

## A COMPARISON OF LOW-MOLECULAR-WEIGHT HEPARIN WITH UNFRACTIONATED HEPARIN FOR ACUTE PULMONARY EMBOLISM

GÉRALD SIMONNEAU, M.D., HERVÉ SORS, M.D., BERNARD CHARBONNIER, M.D., YVES PAGE, M.D.,  
 JEAN-PIERRE LAABAN, M.D., RÉZA AZARIAN, M.D., MARCEL LAURENT, M.D., JEAN-LOU HIRSCH, M.D.,  
 EMILE FERRARI, M.D., JEAN-LUC BOSSON, M.D., DOMINIQUE MOTTIER, M.D., AND BERTRAND BEAU, M.D.,  
 FOR THE THÉSÉE STUDY GROUP\*

**ABSTRACT**

**Background** Low-molecular-weight heparin appears to be at least as effective and safe as standard, unfractionated heparin for the treatment of deep-vein thrombosis, but only limited data are available on the use of low-molecular-weight heparin to treat acute symptomatic pulmonary embolism.

**Methods** We randomly assigned 612 patients with symptomatic pulmonary embolism who did not require thrombolytic therapy or embolectomy to either subcutaneous low-molecular-weight heparin (tinzaparin) given once daily in a fixed dose or adjusted-dose, intravenous unfractionated heparin. Oral anticoagulant therapy was begun between the first and the third day and was given for at least three months. We compared the treatments at day 8 and day 90 with respect to a combined end point of recurrent thromboembolism, major bleeding, and death.

**Results** In the first eight days of treatment, 9 of 308 patients assigned to receive unfractionated heparin (2.9 percent) reached at least one of the end points, as compared with 9 of 304 patients assigned to low-molecular-weight heparin (3.0 percent; absolute difference, 0.1 percentage point; 95 percent confidence interval, -2.7 to 2.6). By day 90, 22 patients assigned to unfractionated heparin (7.1 percent) and 18 patients assigned to low-molecular-weight heparin (5.9 percent) had reached at least one end point ( $P=0.54$ ; absolute difference, 1.2 percentage points; 95 percent confidence interval, -2.7 to 5.1). The risk of major bleeding was similar in the two treatment groups throughout the study.

**Conclusions** Under the conditions of this study, initial subcutaneous therapy with the low-molecular-weight heparin tinzaparin appeared to be as effective and safe as intravenous unfractionated heparin in patients with acute pulmonary embolism. (N Engl J Med 1997;337:663-9.)

©1997, Massachusetts Medical Society.

**L**OW-molecular-weight heparins are an important new class of antithrombotic agents. They differ from standard, unfractionated heparin in having a higher ratio of anti-factor Xa to anti-factor IIa activity, greater bioavailability, a longer half-life, and a more predictable anticoagulant response when administered subcutaneously in fixed doses.<sup>1,2</sup>

The efficacy and safety of low-molecular-weight

heparin for the initial treatment of deep-vein thrombosis are well established.<sup>3-5</sup> However, in most clinical trials comparing low-molecular-weight heparin with unfractionated heparin to treat acute deep-vein thrombosis, associated symptomatic pulmonary embolism either was a criterion for exclusion from the study or occurred in only a minority of the patients. Consequently, although deep-vein thrombosis and pulmonary embolism are generally considered to be different expressions of the same disease, there is limited information on the efficacy and safety of low-molecular-weight heparin for the initial treatment of symptomatic pulmonary embolism.<sup>6,7</sup> Therefore, the role of low-molecular-weight heparin in patients with acute pulmonary embolism must be determined before this therapeutic approach is extended to the overall spectrum of venous thromboembolism.

Because the low-molecular-weight heparins are distinct compounds with different pharmacologic profiles and different dose regimens, it is uncertain whether the results obtained with one preparation can be extended to another. In 1992, Hull et al. reported that a once-daily subcutaneous injection of tinzaparin was at least as effective and safe as continuous intravenous heparin in patients with proximal-vein thrombosis.<sup>8</sup>

We therefore conducted a randomized trial in which patients with symptomatic pulmonary embolism who did not require thrombolytic therapy or pulmonary embolectomy were given either continuous, intravenous unfractionated heparin or a single daily subcutaneous injection of tinzaparin. Considering the trend toward better efficacy and safety

From Hôpital Antoine Bécclère, Clamart (G.S.); Hôpital Laennec, Paris (H.S.); Hôpital Trousseau, Tours (B.C.); Hôpital Bellevue, St. Etienne (Y.P.); Hôpital Hôtel Dieu, Paris (J.-P.L.); Hôpital André Mignot, Versailles (R.A.); Hôpital Hôtel Dieu, Rennes (M.L.); Hôpital Henri Duffaut, Avignon (J.-L.H.); Hôpital Pasteur, Nice (E.F.); Hôpital Universitaire, Grenoble (J.-L.B.); Hôpital de la Cavale Blanche, Brest (D.M.); and Leo Pharmaceuticals, St. Quentin en Yvelines (B.B.) — all in France. Address reprint requests to Dr. Simonneau at the Service de Pneumologie et Réanimation, Hôpital Antoine Bécclère, 157 rue de la Porte de Trivaux, 92141 Clamart, France.

