

A COMPARISON OF ENOXAPARIN WITH PLACEBO FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN ACUTELY ILL MEDICAL PATIENTS

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ABSTRACT

Background The efficacy and safety of thromboprophylaxis in patients with acute medical illnesses who may be at risk for venous thromboembolism have not been determined in adequately designed trials.

Methods In a double-blind study, we randomly assigned 1102 hospitalized patients older than 40 years to receive 40 mg of enoxaparin, 20 mg of enoxaparin, or placebo subcutaneously once daily for 6 to 14 days. Most patients were not in an intensive care unit. The primary outcome was venous thromboembolism between days 1 and 14, defined as deep-vein thrombosis detected by bilateral venography (or duplex ultrasonography) between days 6 and 14 (or earlier if clinically indicated) or documented pulmonary embolism. The duration of follow-up was three months.

Results The primary outcome could be assessed in 866 patients. The incidence of venous thromboembolism was significantly lower in the group that received 40 mg of enoxaparin (5.5 percent [16 of 291 patients]) than in the group that received placebo (14.9 percent [43 of 288 patients]) (relative risk, 0.37; 97.6 percent confidence interval, 0.22 to 0.63; $P < 0.001$). The benefit observed with 40 mg of enoxaparin was maintained at three months. There was no significant difference in the incidence of venous thromboembolism between the group that received 20 mg of enoxaparin (15.0 percent [43 of 287 patients]) and the placebo group. The incidence of adverse effects did not differ significantly between the placebo group and either enoxaparin group. By day 110, 50 patients in the placebo group had died (13.9 percent), 51 in the 20-mg group had died (14.7 percent), and 41 in the 40-mg group had died (11.4 percent); the differences were not significant.

Conclusions Prophylactic treatment with 40 mg per day of enoxaparin subcutaneously safely reduces the risk of venous thromboembolism in patients with acute medical illnesses. (N Engl J Med 1999;341:793-800.)

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VENOUS thromboembolism is commonly found at autopsy in patients who received medical treatment and died in the hospital.^{1,2} Although the frequency of venous thromboembolism in these patients has not been established, it has been reported to be at least as high as in patients who undergo surgery and who are at moderate risk for thromboembolism.^{3,4}

There are extensive data to support both the clinical benefit and the cost effectiveness of routine thromboprophylaxis in surgical patients,³⁻⁹ but the use of this approach in general medical patients remains controversial. For certain groups of patients — such as those who have had a paralytic stroke or myocardial infarction, in whom the incidence of venous thromboembolism ranges from 30 to 75 percent — the prophylactic use of heparin is recommended.^{3,4,10} For other hospitalized medical patients, the situation is less clear because of the heterogeneity of design among available trials, the different methods used to diagnose deep-vein thrombosis, and importantly, the heterogeneity of patient populations.³ In addition, the risk of venous thromboembolism may vary according to the presence of intrinsic risk factors¹¹⁻¹³ and thus may also account for the conflicting results.¹⁴⁻²⁴

Because the frequency of venous thromboembolism is not known and evidence of the efficacy of routine prophylaxis in hospitalized medical patients is lacking, we carried out a double-blind, placebo-controlled, randomized study of such patients with two objectives: to determine the frequency of deep-vein thrombosis and pulmonary embolism and to determine the efficacy and safety of two regimens of low-molecular-weight heparin for the prevention of deep-vein thrombosis and pulmonary embolism.

METHODS

Patients

Medical patients who were older than 40 years, whose projected stay in the hospital was at least six days, and who were not immobilized for more than three days were considered for inclusion in the study. To be eligible, patients had to have congestive heart failure (New York Heart Association class III or IV), acute respira-

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tory failure that did not require ventilatory support, or one of the following medical conditions if it was associated with at least one additional risk factor for venous thromboembolism: acute infection without septic shock; acute rheumatic disorders, including acute lumbar pain or sciatica or vertebral compression (caused by osteoporosis or a tumor), acute arthritis of the legs, or an acute episode of rheumatoid arthritis in the legs; or an episode of inflammatory bowel disease. The additional risk factors were age of more than 75 years, cancer, previous venous thromboembolism, obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], ≥ 30 for men and ≥ 28.6 for women), varicose veins, hormone therapy (antiandrogen or estrogen, except for postmenopausal hormone-replacement therapy), and chronic heart or respiratory failure.

