

# Comparison of Fixed-Dose Weight-Adjusted Unfractionated Heparin and Low-Molecular-Weight Heparin for Acute Treatment of Venous Thromboembolism

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**D**EEP VEIN THROMBOSIS AND pulmonary embolism are usually treated with a minimum of 5 days of heparin therapy overlapped with warfarin, which is continued for at least 3 months.<sup>1</sup> Unfractionated heparin, given by continuous intravenous infusion with ongoing dose adjustment in response to measurements of the activated partial thromboplastin time (APTT) has been the standard approach to initial treatment. Low-molecular-weight heparin administered subcutaneously in fixed weight-adjusted doses is gradually replacing unfractionated heparin.<sup>1</sup> Subcutaneous administration without laboratory monitoring makes low-molecular-weight heparin suitable for outpatient treatment, which,

For editorial comment see p 991.

**Context** When unfractionated heparin is used to treat acute venous thromboembolism, it is usually administered by intravenous infusion with coagulation monitoring, which requires hospitalization. However, subcutaneous administration of fixed-dose, weight-adjusted, unfractionated heparin may be suitable for inpatient and outpatient treatment of venous thromboembolism.

**Objective** To determine if fixed-dose, weight-adjusted, subcutaneous unfractionated heparin is as effective and safe as low-molecular-weight heparin for treatment of venous thromboembolism.

**Design, Setting, and Patients** Randomized, open-label, adjudicator-blinded, non-inferiority trial of 708 patients aged 18 years or older with acute venous thromboembolism from 6 university-affiliated clinical centers in Canada and New Zealand conducted from September 1998 through February 2004. Of the randomized patients, 11 were subsequently excluded from the analysis of efficacy and 8 from the analysis of safety.

**Interventions** Unfractionated heparin was administered subcutaneously as an initial dose of 333 U/kg, followed by a fixed dose of 250 U/kg every 12 hours (n=345). Low-molecular-weight heparin (dalteparin or enoxaparin) was administered subcutaneously at a dose of 100 IU/kg every 12 hours (n=352). Both treatments could be administered out of hospital and both were overlapped with 3 months of warfarin therapy.

**Main Outcome Measures** Recurrent venous thromboembolism within 3 months and major bleeding within 10 days of randomization.

**Results** Recurrent venous thromboembolism occurred in 13 patients in the unfractionated heparin group (3.8%) compared with 12 patients in the low-molecular-weight heparin group (3.4%; absolute difference, 0.4%; 95% confidence interval, -2.6% to 3.3%). Major bleeding during the first 10 days of treatment occurred in 4 patients in the unfractionated heparin group (1.1%) compared with 5 patients in the low-molecular-weight heparin group (1.4%; absolute difference, -0.3%; 95% confidence interval, -2.3% to 1.7%). Treatment was administered entirely out of hospital in 72% of the unfractionated heparin group and 68% of the low-molecular-weight heparin group.

**Conclusion** Fixed-dose subcutaneous unfractionated heparin is as effective and safe as low-molecular-weight heparin in patients with acute venous thromboembolism and is suitable for outpatient treatment.

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despite the higher cost of low-molecular-weight heparin compared with unfractionated heparin, greatly reduces health care costs.<sup>1,2</sup>

Although current practice is to administer unfractionated heparin by intravenous infusion and to adjust the dose based on APTT results, this may not be necessary or optimal. Trials that compared administration of unfractionated heparin by subcutaneous injections with intravenous infusion for initial treatment of venous thromboembolism have found that the subcutaneous route was at least as effective and safe.<sup>3,4</sup>

Whether given subcutaneously or intravenously, the dose of unfractionated heparin was adjusted in response to APTT values in previous studies. However, APTT measurements are of uncertain clinical relevance in patients who are being treated with heparin because they differ depending on the reagents and coagulometers used for the test,<sup>5</sup> they are increased by concomitant warfarin therapy,<sup>6</sup> and they have an uncertain relationship to efficacy and safety. Although some analyses have shown an association between low APTT values during heparin therapy and risk of recurrent venous thromboembolism, the studies included in these analyses often started with a dose of heparin that was lower than is currently recommended.<sup>7-9</sup> In analyses that only included studies in which patients received currently recommended initial doses of heparin, there was no association between low APTT values and recurrent venous thromboembolism.<sup>10-12</sup> Similarly, there is no clear association between high APTT values and risk of bleeding, independent of the dose of heparin that is administered.<sup>13,14</sup> Furthermore, earlier studies that used heparin to treat venous thromboembolism did not choose an initial heparin dose that was proportional to patient weight, whereas weight-based dosing of initial heparin therapy is now recommended.<sup>12,15</sup>