\*The centers and investigators participating in the Tinzaparin ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire (THÉSÉE) study are listed in the Appendix.

with low-molecular-weight heparin as compared with unfractionated heparin,<sup>3-5</sup> we sought to determine whether tinzaparin was clinically superior to unfractionated heparin with regard to the combined outcome of symptomatic recurrent thromboembolism, major bleeding, and death. A secondary aim was to compare the two treatments with respect to changes in scores for scintigraphically detected pulmonary vascular obstruction from day 1 to day 8.

## METHODS

### Study Design

This study was a multicenter, randomized, unblinded trial comparing continuous, adjusted-dose, intravenous unfractionated heparin with once-daily subcutaneous low-molecular-weight heparin (tinzaparin) in patients with acute, symptomatic pulmonary embolism. The study was conducted in 57 centers in France, Belgium, and Switzerland. The study protocol was approved by the institutional review boards of all the participating centers.

### Patients

Consecutive patients over 18 years of age with clinically suspected acute pulmonary embolism were considered for enrollment in the study. Before their inclusion, pulmonary embolism had to be objectively documented by pulmonary angiography, by ventilation-perfusion lung scanning indicating a high probability of pulmonary embolism,<sup>9</sup> or by scanning with indeterminate results that was accompanied by deep-vein thrombosis confirmed by venography or compression ultrasonography.

Patients were excluded from the study if, in the opinion of the physician in charge, they had massive pulmonary embolism requiring thrombolytic therapy or pulmonary embolectomy; if they had active bleeding or disorders contraindicating anticoagulant therapy; if they had received anticoagulant therapy at a therapeutic dose for more than 24 hours before entering the study (the receipt of such therapy for 24 hours or less before randomization was permitted); if their life expectancy was less than three months; if they had severe hepatic or renal failure; if noncompliance was likely; or if they were pregnant. After the patients gave written informed consent, central randomization was performed with the use of a 24-hour computer service.

### Treatment Regimens

The patients assigned to therapy with low-molecular-weight heparin were given a fixed dose of 175 international anti-factor Xa units of tinzaparin (Innohep, Leo Pharmaceutical Products, Ballerup, Denmark) per kilogram of body weight subcutaneously once daily. The patients assigned to therapy with unfractionated heparin (Leo Pharmaceutical Products) received an initial bolus dose of 50 IU per kilogram, followed by a continuous intravenous infusion at an initial rate of 500 IU per kilogram per day. The dose was subsequently adjusted so that the activated partial-thromboplastin time would be two to three times the control value in normal subjects. The tests were performed six hours after the start of treatment, whenever a subtherapeutic activated partial-thromboplastin time had been measured after a dose adjustment, and otherwise daily.

In each patient, oral anticoagulant therapy was begun between the first and third days of the initial heparin therapy and was continued for at least three months on an open-label basis. The dose was adjusted to achieve an international normalized ratio of 2.0 to 3.0. Treatment with either unfractionated heparin or low-molecular-weight heparin was given until the international normalized ratio was 2.0 or above on two measurements made 24 hours apart after at least five days of treatment with heparin. The use of antiplatelet and antiinflammatory drugs was prohibited during the study.

### Surveillance and Follow-up

All the patients were examined daily during the initial therapy; symptoms and signs of recurrent venous thromboembolism or bleeding were sought. When pulmonary embolism was documented by angiography alone, a perfusion lung scan was required within 48 hours of enrollment. For all patients, compression ultrasonography of the lower limbs was strongly encouraged at enrollment.

Patients in whom recurrent pulmonary embolism was suspected on the basis of clinical signs or symptoms underwent ventilation-perfusion scanning or angiography. Recurrent pulmonary embolism was diagnosed if there was a new perfusion defect, segmental or larger, on the lung scan. If the lung scan was inconclusive, pulmonary angiography was performed; a recurrence was defined as a new intraluminal filling defect or a new sudden cutoff in an arterial branch that was not present on the first angiogram. If no previous pulmonary angiogram was available for comparison, a recurrence was diagnosed when the angiogram showed an intraluminal defect or a sudden cutoff in an area where the initial perfusion lung scan showed normal perfusion.

