of heparin treatment, about six hours after

each measurement of the activated partial-thromboplastin time that was subtherapeutic or supratherapeutic, and otherwise daily. Heparin was provided by American Pharmaceutical Partners for all centers except those in France, where it was supplied by Laboratoires Choay.

In both groups, treatment with a vitamin K antagonist was begun as soon as possible and within 72 hours after initiation of the study treatment. Initially, the prothrombin time was measured at least every other day, and the dose of vitamin K antagonist was adjusted to maintain the international normalized ratio (INR) at a value between 2.0 and 3.0. Administration of heparin or fondaparinux was continued for at least five days and until the INR had been greater than 2.0 for two consecutive days. Treatment with a vitamin K antagonist was continued for three months, and the INR was determined at least once per month.

SURVEILLANCE AND FOLLOW-UP

All the patients were contacted daily during the initial treatment period and at one and three months after the start of the study. At each contact, the patient was evaluated for symptoms and signs of recurrent venous thromboembolism and bleeding. All the patients were informed about the symptoms and signs of recurrent pulmonary embolism and deep-vein thrombosis and about the potential for bleeding. They were instructed to report to the study center immediately if any of these conditions occurred. The protocol required objective testing in cases of suspected recurrent pulmonary embolism or deep-vein thrombosis.

ASSESSMENT OF OUTCOMES

The primary efficacy outcome was symptomatic recurrent venous thromboembolism during the three-month study period. Symptomatic recurrent venous thromboembolism was considered to have occurred if recurrent pulmonary embolism or deep-vein thrombosis was documented objectively or if there was a death in which pulmonary embolism was a contributing cause or could not be ruled out. In the absence of objective test results that adequately confirmed or ruled out recurrent venous thromboembolism, the diagnosis was accepted if the condition was managed with therapeutic dosages of low-molecular-weight heparin for more than two days, thrombolysis, a vena caval filter, or thrombectomy.

The objective criterion for the diagnosis of recurrent pulmonary embolism was a new intraluminal

filling defect on spiral CT or pulmonary angiography; cutoff of contrast material in a vessel more than 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75 percent of a segment, with corresponding normal ventilation (i.e., a high-probability lung scan); a new nondiagnostic lung scan accompanied by documentation of deep-vein thrombosis by ultrasonography or venography; or confirmation of a new pulmonary embolism at autopsy.^{5,12} The objective criterion for the diagnosis of new deep-vein thrombosis was a new, noncompressible venous segment or a substantial increase (4 mm or more) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography or a new intraluminal filling defect on venography.^{13,14}

The main safety outcomes were major bleeding during the initial treatment period and death during the three-month study period. Bleeding was considered major if it was clinically overt and associated with a decrease of 2 g per deciliter or more in the hemoglobin level, led to the transfusion of 2 or more units of red cells or whole blood, was retroperitoneal or intracranial, occurred in a critical organ, or contributed to death. Bleeding episodes that were clinically relevant but did not qualify as major (e.g., epistaxis that required intervention, formation of a large hematoma visible on the skin, or spontaneous macroscopic hematuria) were an additional safety outcome and were classified as clinically relevant nonmajor bleeding. All other hemorrhages were categorized as trivial. The cause of death was classified as pulmonary embolism, bleeding, cancer, or another established diagnosis or was considered to be unexplained. All suspected outcome events were reviewed and classified by a central adjudication committee whose members were unaware of the treatment assignments.

Platelet counts were assessed at base line, on day 4, and at the end of initial treatment. Antiplatelet antibodies were measured at base line and at the end of initial treatment and also were measured if heparin-induced thrombocytopenia was suspected because the platelet count was confirmed on retesting to be below 100,000 per cubic millimeter or to have decreased by more than 40 percent from the base line count.¹⁵

STATISTICAL ANALYSIS

We assumed a 5 percent incidence of the primary efficacy outcome in the unfractionated-heparin group and hypothesized that fondaparinux would be as

Table 1. Demographic and Base-Line Characteristics of the Patients Randomly Assigned to a Study Group.*