If unfractionated heparin could be administered by subcutaneous injection

without coagulation monitoring, it would make it easier to use and suitable for outpatient treatment of venous thromboembolism and would provide a less expensive alternative to low-molecular-weight heparin. We therefore performed a randomized trial comparing unfractionated heparin with low-molecular-weight heparin for initial treatment of venous thromboembolism. Both drugs were given subcutaneously, twice daily, in fixed weight-adjusted doses. Our hypothesis was that, used in this way, unfractionated heparin would be as effective and safe as low-molecular-weight heparin.

## METHODS

### Study Patients

Patients aged 18 years or older with newly diagnosed deep vein thrombosis of the legs or pulmonary embolism were potentially eligible. Patients could have symptomatic deep vein thrombosis or asymptomatic deep vein thrombosis that was identified by screening of high-risk postoperative patients. Symptomatic proximal deep vein thrombosis was diagnosed by compression ultrasonography or by venography.<sup>16</sup> Symptomatic deep vein thrombosis that was confined to the calf veins, as well as all asymptomatic deep vein thromboses, required diagnosis by contrast venography.<sup>16</sup> Pulmonary embolism was symptomatic and objectively diagnosed by a high-probability ventilation-perfusion lung scan, by nondiagnostic findings on lung scan accompanied by diagnostic findings for deep vein thrombosis, or by presence of a segmental or more proximal pulmonary artery filling defect on computed tomographic angiography.<sup>17</sup>

Patients who met the inclusion criteria were ineligible if they had a contraindication to subcutaneous therapy, such as shock or major surgery in the past 48 hours, had active bleeding, had a life expectancy of less than 3 months, had already received acute treatment for venous thromboembolism for more than 48 hours, were receiving long-

term anticoagulant therapy, had a contraindication to heparin or to radiographic contrast, had a creatinine level of greater than 200  $\mu\text{mol/L}$  (2.3 mg/dL), were pregnant, were enrolled in a competing study, or were unable to have follow-up assessments because of geographic inaccessibility. There was no exclusion criterion for patient weight. Patients provided written informed consent, and the study was approved by the institutional review boards of all participating clinical centers.

### Randomization and Treatment

Randomization was computer-generated with block sizes of 2 or 4, was stratified by clinical center, and was performed by having clinical centers telephone an automated centralized system. Patients were assigned to initial treatment with open-label unfractionated heparin (experimental group) or low-molecular-weight heparin (control group), each administered subcutaneously, twice daily, in doses that were determined by patient weight, and without subsequent use of coagulation tests to modify those doses (measurement of APTT or heparin levels by the clinical centers was prohibited) (FIGURE). Unfractionated heparin was given as a first dose of 333 U/kg, followed by subsequent doses of 250 U/kg (25 000 U/mL; multidose vials).<sup>1,18</sup>

This regimen was based on 3 factors: a requirement for a 10% higher dose when heparin is given subcutaneously, twice daily, compared with when heparin is given intravenously by continuous infusion<sup>12,19</sup>; acceptance that intravenously heparin should initially be given as a weight-based bolus of 80 U/kg, followed by an infusion of 18 U/kg per hour, when treating venous thromboembolism<sup>12,15</sup>; and results of a preliminary study that shows that therapeutic levels of anticoagulation would rapidly be achieved with the current subcutaneous regimen.<sup>18</sup> Low-molecular-weight heparin was given at 100 IU/kg for all doses (10 000 IU/mL; multidose vials). Subject to local availability, dalteparin or enoxaparin were the low-molecular-weight hepa-

rin preparations that were used. Unfractionated heparin or low-molecular-weight heparin was given for at least 5 days and until the international normalized ratio was 2.0 or higher for 2 consecutive days. Warfarin was usually started the same day as heparin and was continued for a minimum of 3 months with doses adjusted to achieve an international normalized ratio of between 2.0 and 3.0.