Women of childbearing age were excluded if they were pregnant, breast-feeding, or not using contraception; other reasons for exclusion were stroke or major surgery within the previous three months; contraindications to the use of iodinated contrast medium; known thrombophilia; a serum creatinine concentration of more than 1.7 mg per deciliter (150 μ mol per liter); intubation; human immunodeficiency virus infection; uncontrolled arterial hypertension (systolic blood pressure of more than 200 mm Hg, diastolic blood pressure of more than 120 mm Hg, or both), active peptic ulcer, bacterial endocarditis, or other conditions that could increase the risk of hemorrhage; hypersensitivity to heparin or heparin-induced thrombocytopenia; or a platelet count of less than 100,000 per cubic millimeter, a prolonged activated partial-thromboplastin time, a prothrombin ratio of less than 50 percent, or an international normalized ratio of more than 1.2. In addition, patients who required anticoagulant therapy and those who received any type of anticoagulant therapy for more than 48 hours were excluded.

Study Design

Randomization was performed at a central location. Patients were randomly assigned to receive 20 mg or 40 mg of enoxaparin (Lovenox, Clexane, or Klexane, Rhône-Poulenc Rorer, Antony, France) or placebo subcutaneously once daily, beginning within 24 hours after randomization. Treatment was scheduled to last 6 to 14 days in the hospital. Patients were then followed up in person or by telephone between days 83 and 110. At follow-up, patients were instructed to report any symptoms or signs of venous thromboembolism or any other clinical event that had occurred since the completion of treatment.

The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and with local regulations. The protocol was approved by independent ethics committees or institutional review boards where applicable, and written informed consent was obtained from all patients before randomization.

Medications

All study medications were packaged in prefilled, single-dose syringes that contained 40 mg of enoxaparin in 0.2 ml of water for injectable preparations (a concentration of 200 mg per milliliter, equivalent to 20,000 International Factor Xa Inhibitory Units per milliliter), 20 mg of enoxaparin in 0.2 ml (100 mg per milliliter, equivalent to 10,000 International Factor Xa inhibitory units per milliliter), or placebo (0.2 ml of isotonic saline).

Throughout the treatment period, intramuscular injections and treatment with nephrotoxic substances, particularly nephrotoxic antibiotics, were not permitted. Other treatments, elastic bandages or support stockings, and physiotherapy were used according to the usual practice at each center. Centers were advised to avoid giving patients nonsteroidal antiinflammatory drugs if possible.

Outcome Measures

The primary outcome with respect to efficacy was venous thromboembolism (defined as deep-vein thrombosis, pulmonary embolism, or both) between days 1 and 14. The secondary outcome with respect to efficacy was venous thromboembolism be-

tween days 1 and 110. Patients were examined for deep-vein thrombosis by systematic ascending contrast venography of the legs between days 6 and 14, or earlier if thrombosis was clinically suspected. If venography was infeasible, venous ultrasonography was performed. Possible cases of pulmonary embolism were confirmed by high-probability lung scanning, pulmonary angiography,²⁵ or helical computed tomography or at autopsy.

The incidence of death, major and minor hemorrhage, thrombocytopenia, any other adverse event, and abnormal laboratory findings was also assessed. Hemorrhage was classified as major if bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in the hemoglobin concentration of 2.0 g per deciliter or more from base line or if bleeding was retroperitoneal, intracranial, or fatal. Hemorrhage was defined as minor if it was overt but did not meet the other criteria for major hemorrhage. The injection site was evaluated daily for local reactions (hematomas larger than 5 cm in diameter). Complete blood counts were obtained before treatment was begun and every three days thereafter. Thrombocytopenia was defined as a decrease in the platelet count of at least 30 percent from base line or a platelet count of less than 100,000 per cubic millimeter; thrombocytopenia was considered severe if the platelet count was less than 50,000 per cubic millimeter.

Outcomes were reviewed by two independent committees whose members were unaware of the patients' treatment assignment. Two radiologists reviewed all venograms and angiograms, and two specialists in isotopic examination reviewed the pulmonary scintigrams. Any disagreements were settled by consensus. The results of these reviews were transmitted to the critical-events committee, which determined all clinical outcomes.