Patients with suspected new or recurrent deep-vein thrombosis on the basis of the clinical findings underwent ultrasonography or venography, whichever test had been previously performed and had results available for comparison. The criterion for deep-vein thrombosis was either a constant intraluminal filling defect on venography or a lack of compressibility on ultrasonography when that finding represented a change from the results of the base-line test. All the angiograms and venograms were reviewed by three readers who were unaware of the treatment assignments. In addition, perfusion lung scans were systematically repeated in all patients between day 8 and day 11.

Complete blood counts were obtained twice weekly during the initial treatment period (from day 1 to day 8) and whenever there was any bleeding. Severe thrombocytopenia was defined as present if the platelet count fell below 50,000 per cubic millimeter or if it was between 50,000 and 100,000 per cubic millimeter and accompanied by clinical signs of bleeding or thrombosis.

Bleeding was defined as major if it was overt and associated either with a decrease in the hemoglobin concentration by at least 2.0 g per deciliter or with the need for the transfusion of 2 or more units of blood, or if the bleeding was intracranial or retroperitoneal.

Deaths were classified as due to pulmonary embolism (when there was strong clinical evidence or evidence at autopsy), hemorrhage, cancer, or other causes (including unknown causes).

### Outcome Measures

The primary end point was a combined outcome event, defined as death, symptomatic recurrent thromboembolism, or major bleeding within the first eight days of the study. This combined end point was also assessed at day 90. Data on all potential outcome events were submitted to an independent adjudication committee whose members were unaware of the treatment assignments.

A secondary end point was the change from day 1 to day 8 in the extent of scintigraphically detectable pulmonary vascular obstruction, expressed as a percentage. The method used to calculate this percentage has been previously described.<sup>10</sup> Each lobe was assigned a weight based on the regional distribution of blood flow, as follows: right upper lobe, 0.18; right middle lobe, 0.12; right lower lobe, 0.25; left upper lobe, 0.13; lingula, 0.12; left lower lobe, 0.2. The perfusion of each lobe was estimated visually on the basis of the film density and was scored on a scale from 0 (not perfused) to 1 (normally perfused), with use of a semi-quantitative method of evaluation (0, 0.25, 0.50, 0.75, and 1). Each lobar-perfusion score was then calculated by multiplying the weight assigned to the lobe by the estimated perfusion of that lobe and totaling the six separate lobar-perfusion scores. The percentage of vascular obstruction was calculated as:  $(1 - \text{overall perfusion score}) \times 100$ . All the scans were reviewed independently

and scored according to this method by two readers, each unaware of the patient's treatment assignment. Cases in which there were disputes (that is, any absolute differences in scoring by more than 10 percent between the two readers) were reevaluated by both readers, and a consensus was reached.

**Statistical Analysis**

The primary analysis was performed on an intention-to-treat basis. The results in the two treatment groups were compared by Fisher's exact test. Ninety-five percent confidence intervals for the difference between the two groups in the incidence of outcome events were calculated with the normal approximation to the binomial distribution. The log-rank test was used to assess differences in the cumulative incidence of events.

**RESULTS**

**Patients**

The recruitment of patients began in July 1995 and was completed in July 1996. Of 1482 consecutive patients who met the criteria for enrollment, 766 (52 percent) were excluded from the study for the following reasons: massive pulmonary embolism requiring thrombolytic therapy (177 patients) or interruption of the inferior vena cava (55), contraindications to anticoagulant therapy or concomitant use of an unauthorized drug (81), previous treatment with an anticoagulant drug for more than 24 hours (266), short life expectancy (51), any reason that rendered follow-up impracticable (101), and various other reasons (35). Among the 716 eligible patients, 104 (15 percent) declined to participate. Of the remaining 612 patients, 308 were randomly assigned to receive intravenous unfractionated heparin and 304 to receive low-molecular-weight heparin. Four patients (one assigned to unfractionated heparin and three assigned to low-molecular-weight heparin) did not receive the study drug but were included in the follow-up and in the study analysis. The base-line characteristics of the treatment groups were similar (Tables 1 and 2).

**Anticoagulant Therapy**

Among the 612 patients included in the study, 423 (69 percent) — 201 assigned to unfractionated heparin and 222 assigned to low-molecular-weight heparin — received therapeutic doses of unfractionated heparin before randomization. The mean ( $\pm$ SD) duration of anticoagulant treatment at a therapeutic dose before randomization was  $18 \pm 6$  hours in the patients assigned to unfractionated heparin and  $18 \pm 7$  hours in the patients assigned to low-molecular-weight heparin. The doses and duration of the study treatments and of oral anticoagulant agents are shown in Table 3.