Characteristic	Fondaparinux (N=1103)	Unfractionated Heparin (N=1110)
Age — yr	63±16.2	62±16.7
Sex — male/female†	501/601	477/633
Body weight — no. (%)‡	81±18.9	81±19.4
<50 kg	22 (2.0)	25 (2.3)
50–100 kg	945 (86.0)	948 (85.5)
>100 kg	132 (12.0)	136 (12.3)
Creatinine clearance — no. (%)§		
<30 ml/min	26 (2.4)	28 (2.6)
30–49 ml/min	173 (16.1)	164 (15.2)
50–79 ml/min	361 (33.6)	353 (32.8)
≥80 ml/min	516 (48.0)	531 (49.3)
Time between start of symptoms and start of study medication — days	5.1±6.3	5.7±8.3
Diagnostic method — no. (%)¶		
High-probability lung scanning	485 (44.0)	519 (46.8)
Spiral computed tomography	510 (46.2)	510 (45.9)
Pulmonary angiography	39 (3.5)	35 (3.2)
Nondiagnostic lung scanning with documented deep-vein thrombosis	99 (9.0)	78 (7.0)
Concurrent deep-vein thrombosis — no. (%)	425 (38.5)	408 (36.8)
Admission to intensive care unit — no. (%)	291 (26.4)	307 (27.7)
Risk factors — no. (%)		
Previous venous thromboembolism	239 (21.7)	236 (21.3)
Cancer		
Active cancer	112 (10.2)	128 (11.5)
History of cancer	62 (5.6)	54 (4.9)
Surgery or trauma (within the previous 3 mo)	248 (22.5)	260 (23.4)
Estrogen therapy	154 (14.0)	164 (14.8)
Known prothrombotic state	58 (5.3)	41 (3.7)
Two or more of the above risk factors	241 (21.8)	260 (23.4)

* Plus–minus values are means ±SD. Because of rounding, not all percentages total 100.

† Information on sex was missing for one patient in the fondaparinux group.

‡ Information on weight was missing for four patients in the fondaparinux group and one patient in the unfractionated-heparin group.

§ Information on creatinine clearance was missing for 27 patients in the fondaparinux group and 34 patients in the unfractionated-heparin group.

¶ Some patients underwent more than one confirmatory diagnostic test.

|| Active cancer was defined as cancer that had been treated within the previous six months or not cured.

effective as unfractionated heparin.³ Studies in patients with pulmonary embolism or deep-vein thrombosis who received no treatment or inadequate treatment have found recurrence rates of approximately 20 percent.^{2,16,17} On the basis of previous studies, we chose a fixed noninferiority margin of 3.5 percent for the absolute difference between the two treatment groups in the rates of venous thromboembolism.^{4,5,7,12,16,17} From these assump-

tions, we calculated that a study with 1100 patients per group would have 95 percent power, with a one-sided type I error of 0.025, to reject the hypothesis that the rate of recurrence with fondaparinux would be 3.5 percent higher than that with unfractionated heparin.

The primary efficacy analysis was based on the incidence of symptomatic recurrent venous thromboembolism during the entire three-month study period. Analyses of bleeding events included events during the initial treatment period plus three, four, or nine days, according to the creatinine clearance (more than 50, 30 to 50, or less than 30 ml per minute, respectively).¹⁸ Efficacy analyses were based on data from all the patients who had been randomly assigned to a study group, whereas safety analyses were based on data from all the patients who actually received treatment. The 95 percent confidence interval for the absolute difference between the treatment groups in the rates of outcomes were calculated with use of the normal approximation.

The steering committee had the final responsibility for the study protocol, statistical analysis plan, progress of the study and analysis, and reporting of the data.

RESULTS

PATIENTS AND BASE-LINE CHARACTERISTICS

Between May 2000 and March 2002, 5993 patients with pulmonary embolism were screened in the 235 participating centers. Of these patients, 2948 (49 percent) were ineligible because they met one or more of the predefined exclusion criteria. The most common reasons for exclusion were the use of therapeutic anticoagulation for more than 24 hours (1237 patients), contraindications to anticoagulant therapy (470), a life expectancy of less than three months (205), and the use of thrombolytic therapy or a vena cava filter (128). In addition, 832 patients chose not to participate.