Statistical Analysis

To maintain an overall two-sided significance level of 0.05 in the analysis of the primary outcome, the nominal significance level in one interim efficacy analysis was adjusted according to the method of O'Brien and Fleming and in two comparisons with placebo according to Bonferroni's method. Assuming an incidence of venous thromboembolism of 15 percent in the placebo group and 6 percent in one of the enoxaparin groups and a global power of 90 percent, we needed to study 284 patients in each group (a total of 852 patients). The target number of recruited patients was 1020, a number that would allow for failure to obtain efficacy data in up to 20 percent of patients. In April 1998, after 750 patients had been included, the steering committee increased the target number to 1100 to ensure that the required number of 852 patients could be studied.

The analysis of the primary outcome included data on all patients according to the intention to treat. The analysis of adverse effects included data on patients who received at least one dose of study medication. If the results of venograms or ultrasonograms obtained between days 6 and 14 were inconclusive, they were not analyzed.

The analysis of the primary outcome accounted for the possibility that the absolute risks of venous thromboembolism in asymptomatic patients might have differed depending on whether patients were examined by systematic venography or ultrasonography, because of the different sensitivities of these methods. We assumed that the two methods would detect events with similar relative risks between groups. Relative risks of venous thromboembolism were calculated for patients examined by each method, and the relative risks were then combined with use of the Mantel-Haenszel chi-square test.²⁶ The 97.6 percent confidence interval of the common relative risk was calculated, with normal approximation to a binomial distribution. A two-tailed P value of less than 0.02 was considered to indicate statistical significance with respect to the primary outcome. A two-sided chi-square test or Fisher's exact test (where appropriate) was used for qualitative variables, and Student's t-test was used for quantitative variables. The time to death was analyzed by the Kaplan-Meier method.

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

TYPE OF ANALYSIS	TOTAL	PLACEBO	20 mg OF	40 mg OF
	(N=1102)	(N=371)	ENOXAPARIN (N=364)	ENOXAPARIN (N=367)
	number (percent)			
Analysis of primary outcome (days 1–14)				
Evaluated	866 (78.6)	288 (77.6)	287 (78.8)	291 (79.3)
Not evaluated	236 (21.4)	83 (22.4)	77 (21.2)	76 (20.7)
Death	28 (2.5)	11 (3.0)	10 (2.7)	7 (1.9)
Patient's refusal	62 (5.6)	22 (5.9)	20 (5.5)	20 (5.4)
Investigator's decision	58 (5.3)	22 (5.9)	17 (4.7)	19 (5.2)
Venography technically unfeasible	12 (1.1)	3 (0.8)	5 (1.4)	4 (1.1)
Venogram could not be evaluated	72 (6.5)	22 (5.9)	24 (6.6)	26 (7.1)
For unknown reason, venography not performed	4 (0.4)	3 (0.8)	1 (0.3)	0
Analysis of secondary outcome (days 1–110)				
Evaluated	798 (72.4)	263 (70.9)	263 (72.3)	272 (74.1)
Not evaluated	71 (6.4)	26 (7.0)	25 (6.9)	20 (5.4)
Death	61 (5.5)	23 (6.2)	20 (5.5)	18 (4.9)
Lost to follow-up or unscheduled visit before day 90	10 (0.9)	3 (0.8)	5 (1.4)	2 (0.5)
Treatment with at least one dose of study drug	1073 (97.4)	362 (97.6)	351 (96.4)	360 (98.1)

*Assessment data from days 14 and 110 were missing for 71 patients, but 3 patients without efficacy data on day 14 presented with symptomatic venous thromboembolism during follow-up.

The results of one interim analysis of efficacy and three interim analyses of safety were reviewed by an independent data and safety monitoring board. No modification of the protocol was recommended by this board during the trial.

