Subcutaneous Enoxaparin Once or Twice Daily Compared with Intravenous Unfractionated Heparin for Treatment of Venous Thromboembolic Disease

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Background: **Low-molecular-weight heparins administered subcutaneously once or twice daily have been reported to be as safe and efficacious as intravenous unfractionated heparin in the treatment of acute venous thromboembolic disease.**

Objective: **To determine whether subcutaneous enoxaparin administered once or twice daily is as effective as continuously infused unfractionated heparin in acute symptomatic venous thromboembolic disease.**

Design: **Randomized, controlled, partially blinded equivalence trial.**

Setting: **74 hospitals in 16 countries.**

Patients: **900 patients with symptomatic lower-extremity deep venous thrombosis, including 287 (32%) with confirmed pulmonary embolism.**

Interventions: **Initial therapy with dose-adjusted intravenous unfractionated heparin compared with subcutaneous enoxaparin at fixed dosages of 1.0 mg/kg of body weight twice daily or 1.5 mg/kg once daily. Long-term oral anticoagulation was started in all patients within 72 hours of randomization.**

Measurements: **Clinical end points assessed during a 3-month follow-up period.**

Results: **Equivalent efficacy was seen in the heparin group and both enoxaparin groups. Symptomatic venous thromboembolism recurred in 12 of 290 patients receiving unfractionated heparin (4.1%), 13 of 298 patients receiving once-daily enoxaparin (4.4%), and 9 of 312 patients receiving twice-daily enoxaparin (2.9%). Compared with unfractionated heparin, the treatment difference was 0.2% (95% CI, −3.04% to 3.49%) for once-daily enoxaparin and −1.2% (CI, −4.2% to 1.7%) for twice-daily enoxaparin. Incidence of major hemorrhage did not differ among the three treatment groups. Major hemorrhage occurred in 6 of 290 patients (2.1%) in the unfractionated heparin group, 5 of 298 patients (1.7%) in the once-daily enoxaparin group, and 4 of 312 patients (1.3%) in the twice-daily enoxaparin group.**

Conclusions: **Subcutaneous enoxaparin once or twice daily is as effective and safe as dose-adjusted, continuously infused unfractionated heparin in the prevention of recurrent symptomatic venous thromboembolic disease.**

Ann Intern Med. 2001;134:191-202. www.annals.org

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Venous thromboembolic disease causes significant morbidity and mortality in both hospitalized and nonhospitalized patients. The mean annual incidence in the United States is 48 per 100 000 for deep venous thrombosis and 23 per 100 000 for pulmonary embolism, according to an epidemiologic study conducted in Massachusetts (1). A similar study in Sweden showed an annual incidence of 160 new cases of deep venous thrombosis per 100 000 inhabitants (2).

Five to 10 days of unfractionated heparin is a common recommended initial treatment for deep venous thrombosis. This treatment maintains the activated partial thromboplastin time above 1.5 times its control value (3, 4), as calibrated by protamine titration or an anti–factor Xa assay. Another recommended initial treatment is 5 to 10 days of weight-adjusted low-molecular-weight heparin followed by at least 3 months of oral anticoagulant therapy (3–7). Low-molecular-weight heparins are now frequently being used in place of unfractionated heparin for both prevention and treatment of venous thromboembolism (3, 8). Randomized trials and meta-analyses have shown subcutaneously administered low-molecular-weight heparins to have antithrombotic efficacy equal to (9–12) or greater than (13–16) that of continuously infused unfractionated heparin in the initial treatment of deep venous thrombosis and equal to that of unfractionated heparin in the treatment of pulmonary embolism (17, 18). However, many of these studies enrolled small numbers of patients (9–13, 15, 16), used primarily venographic plethysmographic

or scintigraphic end points (9–11, 13, 16), and sometimes excluded patients with pulmonary embolism (11, 15). Most trials of twice-daily low-molecular-weight heparin adjusted treatment regimens according to patient weight without laboratory monitoring. However, several studies suggest that once-daily weight-adjusted dosage of a low-molecular-weight heparin is as effective in the treatment of proximal deep venous thrombosis as adjusted dosages of intravenous unfractionated heparin (14, 19) or twice-daily low-molecular-weight heparin (20).

Since low-molecular-weight heparins differ in their physicochemical and pharmacologic characteristics, study results that apply to one cannot be extended to another (21, 22). We conducted the present study to determine whether enoxaparin administered subcutaneously once or twice per day is as effective as continuously infused unfractionated heparin in the treatment of patients with acute, symptomatic venous thromboembolic disease.