In total, 2213 patients were randomly assigned to receive either fondaparinux (1103) or unfractionated heparin (1110). The base-line characteristics of the patients in the two treatment groups were similar (Table 1). Follow-up with respect to the primary efficacy outcome was incomplete for six of the patients assigned to the fondaparinux group (0.5 percent) and seven of those assigned to the unfractionated-heparin group (0.6 percent), either because of withdrawal of informed consent (six patients) or loss to follow-up (seven).

TREATMENT

Table 2 presents data on the initial treatment and vitamin K-antagonist therapy in the 1092 patients in each group who received treatment. The duration of initial treatment was similar in the two groups. An adequate anticoagulation response to unfractionated heparin (i.e., an activated partial-thromboplastin time above the lower limit) was achieved in a high proportion of patients.

Of the 158 patients in the fondaparinux group (14.5 percent) who received fondaparinux in part on an outpatient basis, 37 did so for one day, 29 for two days, and 92 for three or more days. In both groups, more than 90 percent of the patients had an INR of 2.0 or more at the end of the initial treatment. The intensity of treatment with vitamin K antagonists was similar in the two groups.

RECURRENT VENOUS THROMBOEMBOLISM

Of the 1103 patients assigned to receive fondaparinux, 140 had one or more episodes of clinically suspected recurrent venous thromboembolism, and the diagnosis was confirmed in 42 patients (Table 3). Among the 1110 patients assigned to receive unfractionated heparin, 122 had one or more episodes of clinically suspected recurrent venous thromboembolism, and the diagnosis was confirmed in 56 patients. Thus, the incidence of recurrence was 3.8 percent in the fondaparinux group and 5.0 percent in the unfractionated-heparin group, for an absolute difference in favor of fondaparinux of -1.2 percent (95 percent confidence interval, -3.0 to 0.5). The upper limit of this confidence interval indicates that a true difference of more than 0.5 percent in favor of unfractionated heparin was unlikely (probability of such a difference, 2.5 percent). Hence, the noninferiority of fondaparinux was clearly demonstrated.

BLEEDING COMPLICATIONS

As shown in Table 3, major bleeding during initial treatment occurred in 14 of the patients who received fondaparinux (1.3 percent) and in 12 of those who received unfractionated heparin (1.1 percent) (absolute difference, 0.2 percent; 95 percent confidence interval, -0.7 to 1.1). Bleeding contributed to death in one patient in each treatment group. Among the patients whose creatinine clearance was below 30 ml per minute, major bleeding occurred in 2 of 26 (7.7 percent) in the fondaparinux group and in 1 of 28 (3.6 percent) in the unfractionated-heparin group.

Major or clinically relevant nonmajor bleeding

Table 2. Characteristics of Treatment in Each Study Group.*

Characteristic	Fondaparinux (N=1092)	Unfractionated Heparin (N=1092)
Duration of initial treatment — days	6.5±2.2	6.9±2.2
Dose of unfractionated heparin — IU/day		
Day 1		31,193±11,370
Day 2		26,124±8908
Activated partial-thromboplastin time†		
Day 1		
Above lower limit — no. (%)		953 (93.0)
Below lower limit — no. (%)		72 (7.0)
Data unavailable — no.		67
Day 2		
Above lower limit — no. (%)		1005 (94.5)
Below lower limit — no. (%)		59 (5.5)
Data unavailable — no.		28
One or more days of initial treatment on an outpatient basis — no. (%)	158 (14.5)	0
INR >2.0 at end of initial treatment — no. (%)	1037 (95.0)	1024 (93.8)
Mean percentage of time spent with INR in a given range‡		
INR <2.0	28	28
INR 2.0–3.0	53	52
INR >3.0	19	20

* Plus-minus values are means ±SD. Thirteen patients randomly assigned to the fondaparinux group were not treated. Of the patients randomly assigned to receive unfractionated heparin, 16 were not treated and 2 received fondaparinux. INR denotes international normalized ratio.