RESULTS

Study Populations

Between December 1996 and July 1998, 1102 patients were enrolled in 60 centers in nine countries. By day 14, venography or ultrasonography to detect deep-vein thrombosis had not been performed or the results could not be evaluated in 236 patients (Table 1). Thus, 866 patients were included in the assessment of the primary outcome, which was evaluated by day 14 with venography in 718 patients and with ultrasonography in 148. By day 110, 798 patients had been assessed for the secondary outcome (Table 1), 60.8 percent in person and 39.2 percent by telephone. Of the 1102 patients enrolled in the study, 1073 received at least one dose of study drug and were included in the analysis of safety.

Characteristics of the Patients

Base-line characteristics did not differ significantly between the placebo group and either enoxaparin group (Table 2). A total of 494 patients had two or more reasons for hospitalization: 163 patients in the group assigned to receive placebo, 159 in the group assigned to receive 20 mg of enoxaparin, and 172 in the group assigned to receive 40 mg of enoxaparin. Overall, 1068 patients (96.9 percent of the study

population) had at least one risk factor for venous thromboembolism, and the mean (\pm SD) number of risk factors per patient was 2.1 ± 1.1 in the placebo group, 2.0 ± 1.1 in the 20-mg group, and 2.1 ± 1.1 in the 40-mg group. The median duration of treatment was seven days and did not differ significantly between either enoxaparin group and the placebo group.

Incidence of Venous Thromboembolism

The incidence of venous thromboembolism by day 14 was significantly lower in the group assigned to 40 mg of enoxaparin (5.5 percent [16 of 291 patients]) than in the placebo group (14.9 percent [43 of 288 patients]) (relative risk, 0.37; 97.6 percent confidence interval, 0.22 to 0.63; $P < 0.001$) (Tables 3 and 4). By day 14, symptomatic nonfatal pulmonary emboli had occurred in four patients, three in the placebo group and one in the 20-mg group. Of the 100 deep-vein thromboses detected by day 14 (6 of which were symptomatic), 92 were diagnosed by venography and 8 by ultrasonography (3 symptomatic and 5 asymptomatic). The incidence of any deep-vein thrombosis or of proximal or distal deep-vein thrombosis was significantly lower among patients in the 40-mg group than among those in the placebo group. There were no significant differences in primary outcome between the 20-mg group and the placebo group.

The significant reduction in the incidence of all venous thromboembolism and proximal and distal

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

CHARACTERISTIC	PLACEBO (N=371)	20 mg OF ENOXAPARIN (N=364)	40 mg OF ENOXAPARIN (N=367)
Age — yr	74.1±10.6	72.9±10.1	73.1±10.8
Sex — M/F	192/178	187/176	171/196
Body-mass index	25.0±6.5	25.1±6.2	24.9±5.9
Reason for hospitalization — no. (%)†			
NYHA class III congestive heart failure	95 (25.7)	76 (20.9)	103 (28.1)
NYHA class IV congestive heart failure	32 (8.6)	44 (12.1)	26 (7.1)
Acute respiratory failure	202 (54.6)	192 (52.9)	195 (53.1)
Acute infectious disease	193 (52.2)	194 (53.4)	197 (53.7)
Acute rheumatic disorder	32 (8.6)	40 (11.0)	28 (7.6)
Inflammatory bowel disease	1 (0.3)	1 (0.3)	3 (0.8)
Risk factor — no. (%)			
Age >75 yr	197 (53.2)	172 (47.4)	185 (50.4)
Cancer (previous or current)	56 (15.1)	56 (15.4)	45 (12.3)
History of venous thromboembolism	39 (10.5)	35 (9.6)	30 (8.2)
Obesity‡	71 (19.2)	79 (21.8)	72 (19.6)
Varicose veins	93 (25.1)	88 (24.2)	98 (26.7)
Hormone therapy	9 (2.4)	8 (2.2)	5 (1.4)
Chronic heart failure	124 (33.5)	106 (29.2)	123 (33.5)
Chronic respiratory failure	197 (53.2)	197 (54.3)	195 (53.1)
≥2 Risk factors — no. (%)	247 (66.8)	241 (66.4)	245 (66.8)

*Plus-minus values are means ±SD. Data on two patients were missing (one in the placebo group and one in the 20-mg group). A total of 494 patients (163, 159, and 172 in the groups that received placebo, 20 mg of enoxaparin, and 40 mg of enoxaparin, respectively) had two or more reasons for hospitalization. NYHA denotes New York Heart Association.