**Primary End Points**

During the eight days after randomization, nine patients assigned to receive unfractionated heparin (2.9 percent) died or had symptomatic recurrent venous thromboembolism or major bleeding, as com-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.\***

CHARACTERISTIC	UNFRACTIONATED HEPARIN (N=308)	LOW-MOLECULAR-WEIGHT HEPARIN (N=304)
Age (yr)	67 $\pm$ 16	67 $\pm$ 16
Weight (kg)	73 $\pm$ 14	74 $\pm$ 14
	no. of patients (%)	
Male sex	139 (45)	133 (44)
Predisposing factors		
Previous venous thromboembolism	86 (28)	80 (26)
Surgery in past 3 mo	53 (17)	43 (14)
Known cancer	34 (11)	26 (9)
Bed rest for >72 hr	47 (15)	53 (17)
Heart disease	71 (23)	64 (21)
Deep-vein thrombosis†	204 (70)	217 (74)
Proximal	152	157
Distal	52	60

\*Plus-minus values are means  $\pm$ SD.

†Deep-vein thrombosis was assessed in 293 patients assigned to unfractionated heparin and 295 patients assigned to low-molecular-weight heparin.

**TABLE 2. SELECTED CHARACTERISTICS OF PULMONARY EMBOLISM IN THE STUDY PATIENTS AT ENROLLMENT.**

CHARACTERISTIC*	UNFRACTIONATED HEPARIN (N=308)	LOW-MOLECULAR-WEIGHT HEPARIN (N=304)
Clinical findings — no. of patients (%)		
Dyspnea	265 (86)	281 (92)
Chest pain	133 (43)	124 (41)
Hemoptysis	19 (6)	16 (5)
Heart rate $\geq$ 100 beats/min	80 (26)	75 (25)
Symptoms of DVT	124 (40)	131 (43)
Symptoms suggesting severe embolism†	82 (27)	89 (29)
Mean ( $\pm$ SD) pulmonary vascular obstruction — %	46 $\pm$ 21	47 $\pm$ 20
Obstruction $\geq$ 50% — % of patients	48	47
Criterion used to diagnose pulmonary embolism — no. of patients (%)		
High-probability lung scan	230 (75)	226 (74)
Pulmonary angiogram	42 (14)	38 (12)
Indeterminate lung scan + confirmed DVT	32 (10)	38 (12)
Other‡	4 (1)	2 (1)

\*DVT denotes deep-vein thrombosis. Scintigraphic data on the percentage of pulmonary vascular obstruction at enrollment were not available for 65 patients.

†These symptoms included acute right ventricular failure (in 15 percent of patients), cyanosis (in 13 percent), syncope (in 9 percent), and cardiovascular collapse (in 2 percent).

‡These methods included echocardiography and spiral computed tomographic scanning.

**TABLE 3. ANTICOAGULANT THERAPY PROVIDED TO THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.**

VARIABLE	MEAN VALUE*
Unfractionated heparin	
Days of treatment	7.0±2.4
Dose on day 1 (IU)	32,439
Daily dose, days 1 to 8 (IU)	27,495
Days to start of oral anticoagulation	2.0±1.0
Low-molecular-weight heparin	
Days of treatment	7.3±2.3
Days to start of oral anticoagulation	2.0±1.0

\*Plus-minus values are means ±SD.

**TABLE 4. OUTCOME EVENTS IN THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.**

EVENT AND TIME OF OCCURRENCE	UNFRACTIONATED HEPARIN (N=308)	LOW-MOLECULAR- WEIGHT HEPARIN (N=304)
	no. of patients (%)	
<b>Death</b>		
Days 1-8	3	4
Days 9-90	11	8
Total	14 (4.5)	12 (3.9)
	Difference, 0.6 percentage point (95% confidence interval, -2.6 to 3.8)	
<b>Recurrent venous thrombo- embolism</b>		
Days 1-8	2	3
Days 9-90	4	2
Total	6 (1.9)	5 (1.6)
	Difference, 0.3 percentage point (95% confidence interval, -1.8 to 2.4)	
<b>Major bleeding</b>		
Days 1-8	5	3
Days 9-90	6	4
Total*	8 (2.6)	6 (2.0)
	Difference, 0.6 percentage point (95% confidence interval, -1.8 to 3.0)	
<b>At least one outcome event</b>		
Days 1-8	9	9
Days 9-90	16	12
Total*	22 (7.1)	18 (5.9)
	Difference, 1.2 percentage points (95% confidence interval, -2.7 to 5.1)	

\*Patients who had events both between days 1 and 8 and between days 9 and 90 were counted only once.

pared with nine patients assigned to receive low-molecular-weight heparin (3.0 percent) (Table 4). There was an absolute difference of 0.1 percentage point between the two groups (95 percent confidence interval, -2.7 to 2.6).