† The lower limit was defined as 1.5 times a control value.

‡ The percentage of time spent in each INR category was calculated for each patient with the use of linear interpolation.

during initial treatment occurred in 49 of the patients treated with fondaparinux (4.5 percent) and in 69 of those treated with unfractionated heparin (6.3 percent) (absolute difference, -1.8 percent; 95 percent confidence interval, -3.7 to 0.1). A total of 58 patients treated with fondaparinux and 67 of those treated with unfractionated heparin were considered to have had a trivial hemorrhage. The incidence of bleeding during treatment with a vitamin K antagonist was low and was similar in the two groups (Table 3).

MORTALITY

During the three-month study period, 57 patients who received fondaparinux (5.2 percent) died, as compared with 48 who received unfractionated heparin (4.4 percent) (absolute difference, 0.8 percent; 95 percent confidence interval, -1.0 to 2.6). In the fondaparinux group, the causes of death were pulmonary embolism (in 14 patients), bleeding (in 3), cancer (in 28), and other causes (in 12). In the

Table 3. Clinical Outcomes during the Study Period.

Population	Fondaparinux	Unfractionated Heparin
All patients randomly assigned to a study group		
No. of patients	1103	1110
Recurrent venous thromboembolism		
— no. (%)		
Initial treatment	14 (1.3)	19 (1.7)
Entire study	42 (3.8)	56 (5.0)
Type of recurrence — no.		
Fatal pulmonary embolism	16	15
Nonfatal pulmonary embolism	14	24
Deep-vein thrombosis only	12	17
Patients as treated		
No. of patients	1092	1092
Major bleeding — no. (%)		
Initial treatment	14 (1.3)	12 (1.1)
Entire study	22 (2.0)	26 (2.4)
Clinically relevant nonmajor bleeding only		
— no. (%)		
Initial treatment	35 (3.2)	57 (5.2)
Entire study	62 (5.7)	92 (8.4)
Death — no. (%)		
Initial treatment	9 (0.8)	12 (1.1)
Entire study	57 (5.2)	48 (4.4)

unfractionated-heparin group, the corresponding numbers were 15, 1, 22, and 10.

ADDITIONAL OBSERVATIONS

Of the 158 patients who received some fondaparinux on an outpatient basis, 5 (3.2 percent; 95 percent confidence interval, 1.0 to 7.2) had recurrent venous thromboembolism, and none (95 percent confidence interval, 0.0 to 2.4) had major bleeding or died during the initial treatment.

Among patients with active cancer at the time of enrollment, recurrent venous thromboembolism occurred in 10 of 112 patients in the fondaparinux group (8.9 percent) and in 22 of 128 patients in the unfractionated-heparin group (17.2 percent). Major bleeding occurred in two patients with cancer who received fondaparinux (1.8 percent) and in three patients with cancer who received unfractionated heparin (2.3 percent). The incidences of recurrent venous thromboembolism and major bleeding according to body weight are shown in Table 4.

In the fondaparinux group, thrombocytopenia occurred in 10 patients (0.9 percent), 1 of whom had associated thromboembolism (myocardial infarction) and 1 of whom had major bleeding. Neither of these patients had antiplatelet antibodies. In the un-

fractionated-heparin group, thrombocytopenia occurred in 13 patients (1.2 percent). Two of these 13 patients had recurrent pulmonary embolism without antiplatelet antibodies.

DISCUSSION

In this clinical trial of initial antithrombotic therapy for acute symptomatic pulmonary embolism, therapy with fondaparinux, a selective inhibitor of factor Xa, was not inferior to therapy with unfractionated heparin. The two therapies were associated with a similar incidence of adverse effects.