METHODS

Study Description

This parallel-group, randomized, partially blinded, international, multicenter clinical trial compared continuously infused unfractionated heparin (adjusted to maintain activated partial thromboplastin time within a defined range) with two weight-adjusted dosages of enoxaparin administered subcutaneously once or twice daily. The study was conducted in 74 hospitals in 16 countries, including the United States, several European countries, Australia, and Israel, and was approved by the institutional review board or ethics committees at each location. Written informed consent was obtained from each patient.

Four committees participated in this study: an Advisory Committee; an Outcome Adjudication Committee, which provided blinded outcome assignments for incidence of recurrent venous thromboembolic disease, major or minor hemorrhage, immune thrombocytopenia, and cause of death; an independent Safety Committee; and a Vascular Imaging Committee, which reviewed all baseline venograms and all vascular imaging studies in a blinded manner to determine whether deep venous thrombosis was present at baseline and whether objective evidence of recurrence existed.

Patient Characteristics

Patients were required to be at least 18 years of age and willing to remain hospitalized during randomized therapy. The primary inclusion criteria were symptomatic lower-extremity deep venous thrombosis confirmed by venography or ultrasonography (if venography was inconclusive), symptomatic pulmonary embolism confirmed by high-probability ventilation–perfusion scanning, or positive pulmonary angiography with confirmation of lower-extremity deep venous thrombosis. All eligible patients underwent baseline lung scanning or angiography. Exclusion criteria were more than 24 hours of previous treatment with heparin or warfarin; need for thrombolytic therapy; known hemorrhagic risk, including active hemorrhage, active intestinal ulcerative disease, known angiodysplasia, or eye, spinal, or central nervous system surgery within the previous month; renal insufficiency (serum creatinine concentration > 180 μmol/L [2.03 mg/dL]); severe hepatic insufficiency; allergy to heparin, protamine, porcine products (both heparin and enoxaparin are derived from pork intestinal mucosa), iodine, or contrast media; history of heparin-associated thrombocytopenia or heparin- or warfarin-associated skin necrosis; treatment with other investigational therapeutic agents within the previous 4 weeks; inferior vena cava interruption; or known pregnancy or lactation.

Treatments

Within each center, consecutive eligible patients were randomly assigned sequentially to one of three treatment groups. Randomization was done without stratification in blocks of six, according to ascending randomization number. The numbers were affixed to sealed treatment kits that contained study medication and were provided by the study sponsor. Patients assigned to enoxaparin received a weight-adjusted subcutaneous dose. Two blinded regimens were tested: 1.0 mg/kg of body weight twice daily or 1.5 mg/kg once daily. Several clinical trials have shown the twice-daily regimen to be effective and safe (16, 23, 24). The once-daily dosage was chosen on the basis of results of pharmacokinetic studies that showed it to have a suitable pharmacokinetic profile in healthy volunteers and to be well tolerated in the treatment of patients with venous thromboembolism (25, 26). In these previous studies, therapeutic anti–factor Xa levels were present for up to

18 hours in both volunteers and patients, and measurable levels were present for up to 24 hours. A total of three injections, study drug and placebo, were given each day to maintain blinding for volume of solutions and frequency of administration. Patients assigned to the nonblinded unfractionated heparin group received an intravenous bolus dose and infusion on the basis of an approved institution-specific nomogram. In most cases, administration was as follows: Six hours after the initial bolus, the activated partial thromboplastin time was measured and the dose was adjusted to maintain the specified value, which was between 55 and 80 seconds in most centers (4–7). Activated partial thromboplastin time was measured at least daily during unfractionated heparin treatment. Enoxaparin and heparin treatments were continued for at least 5 days, and warfarin was started within 72 hours of initial study drug administration. Forty-three patients received phenprocoumon in place of warfarin sodium. Prothrombin time was measured daily, and patients could be discharged from the hospital after the international normalized ratio was found to be between 2.0 and 3.0 on 2 consecutive days. Oral anticoagulation was continued for at least 3 months.

Study Assessments

Observers who were aware of treatment assignment assessed patients daily and monthly during the 3-month follow-up for worsening or recurrence of deep venous thrombosis or pulmonary embolism, hemorrhage, adverse events, changes in concomitant medications and adequacy of warfarin use, and warfarin adherence. For patients receiving unfractionated heparin, adherence was defined as an activated partial thromboplastin time within or above the therapeutic range on the second day of treatment. For patients receiving enoxaparin, adherence was defined as at least 10 doses of study medication given with no dosing errors. Adherence to warfarin therapy was defined as having at least one international normalized ratio value greater than or equal to 2.0 between day 4 and the last dose of study treatment during the initial treatment period. These definitions of treatment adherence were established before the analysis of the study outcomes.