From day 1 through day 90, 22 patients (7.1 percent) assigned to unfractionated heparin and 18 patients (5.9 percent) assigned to low-molecular-

weight heparin reached at least one of the clinical end points. There was an absolute difference of 1.2 percentage points (95 percent confidence interval, -2.7 to 5.1), and there was no significant difference between the treatment groups.

Analysis by the log-rank test, which takes into account the length of time to the first clinical event, did not show any significant difference between groups (P=0.55) in the frequency of the combined end point (Fig. 1).

**Mortality**

During the initial treatment (from day 1 to day 8), three patients receiving unfractionated heparin died (1.0 percent), as compared with four patients receiving low-molecular-weight heparin (1.3 percent). During the three-month study period, 14 patients assigned to unfractionated heparin died (4.5 percent), as compared with 12 patients assigned to low-molecular-weight heparin (3.9 percent) (Table 4). The causes of death are shown in Table 5.

**Recurrent Venous Thromboembolism**

Among the 308 patients treated with unfractionated heparin, 30 had at least one episode of clinically suspected recurrent thromboembolism during the three months of the study. Of these patients, six (1.9 percent of the entire treatment group) met the criteria established by the adjudication committee for documented recurrent thromboembolism. Among the 304 patients treated with low-molecular-weight heparin, 32 had suspected recurrences, 5 of whom (1.6 percent) met the committee's criteria. Overall, 5 of the 612 patients had pulmonary embolism, 3 had only deep-vein thrombosis, and 3 had both pulmonary embolism and deep-vein thrombosis.

**Bleeding Complications**

During the initial treatment (from day 1 to day 8), five patients receiving unfractionated heparin (1.6 percent) had major bleeding, as compared with three patients receiving low-molecular-weight heparin (1.0 percent). The activated partial-thromboplastin time was above the therapeutic level in two of the five patients receiving unfractionated heparin. The international normalized ratio was above the therapeutic level in one patient in each group. One patient in the unfractionated-heparin group who had retroperitoneal bleeding on day 6 died on day 7. There were no episodes of fatal bleeding among the patients receiving low-molecular-weight heparin. During the initial treatment, minor bleeding was noted in 8 patients receiving unfractionated heparin and 17 patients receiving low-molecular-weight heparin (P=0.10).

From day 9 through day 90, 10 patients had major bleeding (Table 4) and 22 had minor bleeding (9 patients receiving unfractionated heparin and 13

patients receiving low-molecular-weight heparin). One patient assigned to unfractionated heparin died of a hemorrhagic stroke on day 36, and one patient assigned to low-molecular-weight heparin died with massive hemoptysis on day 68 (Table 5).

Overall, during the three-month study period, there was major bleeding in eight patients assigned to unfractionated heparin (2.6 percent) and six patients assigned to low-molecular-weight heparin (2.0 percent) (Table 4).

**Perfusion Lung Scans**

For 65 patients (34 treated with unfractionated heparin and 31 treated with low-molecular-weight heparin), the percentage of scintigraphically detectable vascular obstruction could not be accurately assessed at enrollment, and these patients were therefore excluded from the analysis of vascular obstruction. For the 547 remaining patients, the mean vascular obstruction at enrollment was 46±21 percent in 274 patients assigned to unfractionated heparin and 47±20 percent in 273 patients assigned to low-molecular-weight heparin. Overall, the base-line extent of scintigraphically detectable vascular obstruction exceeded 50 percent in 47 percent of patients (Table 2).

Twenty-nine additional patients could not be studied at day 8. From day 1 to day 8, the absolute decrease in pulmonary vascular obstruction was 19.0±13.9 percent in 260 patients assigned to unfractionated heparin and 18.4±13.5 percent in 258 patients assigned to low-molecular-weight heparin.