Optimal administration of intravenous unfractionated heparin requires reliable, frequent, and timely blood sampling and laboratory testing with reporting of the activated partial-thromboplastin time to a clinician, who then adjusts the dosage as needed. The minimal duration of treatment is five to seven days.⁴ Deviations in clinical practice from these complex, resource-intensive requirements are well documented, and abandoning heparin for an equally safe and effective but simpler therapy could be considered advantageous.¹⁹

In our study, care was taken to recruit a representative sample of patients with pulmonary embolism. The demographic features, range of risk factors, and spectrum of disease severity at enrollment and the observed rates of recurrent and fatal venous thromboembolic events were consistent with those reported in previous investigations. Hence, our findings regarding the efficacy and safety of fondaparinux apply to a broad range of patients with hemodynamically stable pulmonary embolism and have the potential to simplify care.

Some methodologic aspects of this open-label trial require comment. The procedures used to minimize bias included strict requirements to verify the qualifying pulmonary embolism and any suspected recurrent venous thromboembolic or bleeding events, as well as randomization at a central location, nearly complete follow-up, and masked adjudication of each suspected outcome event. Success at minimizing bias due to unmasked treatment assignment is supported by our finding that the diagnostic procedures at enrollment and at the time of recurrence were similar and that the incidences of a workup for and confirmation of suspected recurrence and bleeding in the two groups were similar.

Three considerations dictated the choice of unfractionated heparin rather than a low-molecular-weight heparin as the comparator drug. Unfraction-

Table 4. Rates of Recurrent Venous Thromboembolism and Major Bleeding, According to Body Weight.

Study Group	Recurrent Venous Thromboembolism during the 3-Month Study Period			Major Bleeding during the Initial Treatment Period		
	<50 kg	50–100 kg	>100 kg	<50 kg	50–100 kg	>100 kg
	<i>number/total number (percent)</i>					
Fondaparinux	5/22 (22.7)	32/945 (3.4)	5/132 (3.8)	0/21 (0)	13/939 (1.4)	1/130 (0.8)
Unfractionated heparin	4/25 (16)	41/948 (4.3)	11/136 (8.1)	1/25 (4)	10/932 (1.1)	1/134 (0.7)

ated heparin is the parenteral anticoagulant most widely used for initial therapy for pulmonary embolism, direct evidence that low-molecular-weight heparins are as effective as unfractionated heparin remains limited, and many clinicians prefer unfractionated heparin for this indication.³

Care was taken to apply the highest treatment standards to the use of unfractionated heparin and vitamin K antagonists. Among the necessary standards were those pertaining to the starting dose and dose adjustments, the minimal duration of treatment, and the target INR to be reached before heparin or fondaparinux could be stopped. Our results indicate that these standards were achieved in almost all the patients.

The objective of the study was to determine whether fondaparinux is noninferior to unfractionated heparin in preventing a recurrence of venous thromboembolism. The predefined margin for the comparison was consistent with those used in previous trials. Whereas an upper 95 percent confidence interval of up to 3.5 percent in favor of unfractionated heparin was allowed, the upper limit of 0.5 percent found in the study firmly establishes the noninferiority of fondaparinux.

Even though patients in the fondaparinux group were not prospectively assigned to early discharge, early discharge was permitted and occurred in 14.5 percent of them, who continued to receive fondaparinux on an outpatient basis. In this subgroup of

158 patients, the rate of recurrence was low (3.2 percent), and no major bleeding occurred.

In the past, bleeding complications were classified as major or minor. Whereas the definition of major bleeding in the setting of treatment for venous thromboembolism is generally well accepted and has been shown to be reliable,²⁰ “minor” bleeding may range from bleeding that is clinically significant but does not quite meet the criteria for major bleeding to much less severe episodes such as gingival bleeding. To overcome this limitation, we introduced and defined a category of “clinically relevant nonmajor bleeding” to identify and assess the relevant hemorrhagic complications associated with antithrombotic therapy more accurately.

In conclusion, once-daily, unmonitored, subcutaneous administration of fondaparinux was not inferior to the use of unfractionated heparin for the initial treatment of hemodynamically stable pulmonary embolism, and rates of adverse events were similar with the two therapies. In our opinion, because of its simplicity, once-daily subcutaneous administration of fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients with this disorder.