Efficacy Analysis

The efficacy analysis was performed on two study samples: all treated patients, who received at least one dose of study medication, and evaluable patients, which excluded all patients who met at least one of the criteria for nonevaluability. These criteria were no confirmed deep venous thrombosis at baseline, insufficient study therapy, placement of an inferior vena cava filter, two random assignments, and no 3-month follow-up. Insufficient study therapy was defined as one or more missed enoxaparin doses among at least eight consecutive enoxaparin doses or less than 4 consecutive days of heparin infusion. The definition of insufficient study therapy was established before analysis of study outcomes. These two study samples were analyzed to strengthen the conclusion of equivalence among the treatment groups. The homogeneity of the results of the two analyses is considered to be more supportive of the conclusion of equivalence than the results of either analysis alone.

Primary clinical end points were recurrent deep venous thrombosis or pulmonary embolism within 3 months of randomization. Patients with symptoms of recurrent thrombosis underwent confirmatory testing with venography, ultrasonography, or both. Patients presenting with signs or symptoms of pulmonary embolism underwent lung perfusion scanning, pulmonary angiography, or both. Clinical symptoms and supportive findings on objective tests; extension of existing thrombi or new thrombi for venography, angiography, or ultrasonography; or high-probability defect patterns on perfusion scans were required to confirm recurrent thrombosis.

Prespecified subgroup analyses were performed on the basis of patient demographic characteristics, physical characteristics, and risk factors for and location of venous thromboembolic disease at presentation. We analyzed subgroups according to age; sex; weight; predefined risk factors, including obesity (defined as body mass index > 26.9 kg/m^2 for women and > 27.2 kg/m^2 for men); history of deep venous thrombosis; history of pulmonary embolism; prolonged immobilization; varicose veins; congestive heart failure; chronic obstructive pulmonary disease; malignant conditions; use of oral estrogen-containing medication; thrombophilia; recent chemotherapy or radiation therapy; cancer; recent surgery; recent trauma; thrombus in the iliac vein; country; and investigator. Multivariate analysis was performed by using the prespecified variables included in the univariate subgroup analysis as candidate variables.

Table 1. **Patient Evaluability and Completion Status**

Variable	Unfractionated Heparin Group (n = 290)	Once-Daily Enoxaparin Group (n = 298)	Twice-Daily Enoxaparin Group (n = 312)	Total (n = 900)
	← n (%) →			
Evaluability				
Patients randomly assigned to treatment groups	290 (100)	298 (100)	312 (100)	900 (100)
Evaluable patients	235 (81.0)	247 (82.9)	258 (82.7)	740 (82.2)
Nonevaluable patients	55 (19.0)	51 (17.1)	54 (17.3)	160 (17.8)
Deep venous thrombosis not confirmed by venography	17 (5.9)	17 (5.7)	22 (7.1)	56 (6.2)
No 3-month follow-up visit	6 (2.1)	7 (2.3)	6 (1.9)	19 (2.1)
Inferior vena cava filter placement	0 (0)	0 (0)	2 (0.1)	2 (0.2)
Randomly assigned twice	0 (0)	1 (0.3)	1 (0.3)	2 (0.2)
Insufficient or incorrect study treatment	32 (11.0)	26 (8.7)	23 (7.4)	81 (9.0)
Completion status				
Data missing	1 (0.3)	0 (0)	1 (0.3)	2 (0.2)
Completed	223 (77.2)	264 (88.6)	275 (88.4)	762 (84.9)
Discontinued*	66 (22.8)	34 (11.4)	36 (11.6)	136 (15.1)
Adverse event	6 (2.1)	9 (3.0)	5 (1.6)	20 (2.2)
Deviation from protocol	39 (13.5)	16 (5.4)	20 (6.4)	75 (8.4)
Other	21 (7.3)	9 (3.0)	11 (3.5)	41 (4.6)

* Situations in which study drug treatment was stopped by the investigator but the patient was still followed for 3 months, as required by the protocol.

Safety Analyses

Safety analyses were performed on all patients to capture all adverse safety events regardless of adherence to protocol. This approach allows the largest population exposed to study medication to be analyzed for safety. Patients were assessed for clinically overt major or minor hemorrhage. Major hemorrhage was defined as being associated with at least one of the following: a decrease in hemoglobin level of at least 20 g/L; need for transfusion of at least two units of blood; retroperitoneal, intracranial, or intraocular bleeding; other associated serious clinical event; need for surgical or medical intervention; or death. Minor hemorrhages were other hemorrhages that were clinically overt but did not meet the criteria for major hemorrhage.