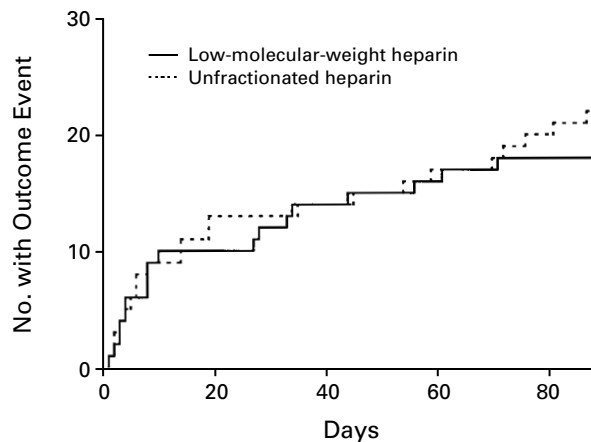
Among the patients assigned to unfractionated heparin, the perfusion lung scans improved in 81 percent, remained unchanged in 17 percent, worsened in 0.3 percent, and could not be properly compared from day 1 to day 8 in 1.7 percent. Among the patients assigned to low-molecular-weight heparin, the scans improved in 80 percent, remained unchanged in 17 percent, worsened in 0.7 percent, and could not be properly compared from day 1 to day 8 in 2.1 percent.

**Other Findings**

Heparin-induced thrombocytopenia developed on day 7 in one patient receiving unfractionated heparin (platelet count, 29,000 per cubic millimeter) and in no patient receiving low-molecular-weight heparin. On day 2, one patient treated with low-molecular-weight heparin had an ischemic stroke associated with pulmonary hypertension and a patent foramen ovale, suggesting a paradoxical embolism.

**DISCUSSION**

Pulmonary embolism is a potentially fatal disease in which anticoagulant therapy has been shown to improve outcomes dramatically.<sup>11</sup> Unfractionated heparin is considered the treatment of choice for most



**Figure 1.** Time-to-Event Analysis of the Occurrence of Recurrent Thromboembolism, Major Bleeding, or Death, Studied as a Combined Outcome.

There was no significant difference between the treatment groups in the frequency of the combined outcome (P=0.55 by the log-rank test).

**TABLE 5.** CAUSES OF DEATH IN THE TWO TREATMENT GROUPS.

CAUSE OF DEATH	UNFRACTIONATED HEPARIN		LOW-MOLECULAR-WEIGHT HEPARIN	
	NO. WHO DIED	NO. OF DAYS AFTER START OF THERAPY	NO. WHO DIED	NO. OF DAYS AFTER START OF THERAPY
Pulmonary embolism*	3	1, 2, 19	3	1, 4, 9
Major bleeding	2	7, 36	1	68
Cancer	4	45, 54, 81, 82	2	10, 71
Other†	1	19	3	24, 44, 61
Unknown	4	59, 70, 76, 87	3	2, 8, ‡ 40

\*This cause was judged certain or highly probable.

†These causes included septic shock (in one patient) and congestive heart failure (in three patients).

‡This patient's autopsy ruled out the possibility that the death was due to a recurrence of pulmonary embolism.

patients with pulmonary embolism, except those with hemodynamic instability, who may need thrombolytic therapy.<sup>2,12</sup>

Our study indicates that tinzaparin, a low-molecular-weight heparin, can be used safely and effectively when given once daily to treat patients with acute, symptomatic pulmonary embolism. Indeed, in both the group receiving unfractionated heparin and the group receiving low-molecular-weight heparin, rates of recurrence, major bleeding, and death were both similar and low. During the initial eight days of treatment, the overall incidence of severe critical events was similar in both groups (roughly 3 percent). During the three months of follow-up, there was a non-

significant trend favoring low-molecular-weight heparin as compared with unfractionated heparin, with overall rates of recurrence, major bleeding, and death of 5.9 percent and 7.1 percent, respectively.

Our study was unblinded, but we took special care to minimize potential biases. For this purpose, consecutive patients were included, all suspected recurrences of thromboembolism had to be confirmed by objective tests, and all the critical events were assessed by an independent adjudication committee.

Our findings are consistent with those of recent studies of the treatment of deep-vein thrombosis with low-molecular-weight heparins.<sup>3-5</sup> In one study, among patients treated with tinzaparin for proximal deep-vein thrombosis, after three months the reported incidence of recurrence was 2.8 percent, that of major bleeding was 2.8 percent, and that of death was 4.7 percent.<sup>8</sup> Using the same regimen of tinzaparin to treat acute pulmonary embolism, we observed similar rates of recurrent thromboembolism (1.6 percent), major bleeding (2.0 percent), and death (3.9 percent).