Supported by an unrestricted grant from NV Organon (Oss, the Netherlands) and Sanofi-Synthelabo (Paris).

Drs. van den Berg-Segers, Cariou, Leeuwenkamp, and Lensing are employees of the study sponsors (NV Organon and Sanofi-Synthelabo). Drs. Büller and Prins report having served as paid consultants and members of speakers bureaus for the sponsors.

APPENDIX

The following institutions and investigators participated in the study. **Steering committee:** H.R. Büller, B.L. Davidson, H. Decousus, A. Gallus, M. Gent, F. Piovela, M.H. Prins, G. Raskob, J. Bouthier, A.W.A. Lensing. **Data safety and monitoring board:** J. Hirsh, R. Roberts, J.W. ten Cate. **Adjudication committee:** M.H. Prins, Y. Graafsma, M. Levi, M.M.W. Koopman, S. Middeldorp, E. van Beek, P. Friedrich. **Study directors:** O. Leeuwenkamp, Organon; R. Cariou, Sanofi-Synthelabo. **Participating investigators:** Argentina (11 patients, 3 centers): J. Bono, Cordoba; J. Ceresetto, Buenos Aires; J. Vallejos, Corrientes. Austria (19 patients, 3 centers): F. Kummer, E. Minar, Wien; E. Pilger, Graz. Australia (203 patients, 12 centers): A. Gallus, Adelaide; R. Baker, Perth; T. Brighton, Sydney; B. Chong, Sydney; C. Denaro, Brisbane; D. Ma, Sydney; Kam Narayan, Melbourne; I. Prosser, Canberra; H. Salem, Melbourne; C. Steinfert, Geelong; P. Wood, Brisbane. Belgium (28 patients, 4 centers): M. Delcroix, Leuven; P. Hainaut, Brussels; G.R. Heyndrickx, Aalst; R. Naeye, Brussels. Brazil (63 patients, 8 centers): A.C. Amaral Baruzzi, São Paulo; L. Bodanese, Porto Alegre; B. van Bellen, São Paulo; J.P. Esteves, Salvador-Bahia; E.T. Mesquita, Rio de Janeiro; L. Piegas, São Paulo; S. Rassi, Goiânia; C. Silva, São Paulo. Canada (142 patients, 15 centers): D. Anderson, Halifax; A. Balsys, Weston; R. Bhargava, Oshawa; S. Blackie, New Westminster; L. Desjardins, Ste. Foy; R. Hanmiah, Winnipeg; A. Hirsch, Montreal; A. Karovitch, Ottawa; C. Licksai, Windsor; M. Mant, Edmonton; Y. Pesant, Saint-Jérôme; D. Rolf, Kelowna; H. Stelzer, Peterborough; A.G.G. Turpie, Hamil-