Complete blood count, leukocyte differential, platelet count, prothrombin time, activated partial thromboplastin time, serum or plasma tests (including alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, creatinine, and potassium), and occult hemorrhage screening of urine and stools were carried out at study entry and on a scheduled basis throughout the study. We also recorded any undesirable events, regardless of relation to a drug, that occurred during the use of a drug, including any side effect, injury, toxicity, or sensitivity reaction.

Statistical Analysis

The primary efficacy variable was occurrence of symptomatic recurrent venous thromboembolism within 3 months after randomization. The equivalence of each enoxaparin treatment to the unfractionated heparin treatment was assessed separately. In addition, after the primary study outcomes had been analyzed, the equivalence of the two enoxaparin treatment groups was assessed. We calculated the sample size by using a 95% CI method of treatment difference for evaluating therapeutic equivalence (27) and a type 1 error rate of 5%. A 10% incidence of recurrent venous thromboembolic events was assumed for each treatment on the basis of outcomes reported in contemporaneous clinical studies (14, 15). With 190 evaluable patients in each treatment group, the power was 0.9 for concluding that the 95% CI of the enoxaparin–heparin treatment difference was within −10% to 10% limits; that is, that enoxaparin was not worse than heparin by more than 10% (27–29). A total of 900 patients were enrolled to ensure sufficient sample sizes for the evaluable patient analyses. The treatment effect was evaluated by using univariate and multivariate analyses. We identified "predictive" factors of recurrent venous thromboembolism among the subgroups defined in the previous section by using univariate and multivariate analyses of those with a univariate P value

less than 0.2. In addition, a similar analysis was used for enoxaparin-treated patients to evaluate whether one or a few of these factors would discriminate the two enoxaparin regimens. A two-tailed Fisher exact test at a 5% level of significance was used to compare incidence of hemorrhagic episodes and adverse events. Descriptive statistics were used to summarize baseline characteristics, changes in laboratory variables, and adverse events.

Role of the Funding Source

Aventis Pharmaceuticals, Inc., Bridgewater, New Jersey, and Aventis Pharma SA, Antony, France (formerly known as Rhône-Poulenc Rorer Pharmaceuticals, Collegeville, Pennsylvania, and Rhône-Poulenc Rorer SA, Antony, France) performed and sponsored the study.

RESULTS

Patient Characteristics

Of the 5254 patients who were screened for enrollment, 4354 patients were not eligible to participate. Of these 4354, 1250 did not have clinically suspected venous thromboembolic disease confirmed by a diagnostic test, 720 were already receiving treatment for venous thromboembolic disease, and 1271 were excluded according to the inclusion or exclusion criteria. In addition, 110 patients withdrew consent before randomization and 1003 patients had no available information about reasons for ineligibility.

Nine hundred patients were randomly assigned to treatment groups; 290 received unfractionated heparin, 298 received enoxaparin once daily, and 312 received enoxaparin twice daily (**Table 1**). Of these, 223 of those receiving unfractionated heparin (77.2%), 264 of those who received once-daily enoxaparin (88.6%), and 275 of those who received twice-daily enoxaparin completed treatment (88.4%). One hundred thirty-six patients were considered to have discontinued therapy with study medication prematurely (**Table 1**). Treatment regimen–related deviations from the protocol (usually due to insufficient dosage or duration) occurred in 31 patients receiving unfractionated heparin, compared with only 11 patients receiving once-daily enoxaparin and 12 patients receiving twice-daily enoxaparin. Seven hundred forty patients (82.2%) were evaluable. The most common reason for nonevaluability was insufficient administration of the study drug (inadequate duration of

Table 2. **Patient Characteristics and Risk Factors for Venous Thromboembolism for All Treated Patients**