In patients with pulmonary embolism receiving unfractionated heparin, rates of recurrence, major bleeding, and death in the first three months of treatment have been reported to be markedly higher than in our study — about 5 to 10 percent higher for each end point.<sup>13-15</sup> However, these data were derived from small trials performed 5 to 20 years ago. At that time, the diagnosis of pulmonary embolism was generally based on pulmonary angiography, which is associated with an increased incidence of severe hemorrhagic complications.<sup>16</sup>

The selection criteria we used probably caused some patients who were at high risk of death, recurrence, or major bleeding to be excluded from the study. Indeed, among the 1482 patients who met the criteria for enrollment, 12 percent were excluded because they required thrombolytic therapy, 3.7 percent because they needed interruption of the vena cava, 3.4 percent because of a short life expectancy, and 5.5 percent because of a contraindication to anticoagulant therapy. However, all the patients included in our study presented with clinical symptoms due to pulmonary embolism, and 28 percent had clinical features compatible with major pulmonary embolism, including cyanosis, syncope, acute right ventricular failure, and even shock (in 2.0 percent). Also, 47 percent of our patients had evidence on perfusion scanning of vascular obstruction exceeding 50 percent. In that subgroup, the event rate was slightly higher (8.7 percent) than it was in the subgroup of patients whose perfusion scans showed less than 50 percent obstruction (5.8 percent). In the subgroup with more severe obstruction, the trend continued to favor low-molecular-weight heparin over unfractionated heparin.

Nevertheless, the unexpectedly low event rate in

the overall study population markedly reduced the statistical power of the study to detect a significant difference between the treatment groups. However, the general trend suggests that low-molecular-weight heparin is as effective and safe as intravenous unfractionated heparin under the conditions of the study. Had the trend favoring low-molecular-weight heparin continued, almost 10,000 patients would have been required for the study to show a statistically significant difference.

Among patients with deep-vein thrombosis, a major advantage of low-molecular-weight heparin over continuous intravenous unfractionated heparin is that the therapeutic regimen is greatly simplified, increasing convenience to patients and allowing the possibility of outpatient treatment that could substantially reduce costs.<sup>17,18</sup> Our study suggests that the use of low-molecular-weight heparin may be extended to patients with acute symptomatic pulmonary embolism after those with hemodynamic instability are excluded.

Supported by Leo Pharmaceuticals, France.

*We are indebted to John Stinson, M.D. (Dublin, Ireland), for reviewing the manuscript.*

#### APPENDIX

The following investigators, all in France except as otherwise noted, also participated in this study. Study Centers: Hôpital Laennec, Paris — G. Meyer; Hôpital Antoine Bécclère, Clamart — F. Parent; Hôpital Trouseau, Tours — G. Pacouret; Hôpital Bellevue, St. Etienne — H. Decousus and B. Tardy; Hôpital Hôtel Dieu, Paris — A. Achkar; Hôpital André Mignot, Versailles — J. Schwob and J.P. Normand; Hôpital Hôtel Dieu, Rennes — C. Almange; Hôpital Robert Debré, Reims — J. Elaerts and D. Maes; Centre Hospitalier Schaffner, Lens — P. Pignon; Centre Hospitalier, Pau — N. Delarache and M. Le Blay; Centre Hospitalier Général, Narbonne — P. Battistella; Hôpital Bichat, Paris — P.G. Steg and D. Czitorom; Hôpital Gabriel Montpied, Clermont Ferrand — B. Citron; Centre Hospitalier Lyon Sud, Lyon — D. Vital Durand and C. Grange; Hôpital Bon Secours, Metz — K. Khalife; Centre Hospitalier Général, Angoulême — M. Waynberger; Centre Hospitalier Général Lucien Hussen, Vienne — M. Madignier; Hôpital Sud, Amiens — J.C. Quiret and G. Jarry; Hôpital Edouard Herriot, Lyons — J. Ninet; Hôpital Broussais, Paris — J.N. Fiessinger and J. Emmerich; Hôpital Boucicaud, Paris — J. Labrousse and J.L. Diehl; Centre Hospitalier Général, Firminy — P. Sagnol; Hôpital d'Instruction des Armées Sainte Anne, Toulon — G.V. Dussarat; Centre Hospitalo-Universitaire, Lille — G. Ducloux and O. Nugue; Clinique des Franciscaines, Nîmes — E. Bosc; Gasthuisberg Hospital, Leuven, Belgium — R. Verhaeghe; Centre Hospitalier, Blois — M. Lang; Hôpital Victor Provo, Roubaix — P. Quandalle and X. Demarcq; Centre Hospitalo-Universitaire Dupuytren, Limoges — C. Cassat and G. Rambaud; Hôpital Central, Nancy — M.C. Laprevote and G. Thibaut; Hôpital Victor Dupouy, Argenteuil — J.P. Sollet; Centre Hospitalier Général Robert Ballanger, Aulnay-sous-Bois — O. Sitbon; Hôpital du Bocage, Dijon — B. Lorcerie and B. Bonnotte; Centre Hospitalo-Universitaire, Caen — G. Grollier; Centre Hospitalier, Martigues — A. Ebagosti; Hôpital Saint Jacques, Besançon — J.P. Bassand; Hôpital Cantonal Universitaire, Geneva — A. Perrier; Hôpital Beaujon, Clichy — R. Pariente, A. Cohen-Solal, and G. Jebrak; Centre Hospitalo-Universitaire, Rouen — H. Levesque; Hôpital de la Timone, Marseille — M. Bory; Centre Hospitalo-Universitaire la Milettrie, Poitiers — R. Barraine; Centre Hospitalier Gustave Dron, Tourcoing — E. Decoulx; Hôpital Hôtel Dieu, Angers — P. Geslin and P. Tron; Hôpital de Rangueil, Toulouse — A. Elias; Hôpital Louis Mourrier, Colombes — D. Dreyfuss; Centre Hospitalo-Universitaire, Le Krémlin-Bicêtre — O. Taravella; Hôpital Saint Eloi, Montpellier — C. Janbon; Centre Hospitalier, Le Mans — D. Fagart; Centre Hospitalier de la Côte Basque, Bayonne — A. Blanc; Hôpital du Val de Grâce, Paris — J.P. Ollivier; Hôpital Arnaud de Villeneuve, Montpellier — J.M. Davy; Hôpital Louis Pradel,