ton; T. Wong, Winnipeg. Czech Republic (46 patients, 4 centers): J. Chlumsky, I. Oliva, R. Spacek, Prague; I. Storlarova, Ostrava. Denmark (15 patients, 6 centers): P. Clemmensen, København Ø; J. Dalsgaard Nielsen, Hellerup; K. Egstrup, Svendborg; S. Husted, Århus C; S. Kiilerich, Hillerød; H. Kraemer Nielsen, B. Randrup, Braedstrup. Finland (27 patients, 2 centers): I. Kantola, Turku; M. Kotila, Seinäjoki. France (345 patients, 19 centers): J.P. Bassand, P. Lagalery, Besançon; G. Bessede, Gueret; B. Charbonnier, G. Pacouret, Tours; B. Crestani, F. Delatour, Paris; P. Mismeti, B. Tardy, Saint-Etienne; M. Elkohen, Roubaix; G. Janvier, Pessac; J.Y. Ketelers (Armentière), G. Traisnel, Lille; J.P. Laaban, B. Lebeau, F. Gagnadoux, Paris; H. Levesque, Bois Guillaume; P. Mathern, Firminy CEDEX; D. Mottier, F. Couturaud, Brest; J. Ninet, Lyons; G.E. Poulard, Abbeville; M. Richard, Saint Malo; H. Simonneau, F. Parent, Clamart; H. Sors, G. Meyer, Paris. Germany (103 patients, 10 centers): E. Altmann, Dresden; R. Bauersachs, Frankfurt am Main; C. Diem, Karlsbad-Langensteinbach; J. Harenberg, Mannheim; C. Ranke, Herne; M. Ritter, Ibbenbüren; S. Schellong, Dresden; J. Schweizer, Chemnitz; T. Voigtlaender, Mainz; J. Zahn, Ludwigshafen. Italy (200 patients, 13 centers): G. Agnelli, Perugia; G.M. Ambrosio, Venezia; F. Ghirarduzzi, Reggio Emilia; C. Giuntini, Pisa; D. Imberti, Piacenza; A. D'Angelo, I. Martinelli, F. Porro, Milan; V. Pengo, P. Prandoni, Padova; M. Barone, Pavia; R. Poggio, Genoa; G. Scannapieco, Treviso; P.F. Tropeano, Pordenone. Israel (28 patients, 5 centers): B. Brenner, Haifa; M.H. Ellis, Kfar-Saba; G. Lugassy, Ashkelon; E. Naparstek (A. Eldor), Tel Aviv; D. Varon, Tel-Hashomer. Poland (91 patients, 8 centers): J. Kloczko, Białystok; P. Kolodziej, Siedlce; J. Lewczuk, Wrocław; J. Michalak, Lublin; L. Polonski, Zabre; P. Pruszczyk, W. Tomkowski, Warsaw; K. Zawilska, Poznan. Spain (32 patients, 5 centers): R. Barba, Alcorcón; J. Lasierra, Logroño; M. Monreal-Bosch, Barcelona; M. Otero, Seville; F. Uresandi, Baracaldo. Sweden (51 patients, 6 centers): J. Aagesen, Jönköping; H. Eriksson, L. Lapidus, Göteborg; Gerd Lärffars, B. Leijd, S. Schulman, Stockholm. Switzerland (60 patients, 6 centers): E. Bächli, Zurich; P.A. Cerny, Lugano; C. Henzen, Luzern; H. Kohler, Bern; G. Nosedá, Mendrisio; J. Schifferli, Basel. The Netherlands (243 patients, 13 centers): J.D. Banga, Utrecht; E. ten Berge, Hengelo; D.H. Biesma, Nieuwegein; T. Haitjema, Alkmaar; C. van de Heul, Nieuwegein; D. Brandjes, M.M.W. Koopman, M. ten Wolde, P.E. Postmus, Amsterdam; T. Koster, Gouda; M. van Marwijk-Kooy, Zwolle; J. van der Meer, Groningen; P.J. Stijnen, Breda; J. Creemers, Eindhoven. United Kingdom (29 patients, 5 centers): D. Bevan, A.T. Cohen, P. Dillworth, P. Shah, London. United States (479 patients, 69 centers): C.L.V. Anderson, Bay Pines, Fla.; J. Ansell, Boston; W.C. Bazemore, Asheville, N.C.; D.E. Bechar, Richmond, Va.; D. Bloomfield, Staten Island, N.Y.; W.C. Botnick, Vidalia, Ga.; W.R. Breitweiser, Grand Forks, N.D.; D.E. Buffington, Tampa, Fla.; W. Caras, Tacoma, Wash.; S.N. Chohan, Oklahoma City; R. Dobbin Chow, Baltimore, Md.; M. Cipolletti, Allentown, Pa.; G.L. Colice, Washington, D.C.; P.C. Comp, Oklahoma City; J. Cooper, Alexandria, Va.; B.L. Davidson, Seattle; S.R. Deitcher, Cleveland; A. Dunn, New York; S. Durica, Norman, Okla.; C.G. Elliott, Salt Lake City; W. Farra, Southfield, Mich.; C.M. Fogarty, Spartanburg, S.C.; C.W. Francis, Rochester, N.Y.; E.L. Franks, Kansas City, Mo.; L.M. Gilliard, Orlando, Fla.; J.E. Godwin, Maywood, Ill.; J. Gossage, Augusta, Ga.; W. Greth, R. Griffin, West Reading, Pa.; J. Guzman, Detroit; K. Hassell, Denver; D.E. Heiselman, Akron, Ohio; D. Bratzler, D. Hitzeman, Tulsa, Okla.; T.M. Hyers, St. Louis; S. Idell, Tyler, Tex.; J. Ilowite, Mineola, N.Y.; D. Katula, Columbus, Ohio; L.W. Kendrick, North Little Rock, Ark.; D. Kereiakes, Cincinnati; H. Khoulfi, New York; S. Knoper, Tucson, Ariz.; D.P. Lawlor, Olathe, Kans.; R.G. Lerner, Valhalla, N.Y.; D.G. Lorch, Brandon, Fla.; T.A. Morris, San Diego, Calif.; A. O'Brien-Ladner, Kansas City, Kans.; D. Olson, Toledo, Ohio; D. Ost, Manhasset, N.Y.; V. Patel, Richmond, Va.; S. Rathbun, Oklahoma City; J.R. Rehm, Fredericksburg, Va.; L. Rice, Houston; F. Roberts, Baton Rouge, La.; G. Rodgers, Salt Lake City; L.J. Rosenthal, Pontiac, Mich.; M.J. Rumbak, Tampa, Fla.; R. Saizow, Tulsa, Okla.; R. Schein, Miami; L.S. Schwartzberg, Memphis, Tenn.; M.M. Seelagy, Trenton, N.J.; D.C. Thornton, Lackland AFB, Tex.; M. Tidswell, Springfield, Mass.; K. Voelker, Sarasota, Fla.; G.D. Wendell, Upland, Pa.; T.L. Whitsett, R.G. Wood, Oklahoma City; M.P. Young, Burlington, Vt.; R.D. Yussen, St. Louis.