Characteristic or Risk Factor	Unfractionated Heparin Group (n = 290)	Once-Daily Enoxaparin Group (n = 298)	Twice-Daily Enoxaparin Group (n = 312)	Total (n = 900)
Characteristic				
Mean age (range), *y*	60.9 (18.0–91.0)	60.7 (19.0–91.0)	60.7 (18.0–92.0)	60.7 (18.0–92.0)
Sex (male/female), *n/n*	150/140	161/137	181/131	492/408
Mean weight (range), *kg*	78.5 (41–146)	80.0 (44–151)	81 (47–155)	79.9 (41–155)
Deep venous thrombosis at baseline confirmed by venography or ultrasonography, *n*	275	286	298	859
Proximal deep venous thrombosis, *n (%)*	222 (80.7)	235 (82.2)	237 (79.5)	694 (80.8)
Iliac vein thrombosis	22 (8.0)	23 (8.0)	21 (7.0)	66 (7.7)
Distal deep venous thrombosis	51 (18.5)	46 (16.1)	57 (19.1)	154 (17.9)
Confirmed pulmonary embolism, *n (%)**	88 (30.3)	94 (31.5)	105 (33.7)	287 (31.9)
Risk factors, *n (%)*†				
Obesity	122 (42.1)	137 (46.0)	146 (46.8)	405 (45.0)
History of deep venous thrombosis or pulmonary embolism (excluding present episode)	77 (26.6)	66 (22.1)	74 (23.7)	217 (24.1)
Prolonged immobilization	38 (13.1)	38 (12.8)	40 (12.8)	116 (12.9)
Varicose veins	41 (14.1)	45 (15.1)	52 (16.7)	138 (15.3)
Congestive heart failure	9 (3.1)	12 (4.0)	8 (2.6)	29 (3.2)
Chronic obstructive pulmonary disease	25 (8.6)	19 (6.4)	28 (9.0)	72 (8.0)
Estrogen-containing medication	26 (9.0)	21 (7.0)	25 (8.0)	72 (8.0)
Cancer	45 (15.5)	49 (16.4)	47 (15.1)	141 (15.7)
Recent surgery	55 (19.0)	57 (19.1)	65 (20.8)	177 (19.7)

* Pulmonary embolism was diagnosed on the basis of a high-probability lung scan, according to PIOPED (Prospective Investigation of Pulmonary Embolus Diagnosis) criteria. Patients with pulmonary embolism were also included in the summary of patients with confirmed deep venous thrombosis at baseline.
† Obesity was defined as a body mass index > 26.9 kg/m^2 for women and > 27.2 kg/m^2 for men. All other risk factors were obtained from medical history.

Table 3. **Recurrence of Venous Thromboembolism and Attendant Risk Factors for All Treated Patients and Evaluable Patients**

Clinical Outcome	Unfractionated Heparin Group	Once-Daily Enoxaparin Group	Twice-Daily Enoxaparin Group	Total
All treated patients, *n*	290	298	312	900
Recurrent venous thromboembolic event, *n (%)**	12 (4.1)	13 (4.4)	9 (2.9)	34 (3.8)
Deep venous thrombosis (lower extremity), *n*	7	11	6	24
Deep venous thrombosis (upper extremity), *n*	1	0	1	2
Pulmonary embolism, *n*	1	1	2	4
Deep venous thrombosis and pulmonary embolism, *n*	3	1	0	4
Evaluable patients, *n*	235	247	258	740
Recurrent venous thromboembolic event, *n (%)*†	10 (4.3)	11 (4.5)	8 (3.1)	29 (3.9)
Risk factors for recurrent thromboembolism for all treated patients (occurrences/patients at baseline), *n/n (%)*				
Obesity	3/122 (2.5)	10/137 (7.3)	5/146 (3.4)	18/405 (4.4)
Pulmonary embolism at baseline	4/88 (4.5)	5/94 (5.3)	5/105 (4.8)	14/287 (4.9)
Asymptomatic	0/44 (0.0)	1/54 (1.9)	2/59 (3.4)	3/157 (1.9)
Symptomatic	4/44 (9.1)	4/40 (10.0)	3/46 (6.5)	11/130 (8.5)
Cancer	3/45 (6.7)	6/49 (12.2)	3/47 (6.4)	12/141 (8.5)

* Treatment difference was 0.2% (95% CI, −3.04% to 3.49%) for once-daily enoxaparin compared with heparin and −1.2% (CI, −4.2% to 1.7%) for twice-daily enoxaparin compared with heparin.
† Treatment difference was −0.2% (CI, −3.45% to 3.84%) for once-daily enoxaparin compared with heparin and −0.6% (CI, −4.49% to 2.18%) for twice-daily enoxaparin compared with heparin.

heparin infusion or number of enoxaparin injections administered).

Patient characteristics are summarized in **Table 2**. No clinically relevant differences were seen among the three treatment groups in age, sex, ethnicity, height, weight, risk factors for venous thromboembolic disease, or location of thrombosis at presentation. Most patients ($n = 694$ [80.8%]) had proximal lower-extremity deep venous thrombosis. Of these, 66 (7.7%) had iliac vein involvement. A total of 287 patients had documented pulmonary embolism and lower-extremity deep venous thrombosis at presentation. Baseline characteristics for the evaluable group were similar to those of all treated patients. Treatment groups were similar with respect to all a priori risk factors.