†Patients who had only an acute infectious disease, acute arthritis or rheumatic disorder, or inflammatory bowel disease had to have at least one additional risk factor for venous thromboembolic events to be included in the study.

‡Obesity was defined as a body-mass index of at least 30 in men and 28.6 in women.

deep-vein thrombosis in the 40-mg group was maintained during the three-month follow-up period (Table 3). Eight additional venous thromboembolic events occurred between days 15 and 110, of which four were fatal pulmonary emboli: one in the placebo group (three weeks after the discontinuation of treatment), one in the 20-mg group, and two in the 40-mg group (two months after discontinuation of the study treatment).

Adverse Events

By day 110, 142 patients had died: 50 in the placebo group (13.9 percent), 51 in the 20-mg group (14.7 percent), and 41 in the 40-mg group (11.4 percent) (Table 5). The risk of death was lower in the 40-mg group than in the placebo group, but this difference was not significant (relative risk, 0.83; 95 percent confidence interval, 0.56 to 1.21; $P=0.31$) (Fig. 1). There was no significant difference in the risk of death between the 20-mg group and the placebo group (relative risk in the 20-mg group, 1.05; 95 percent confidence interval, 0.71 to 1.56; $P=0.80$). In addition, by day 110, eight patients who had not received any study medication had died (three in the placebo group and five in the 20-mg group), but

data on these patients were not included in the analysis of safety.

During the treatment period, major hemorrhage occurred in 11 patients (Table 5). One patient in the 40-mg group died, but the hemorrhage was not considered to be related to treatment (it was characterized as massive hemoptysis due to bronchial carcinoma). There were no instances of retroperitoneal or intracranial hemorrhage during the treatment period. During follow-up, two additional patients died as a result of hemorrhage, one in the 20-mg group (from massive hematemesis) eight weeks after completion of treatment and one in the 40-mg group (from intracerebral hemorrhage) three weeks after completion of treatment.

Among the 31 cases of thrombocytopenia during the treatment period, 14 were considered to be possibly or probably related to treatment; these 14 cases involved 8 patients in the placebo group, 4 in the 20-mg group, and 2 in the 40-mg group. Three patients in the placebo group had severe thrombocytopenia (Table 5). Thrombocytopenia was associated with arterial or venous thromboembolism in five patients (four in the placebo group and one in the 20-mg group) during the treatment period.

TABLE 3. INCIDENCE OF VENOUS THROMBOEMBOLIC EVENTS.

OUTCOME	PLACEBO	20 mg of	40 mg of
		ENOXAPARIN	ENOXAPARIN
	number (percent)		
Primary outcome			
No. of patients evaluated	288	287	291
Venous thromboembolic events	43 (14.9)	43 (15.0)	16 (5.5)
Deep-vein thrombosis alone	40 (13.9)	42 (14.6)	16 (5.5)
Pulmonary embolism alone	2 (0.7)	0	0
Deep-vein thrombosis and pulmonary embolism	1 (0.3)	1 (0.3)	0
Proximal deep-vein thrombosis	14 (4.9)	13 (4.5)	5 (1.7)
Distal deep-vein thrombosis	27 (9.4)	30 (10.5)	11 (3.8)
Symptomatic deep-vein thrombosis	2 (0.7)	3 (1.0)	1 (0.3)
Death from pulmonary embolism	0	0	0
Secondary outcome			
No. of patients evaluated	263	263	272
Venous thromboembolic events	45 (17.1)	46 (17.5)	19 (7.0)
Deep-vein thrombosis alone	41 (15.6)	44 (16.7)	17 (6.2)
Pulmonary embolism alone	2 (0.8)	0	0
Deep-vein thrombosis and pulmonary embolism	1 (0.4)	1 (0.4)	0
Proximal deep-vein thrombosis*	17 (6.5)	14 (5.3)	6 (2.2)
Distal deep-vein thrombosis*	27 (10.3)	31 (11.8)	12 (4.4)
Symptomatic deep-vein thrombosis	4 (1.5)	6 (2.3)	3 (1.1)
Death from pulmonary embolism	1 (0.4)	1 (0.4)	2 (0.7)

*If a patient had deep-vein thrombosis during the treatment period and again during follow-up, the recurrence was not counted as a new event. If the location (proximal or distal) of the recurrence differed from that of the first event, the two events are listed separately according to location.