REFERENCES

- Goldhaber SZ. Pulmonary embolism. *N Engl J Med* 1998;339:93-104.
- Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* 1960;1:1309-12.
- van Den Belt AG, Prins MH, Lensing AW, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2000;2:CD001100.
- Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 2001;119:Suppl 1:176S-193S.
- The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-62.
- Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337:663-9.
- Merli G, Spiro TE, Olsson CG, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134:191-202.
- Petitou M, Duchaussoy P, Herbert JM, et al. The synthetic pentasaccharide fondaparinux: first in the class of antithrombotic agents that selectively inhibit coagulation factor Xa. *Semin Thromb Hemost* 2002;28:393-402.
- The Rembrandt Investigators. Treatment of proximal deep vein thrombosis with a novel synthetic compound (SR90107A/ORG31540) with pure anti-factor Xa activity: a phase II evaluation. *Circulation* 2000;102:2726-31.
- Lensing AW, Prandoni P, Prins MH, Büller HR. Deep-vein thrombosis. *Lancet* 1999;353:479-85.
- Anand SS, Bates S, Ginsberg JS, et al. Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin times. *Arch Intern Med* 1999;159:2029-32.
- Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996;334:682-7.
- Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. *Circulation* 1993;88:1730-5.
- Prandoni P, Lensing AW, Bernardi E, Villalta S, Bagatella P, Girolami A. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *Thromb Haemost* 2002;88:402-6.
- Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5.
- Brandjes DP, Heijboer H, Büller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992;327:1485-9.
- Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1986;315:1109-14.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
- Reilly BM, Raschke R, Srinivas S, Nieman T. Intravenous heparin dosing: patterns and variations in internists' practices. *J Gen Intern Med* 1993;8:536-42.
- Graafsma YP, Prins MH, Lensing AW, de Haan RJ, Huisman MV, Büller HR. Bleeding classification in clinical trials: observer variability and clinical relevance. *Thromb Haemost* 1997;78:1189-92.

Copyright © 2003 Massachusetts Medical Society.

CORRECTION

Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism

Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism . On page 1702, in the Appendix, the list of participating investigators should have included A. Palla in Pisa, Italy.