The number of patients with prerandomization heparin exposure (43.8%) and the duration of postrandomization treatment (7.1 days) were similar in the three treatment groups. The mean dose of heparin administered on the second day of treatment was 29 050 units. Seventy of 290 heparin-treated patients (24.1%) did not achieve an activated partial thromboplastin time above the lower limit of the therapeutic range on the second day of treatment; accordingly, adherence was verified for 220 (75.9%) of 290 heparin-treated patients. Adherence, defined as receipt of at least 10 doses of enoxaparin without error, was verified for 249 of 298 patients who received once-daily enoxaparin (83.6%) and for 256 of 312 patients who received twice-daily enoxaparin (85.3%).

Recurrent Venous Thromboembolism

Among all treated patients, venous thromboembolism recurred in 4.1% of the heparin group (12 of 290 patients), 4.4% of the once-daily enoxaparin group (13 of 298 patients), and 2.9% of the twice-daily enoxaparin group (9 of 312 patients) (**Table 3**). The 95% CIs for the absolute treatment differences in occurrence of recurrent venous thromboembolism were −3.04% to 3.49% for once-daily enoxaparin compared with heparin and −4.2% to 1.7% for heparin compared with twice-daily enoxaparin. Both enoxaparin treatments met preestablished criteria for efficacy equivalent to that of unfractionated heparin. The comparison of the two enoxaparin treatment groups also met preestablished criteria for efficacy equivalence (CIs for the treatment difference, −1.5% to 4.5%).

Among evaluable patients, venous thromboembolic disease occurred in 10 of those receiving unfractionated heparin (4.3%). Eleven patients receiving once-daily enoxaparin (4.5%) and 8 patients receiving twice-daily enoxaparin (3.1%) developed recurrent venous thromboembolism. The 95% CIs for the absolute treatment differences in evaluable patients were −3.45% to 3.84% for once-daily enoxaparin and −4.49% to 2.18% for twice-daily enoxaparin compared with heparin. These

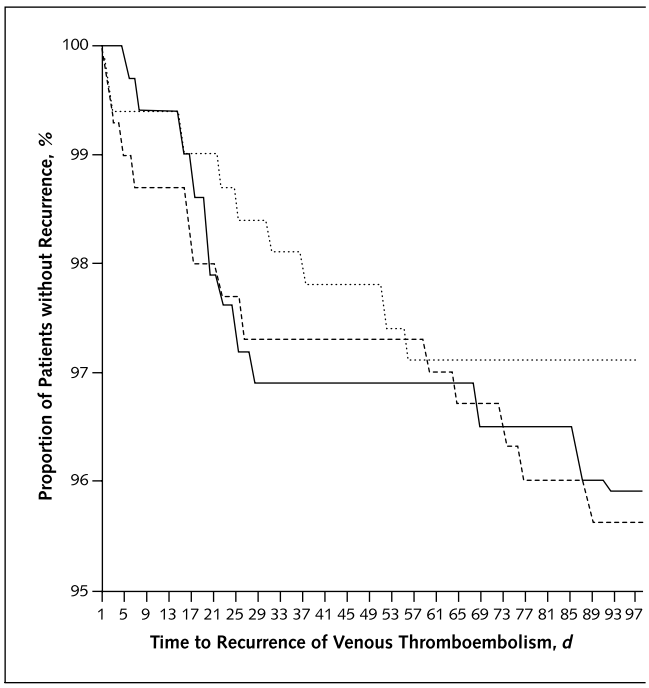
findings also met the protocol-specified definition for treatment equivalence.

Exploratory subgroup analyses (univariate and multivariate) indicated that cancer (odds ratio, 3.7 [CI, 1.27 to 11]) and symptomatic pulmonary embolism (odds ratio, 3.4 [CI, 1.55 to 7.3]) were significant risk factors for recurrence, regardless of treatment. When we considered only enoxaparin-treated patients, obesity was also a significant risk factor (odds ratio, 4.0 [CI, 1.08 to 15]). In addition, in obese patients, a statistically nonsignificant trend toward recurrence with once-daily enoxaparin was observed. Groups did not differ in recurrence of venous thromboembolism among patients who presented with pulmonary embolism (**Table 3**). The **Figure** presents the time to first recurrence for all treated patients.

Safety Results

Treatment groups did not differ significantly in safety profile (**Table 4**). We found no significant or clinically relevant differences among groups in the incidence of all and major hemorrhagic complications or transfusion requirements. Major hemorrhage occurred in 6 patients receiving unfractionated heparin (2.1%), 5 patients receiving once-daily enoxaparin (1.7%) (absolute difference, −0.4 percentage point [CI, −2.6 to 1.8 percentage points]), and 4 patients receiving twice-daily enoxaparin (1.3%) (absolute difference, −0.8 percentage point [CI, −2.9 to 1.3 percentage points]).