There were no significant differences between either enoxaparin group and the placebo group in the incidence of any other adverse event during treatment or follow-up.

DISCUSSION

In our placebo-controlled study, daily injections of 40 mg of enoxaparin significantly reduced the incidence of venous thromboembolism in acutely ill medical patients during hospitalization without increasing the risk of major hemorrhage. The 14.9 percent incidence of venous thromboembolism and 4.9 percent incidence of proximal deep-vein thrombosis in the placebo group during the treatment period support the hypothesis that this population of patients was at moderate risk for venous thromboembolism, according to the Thromboembolic Risk Factors Consensus Group classification.¹³ These values fall within the range of 9 to 26 percent reported in smaller studies.^{14,21,22,24} The use of a placebo group was considered to be ethically justifiable because the incidence of venous thromboembolism among such patients had not been established, there was no established method of thromboprophylaxis for these patients, and patients with a very high risk of venous thromboembolism were excluded.^{3,4,13} Although low-dose unfractionated heparin is widely used as prophylaxis against thrombosis, it could not be considered a validated control treatment for medical patients. Indeed, the few studies supporting its use included

TABLE 4. RELATIVE RISKS OF PRIMARY AND SECONDARY OUTCOMES FOR EACH ENOXAPARIN REGIMEN AS COMPARED WITH PLACEBO.*

OUTCOME	20 mg of ENOXAPARIN		40 mg of ENOXAPARIN	
	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Primary outcome				
Venous thromboembolic events†‡	1.02 (0.70–1.51)	0.90	0.37 (0.22–0.63)	<0.001
Deep-vein thrombosis alone§	1.05 (0.71–1.57)	0.81	0.40 (0.23–0.69)	<0.001
Proximal deep-vein thrombosis§	0.93 (0.45–1.94)	1.00	0.35 (0.13–0.97)	0.04
Distal deep-vein thrombosis§	1.11 (0.68–1.83)	0.68	0.40 (0.20–0.80)	0.01
Secondary outcome				
Venous thromboembolic events¶	1.02 (0.70–1.49)	0.91	0.41 (0.25–0.68)	<0.001
Deep-vein thrombosis alone§	1.07 (0.73–1.58)	0.81	0.40 (0.23–0.69)	<0.001
Proximal deep-vein thrombosis§	0.83 (0.42–1.64)	0.71	0.34 (0.14–0.86)	0.02
Distal deep-vein thrombosis§	1.15 (0.71–1.88)	0.58	0.43 (0.22–0.84)	0.01

*CI denotes confidence interval.

†In the analysis of primary outcome with respect to all venous thromboembolic events, the range in parentheses is the 97.6 percent confidence interval (see the Methods section).

‡The Mantel–Haenszel chi-square test was used.

§Fisher’s exact test was used.

¶The chi-square test was used.

TABLE 5. INCIDENCE OF ADVERSE EVENTS.*

ADVERSE EVENT	PLACEBO	20 mg OF	40 mg OF
		ENOXAPARIN	ENOXAPARIN
	number (percent)		
Treatment period (days 1–14)			
No. of patients evaluated	362	351	360
Death from any cause	16 (4.4)	15 (4.3)	12 (3.3)
Hemorrhage†	31 (8.6)	41 (11.7)	45 (12.6)
Major	4 (1.1)	1 (0.3)	6 (1.7)
Fatal	0	0	1 (0.3)
Minor	27 (7.5)	40 (11.4)	39 (10.8)
Local reaction at injection site (hematoma >5 cm in diameter)	0	4 (1.1)	5 (1.4)‡
Thrombocytopenia§	13 (3.6)	10 (2.8)	8 (2.2)
Severe thrombocytopenia¶	3 (0.8)	0	0
Study period (days 1–110)			
No. of patients evaluated	362	351	360
Death from any cause	50 (13.9)	51 (14.7)	41 (11.4)
Hemorrhage**	51 (14.3)	59 (17.2)	62 (17.4)
Major	7 (2.0)	4 (1.2)	12 (3.4)
Fatal	0	1 (0.3)	2 (0.6)
Minor	45 (12.6)	57 (16.6)	51 (14.4)
Thrombocytopenia††	17 (4.8)	11 (3.2)	10 (2.8)
Severe thrombocytopenia¶	3 (0.8)	0	0

*Data on eight patients who had not received any study medication and who had died by day 110 (three patients in the placebo group and five in the 20-mg group) were not included in the analysis of adverse events.