Lyons — J.F. Cordier. Central Data Management Office and Biostatistics: Leo Pharmaceuticals France, St. Quentin en Yvelines — A. Rakotomanga, J.J. Heilmann, L. Nguyen Trong, C. El Rawadi, J.C. Dhuin, and L. Goncalves. Adjudication Committee: P. Girard (Paris), B. Jarrousse (Bobigny), and M. Stern (Suresnes). Independent Supervision Committee: H. Bounameaux (Geneva), M. Dechavanne (Lyons), and A. Leizorovicz (Lyons). Central reading of lung scans: M.A. Collignon (Paris) and M. Wartski (Le Plessis-Robinson).

REFERENCES

1. Hirsh J, Levine MN. Low molecular weight heparin. *Blood* 1992;79:1-17.
2. Ginsberg JS. Management of venous thromboembolism. *N Engl J Med* 1996;335:1816-28.
3. Leizorovicz A, Simonneau G, Decousus H, Boissel JP. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. *BMJ* 1994;309:299-304.
4. Lensing AWA, Prins MH, Davidson BL, Hirsh J. Treatment of deep venous thrombosis with low-molecular-weight heparins: a meta-analysis. *Arch Intern Med* 1995;155:601-7.
5. Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. *Am J Med* 1996;100:269-77.
6. Théry C, Simonneau G, Meyer G, et al. Randomized trial of subcutaneous low-molecular-weight heparin CY 216 (Fraxiparine) compared with intravenous unfractionated heparin in the curative treatment of submassive pulmonary embolism: a dose-ranging study. *Circulation* 1992;85:1380-9.
7. Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low-molecular-weight heparin Fragmin versus intravenous unfractionated heparin in the

treatment of acute non massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost* 1995;74:1432-5.

8. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992;326:975-82.
9. 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.
10. Meyer G, Collignon MA, Guinet F, Jeffrey AA, Barritault L, Sors H. Comparison of perfusion lung scanning and angiography in the estimation of vascular obstruction in acute pulmonary embolism. *Eur J Nucl Med* 1990;17:315-9.
11. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* 1960;1:1309-12.
12. Hyers TM, Hull RD, Weg JG. Antithrombotic therapy for venous thromboembolic disease. *Chest* 1995;108:Suppl:335S-351S.
13. The Urokinase Pulmonary Embolism Trial: a national cooperative study. *Circulation* 1973;47:Suppl II:II-1-II-108.
14. Monreal M, Ruiz J, Salvador R, Morera J, Arias A. Recurrent pulmonary embolism: a prospective study. *Chest* 1989;95:976-9.
15. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet* 1993;341:507-11.
16. Stein PD, Hull RD, Raskob G. Risks for major bleeding from thrombolytic therapy in patients with acute pulmonary embolism: consideration of noninvasive management. *Ann Intern Med* 1994;121:313-7.
17. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;334:677-81.
18. Koopman MMW, 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.

---

RECEIVE THE *JOURNAL'S* TABLE OF CONTENTS EACH WEEK BY E-MAIL

---

To receive the table of contents of the *New England Journal of Medicine* by e-mail every Thursday morning, send an e-mail message to:

listserv@massmed.org

Leave the subject line blank, and type the following as the body of your message:

subscribe TOC-L

You can also sign up through our website at: <http://www.nejm.org>

---