Figure. **Product-limit analysis of time to first recurrence of a venous thromboembolic event among all treated patients.**



Dotted line represents twice-daily enoxaparin; solid line represents unfractionated heparin; dashed line represents once-daily enoxaparin.

The total number of deaths in each treatment group was similar: 9 in the heparin group (3.1%), 11 in the once-daily enoxaparin group (3.7%) (absolute differ-

Table 4. **Death, Hemorrhage, and Thrombocytopenia for All Treated Patients**

Variable	Unfractionated Heparin Group (n = 290)	Once-Daily Enoxaparin Group (n = 298)	Twice-Daily Enoxaparin Group (n = 312)	Total (n = 900)
	←	*n (%)*		→
Deaths during study period*	9 (3.1)	11 (3.7)	7 (2.2)	27 (3.0)
Associated with pulmonary embolism	2 (0.7)	1 (0.3)	2 (0.6)	5 (0.6)
Hemorrhage	0 (0)	1 (0.3)	0 (0)	2 (0.2)
Associated with hemorrhage	2 (0.7)	4 (1.3)	0 (0)	6 (0.7)
Other	9 (3.1)	11 (3.7)	7 (2.2)	27 (3.0)
Deaths during heparin or enoxaparin treatment	0 (0)	2 (0.7)	0 (0)	2 (0.2)
Hemorrhage	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Other	0 (0)	1 (0.3)	0 (0)	1 (0.1)
Any hemorrhagic episode during treatment period†	39 (13.4)	46 (15.4)	54 (17.3)	139 (15.4)
Major hemorrhage‡	6 (2.1)	5 (1.7)	4 (1.3)	15 (1.7)
Thrombocytopenia during treatment period§	4 (1.4)	5 (1.7)	7 (2.2)	16 (1.8)

* Study period includes both the initial treatment period and the entire 3-month follow-up period. Treatment difference was 0.6 percentage point (95% CI, −2.3 to 3.5 percentage points) for once-daily enoxaparin compared with heparin and −0.9 percentage point (CI, −3.5 to 1.7 percentage points) for twice-daily enoxaparin compared with heparin.
† Treatment difference was −2.0 percentage points (CI, −3.7 to 7.7 percentage points) for once-daily enoxaparin compared with heparin and 2.0 percentage points (CI, −1.9 to 9.6 percentage points) for twice-daily enoxaparin compared with heparin.
‡ Treatment difference was −0.4 percentage point (CI, −2.6 to 1.8 percentage points) for once-daily enoxaparin compared with heparin and −0.8 percentage point (CI, −2.9 to 1.3 percentage points) for twice-daily enoxaparin compared with heparin.
§ Thrombocytopenia was defined as platelet count $< 100 \times 10^9$ cells/L.

ence, 0.6 percentage point [CI, −2.3 to 3.5 percentage points]), and 7 in the twice-daily enoxaparin group (2.2%) (absolute difference, −0.9 percentage point [CI, −3.5 to 1.7 percentage points]). These differences are not clinically relevant. Two patients receiving once-daily enoxaparin died during the initial treatment period: 1 on day 4 of a fatal retroperitoneal hemorrhage and one on day 2 of complications of chronic obstructive pulmonary disease, pulmonary hypertension, and associated pulmonary embolus. No patient deaths during the initial treatment period were reported in the other treatment groups. Although no deaths were caused directly by pulmonary embolus, 2 deaths in the heparin group, 2 deaths in the once-daily enoxaparin group, and 2 deaths in the twice-daily enoxaparin group were associated with it.

The incidence of thrombocytopenia, defined as a platelet count equal to or less than 100×10^9 cells/L, was similar in the three treatment groups. Only one case of immune thrombocytopenia occurred in any of the treatment groups. The affected patient was receiving twice-daily enoxaparin and had received unfractionated heparin the day before randomization.