†If patients had both major and minor hemorrhages, they are listed separately for these categories but only once for total hemorrhages. Data on hemorrhage during the treatment period were missing for three patients (one in the placebo group and two in the 40-mg group).

‡ $P=0.03$ for the comparison with the placebo group.

§Data on thrombocytopenia during the treatment period were missing for four patients (one in the placebo group and three in the 40-mg group).

¶Severe thrombocytopenia was defined as a platelet count of less than 50,000 per cubic millimeter.

||Data on death from any cause during the study period were missing for six patients (one in the placebo group, four in the 20-mg group, and one in the 40-mg group).

**If patients had both major and minor hemorrhages, they are listed separately for these categories but only once for total hemorrhages. Data on hemorrhage during the study period were missing for 18 patients (6 in the placebo group, 8 in the 20-mg group, and 4 in the 40-mg group).

††Data on thrombocytopenia during the study period were missing for 19 patients (6 in the placebo group, 9 in the 20-mg group, and 4 in the 40-mg group).

small numbers of patients,^{14,22,24} the results of two studies that evaluated mortality among medical patients given 5000 U of unfractionated heparin twice daily are conflicting,^{18,20} and the recommendations of consensus conferences are not definitive.^{13,27-32}

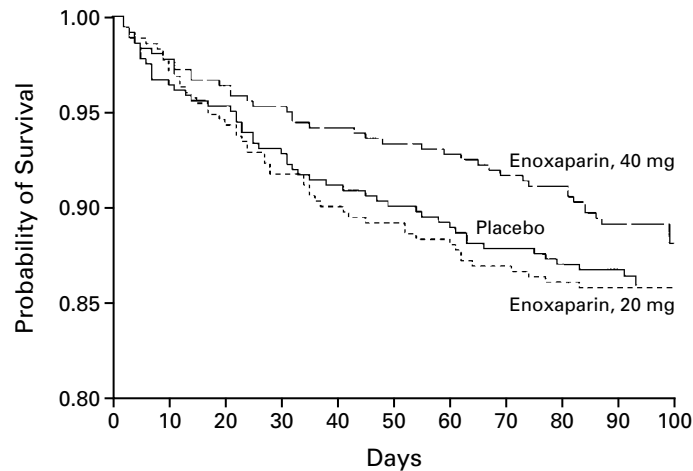
Our finding of a 63 percent decrease in the risk of venous thromboembolism in the group given 40 mg of enoxaparin daily is similar to the 66 to 80 percent reduction reported in small studies of medical patients given 5000 U of unfractionated heparin twice daily^{14,24} or three times daily²² or 60 mg of enoxaparin once daily.²¹ It is also similar to the decrease usually seen with heparin prophylaxis among surgical

patients.^{3,4} In our study, the incidence of venous thromboembolism during treatment in the 40-mg group was less than that reported for either treatment group in a recent study that compared treatment with 40 mg of enoxaparin once daily to 5000 U of unfractionated heparin three times daily in patients with severe respiratory disease or New York Heart Association class III or IV heart failure³³; in that study, the incidence of venous thromboembolism was 8.4 percent in the enoxaparin group and 10.4 percent in the unfractionated-heparin group. The difference in the rates may be explained by the fact that the other study included patients who were sicker than ours. We found no decrease in the incidence of venous thromboembolism with the use of a 20-mg dose of enoxaparin, although the efficacy of this dose was similar to that of a twice-daily dose of 5000 U of unfractionated heparin in another trial of medical patients who were probably less severely ill than ours²³ and is known to be effective in surgical patients at moderate risk.³⁴⁻³⁶

In our study, the diagnosis of deep-vein thrombosis was mainly made with use of venography, which remains the reference method of screening for deep-vein thrombosis in asymptomatic patients. Ultrasonography has a low sensitivity in asymptomatic patients undergoing medical treatment^{15,16} or orthopedic surgery.³⁷ Twenty-two percent of patients were not included in the analysis of the primary outcome for a variety of reasons, most related to the relative severity of the illnesses involved and the clinical difficulty of performing venography in those patients. However, the numbers of those patients who were not assessed for the primary outcome were similar among the three groups.

The clinical relevance of asymptomatic deep-vein thrombosis, particularly distal deep-vein thrombosis, as detected by objective tests has been questioned. As expected, symptomatic events were rare in our study. In addition, most patients identified as having asymptomatic deep-vein thrombosis by day 14 received a therapeutic dose of anticoagulant therapy. Thus, the natural history of their disease was altered, and the association between the decrease in the incidence of asymptomatic events and clinical events cannot be evaluated. Although three studies have assessed the ability of thromboprophylaxis to reduce the risk of death among general medical in-patients,¹⁸⁻²⁰ the results are still controversial because of concern about the methods used. Our trial, which was not designed to investigate differences in mortality, revealed a clinically relevant trend, with a 2.5 percent absolute reduction in the overall risk of death at three months in the group assigned to 40 mg of enoxaparin.

We chose a duration of prophylaxis of 6 to 14 days in order to match the usual duration of hospitalization among medical patients. We cannot rule out the pos-



No. AT RISK						
Total	1073	1022	983	965	943	231
Placebo	362	344	329	322	314	77
Enoxaparin, 20 mg	351	332	316	310	302	81
Enoxaparin, 40 mg	360	346	338	333	327	73

Figure 1. Kaplan–Meier Estimate of the Probability of Survival. The risk of death was lower in the group assigned to 40 mg of enoxaparin than in the group assigned to placebo (relative risk, 0.83; 95 percent confidence interval, 0.56 to 1.21; P=0.31).

sibility that treatment was too short in the case of some patients and that it was discontinued while they were still at risk for venous thromboembolism. Indeed, two fatal pulmonary emboli occurred in the 40-mg group several weeks after prophylaxis had been discontinued. From a practical point of view, therefore, the decision to prolong prophylaxis should be made on an individual basis. Future studies could examine the effects of prolonging prophylaxis in these patients, as has been done in patients undergoing hip surgery.³⁸⁻⁴⁰

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APPENDIX

The following investigators and centers participated in the trial: **Steering Committee** — M.M. Samama (study chair), A.T. Cohen, J.-Y. Darmon, L. Desjardins, A. Eldor, C. Janbon, C.-G. Olsson, A.G. Turpie, N. Weisslinger (project director); **Writing Committee** — A.T. Cohen, A. Leizorovicz, M.M. Samama, A.G. Turpie, N. Weisslinger; **Data Monitoring Committee** — A. Leizorovicz (chair), H. Decousus, T. Lecompte; **Critical Event Committee** — Y. Gruel (chair), C. Lamer, F. Parent; **Central Reading Committee** — P. Girard (chair), M.-A. Collignon, P. Lacombe, D. Musset, M. Wartski; **Project Management** — H. Nguyen (associate project director), C. Dole, N. Esposito, L. Laperriere; **Data Management and Statistical Analysis Center** — Clinical Pharmacology Unit, Hôpital Neuro-Cardiologique, Lyons, France: F. Boutitie (project director and statistician), V. Bost (critical-events physician), E. Gauthier (trial coordinator), A. Chérief (secretary), M. Hervé (data manager); **Monitoring Coordinators** — Rhône–Poulenc Rorer (France): A. Bone, A. Dal Pra, F. Kogan, F. Le Barbenchon; Chiltern International, London: E. Delisle, T.K. Sohal, N. Spinnewyn; **Investigators** — Canada (246 patients, 17 centers): M. Alexander, D. Anderson, P. Brill-Edwards, C. Demers, R. Delage, L. Desjardins, S. Desmarais, M. Fitzgerald, R. Abboud, K. Grewal, J. Kassis, A. Kirby, S. Martel, J. Muscedere (2 centers), D. Rolf, R. Anderton, A.G. Turpie, J. Weitz, P. Wells; France (163 patients, 17 centers): J.-F. Bergmann, G. Simoneau, I. Mahé,

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