DISCUSSION

Our study demonstrated that enoxaparin administered subcutaneously once or twice daily was as effective as unfractionated heparin in preventing recurrence of venous thromboembolic disease. The protocol-specified definition of equivalence was achieved by both enoxaparin regimens for all treated patients and evaluable patients. Our equivalence definition specified a 10% upper limit for the 95% CI of the observed treatment difference. This limit was selected on the basis of existing regulatory guidelines for the conduct of trials involving treatment equivalency when treatment success rates of greater than 90% are anticipated (28, 29). Given the number of treatment failures in our study, an upper limit confidence boundary of 5% or less seems justifiable. Such limits have been used in similar recently reported studies (14, 18, 20, 30, 31). We found that the observed lower-than-expected incidence of recurrence and the smaller-than-expected absolute treatment difference favored demonstration of equivalence as defined by the protocol. Although the absolute treatment difference between the twice-daily enoxaparin regimen and the unfractionated heparin regimen was 1.25%, corresponding to a 30% relative risk reduction in favor of enoxaparin, we cannot draw conclusions other than those relating to equivalence due to the study design and study sample.

The results seen with once-daily enoxaparin treatment are similar to those reported for once-daily treatment with other low-molecular-weight heparins. In those studies, daily per-kilogram dosages of approximately 200 mg/kg (dalteparin and nadroparin) and 175 anti–factor Xa units of body weight (tinzaparin) were used (14, 19, 20). We used a daily per-kilogram dosage of enoxaparin that was equivalent to approximately 150 anti–factor Xa units.

Prespecified subgroups of patients with cancer and symptomatic pulmonary embolism were more likely to develop recurrence regardless of treatment group. Subgroup analysis of obese patients and patients with cancer suggested that once-daily enoxaparin may be more likely to be associated with recurrent thromboembolism than twice-daily enoxaparin, although these findings were not statistically significant. The number of patients randomly assigned in our study was too small to allow conclusions to be drawn regarding efficacy outcomes in patient subgroups. Because most published clinical trials do not present the results of subgroup analyses, we cannot compare our findings with those of other studies.

The analysis of 287 patients with confirmed pulmonary embolism at study entry (32%), 130 of whom had symptoms, suggests that enoxaparin may be as effective as unfractionated heparin in the treatment of pulmonary embolism. These results support the findings of previous studies of other low-molecular-weight heparins (17, 18, 32). One hundred ninety-five patients (23%) had symptoms consistent with pulmonary embolism at the time of randomization. Of these, 130 (14.4%) had this diagnosis confirmed, mainly by high-probability lung scan. Since most patients with abnormal but non–high-probability lung scans did not undergo pulmonary angiography, it is likely that more than 32% of patients presented with pulmonary embolism, mainly asymptomatic (33). Patients with documented symptomatic pulmonary embolism did not have a higher recurrence rate than those without pulmonary embolism. Although our study was not primarily designed to assess treatment of pulmonary embolism, the results are consistent with those of other studies (17, 18).

All treatments were well tolerated. The only apparent differences among treatments were related to injec-

tion-site hemorrhage with enoxaparin. No trends were apparent for adverse events that led to withdrawal from the study. The incidence of thrombocytopenia was low and was similar to that in previous studies of unfractionated and low-molecular-weight heparin (34, 35). Enoxaparin has been reported to be associated with a lower incidence of this adverse effect than unfractionated heparin (36).

The unfractionated heparin group had more patient discontinuations due to deviations from the protocol, mostly in those who received less than 4 full days of therapy or did not achieve the target activated partial thromboplastin time on the second day of treatment. The proportion of patients in the unfractionated heparin group who were nonadherent on day 2 of randomized therapy (25%) does not differ from that reported in other studies (37–39). The lower adherence rate in the heparin group reflects intrinsic problems in successfully administering this type of therapy.

Our study had several limitations. Overall, 5254 patients were screened to enroll 900 patients. When 1250 patients without venous thromboembolic disease were excluded, approximately 22% of patients with venous thromboembolic disease qualified for study entry. However, in two similar clinical trials, 29.5% and 22.4% of patients screened were subsequently enrolled in the trials. As discussed previously, the specified definition of equivalence—a 95% CI boundary of 10% for treatment difference—is larger than current norms.

Subcutaneous dosage regimens, such as the once- and twice-daily regimens used in this study, facilitate outpatient treatment of deep venous thrombosis, have obvious resource implications, and have been shown to be feasible in patients with proximal deep venous thrombosis who do not require hospitalization (30, 31). A recent clinical trial comparing subcutaneous twice-daily enoxaparin (administered mainly to outpatients) with intravenous unfractionated heparin (administered to hospital patients) in the treatment of acute proximal deep venous thrombosis showed low and similar rates of recurrent venous thromboembolism and major hemorrhage in both groups (30). Similar findings were reported for nadroparin (31).

We demonstrated that subcutaneous enoxaparin, 1.0 mg/kg twice daily or 1.5 mg/kg once daily, is as effective and safe as intravenously infused unfractionated heparin in the treatment of patients with acute venous thromboembolic disease.

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APPENDIX

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