### Follow-up and Outcome Measures

Patients were assessed 3 days, 1 month, and 3 months after initiation of study drug treatment and were told to report immediately if they developed symptoms suggestive of venous thromboembolism or bleeding. Symptoms suggestive of recurrent venous thromboembolism were evaluated using standardized diagnostic testing as described previously.<sup>20</sup> To diagnose recurrent venous thromboembolism, the same criteria that were used to diagnose an initial episode of venous thromboembolism had to be satisfied in segments of the deep veins or pulmonary arteries that were previously unaffected with thrombosis. No routine testing was performed to detect asymptomatic extension or recurrence of thrombosis; therefore, all episodes of recurrent venous thromboembolism were associated with new symptoms. Sudden unexplained deaths were counted as pulmonary embolism. Bleeding was defined as major if it was clinically overt and associated with a decrease in hemoglobin level of at least 2.0 g/dL, involved a need for transfusion of 2 or more units of red blood cells, or involved a critical site (eg, retroperitoneal, intracranial). Platelet counts were not routinely monitored, but it was recorded if heparin therapy was stopped early because of thrombocytopenia. All outcome events and deaths were classified by a central adjudication committee whose members were unaware of treatment assignment.

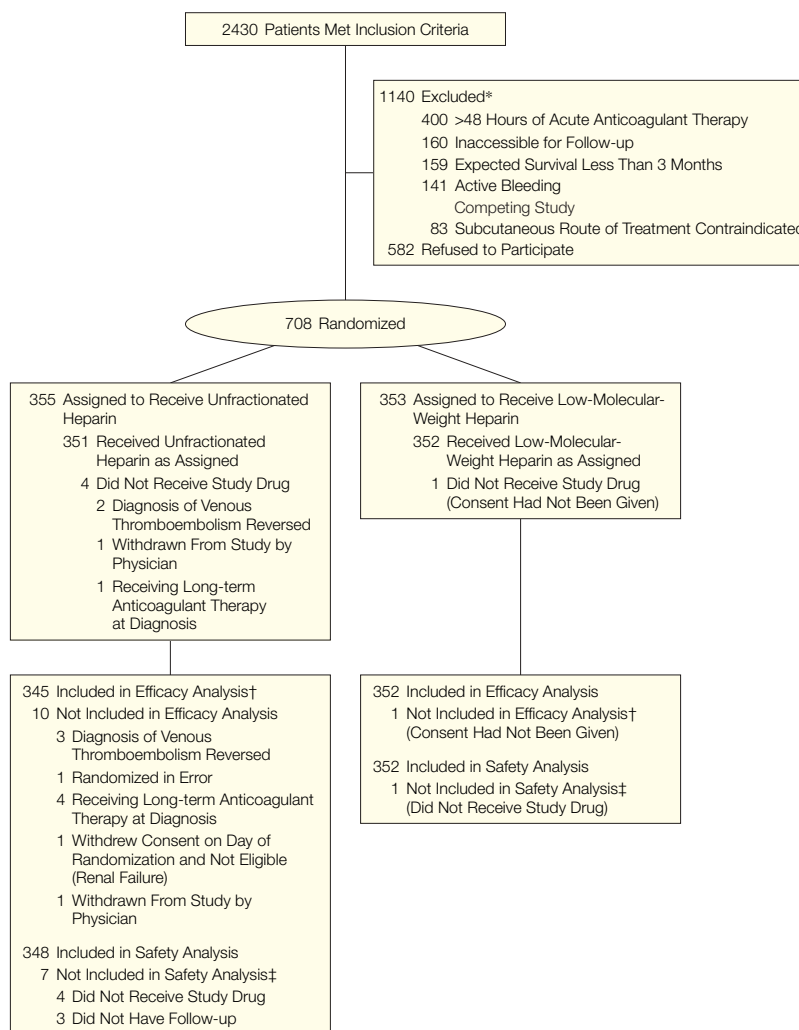
### Statistical Analyses

The trial was designed to determine if initial treatment with fixed-dose unfractionated heparin was as effective as (ie, not inferior to) treatment with low-

molecular-weight heparin. A frequency of recurrent venous thromboembolism of 6% in the 3 months after starting treatment was expected with low-molecular-weight heparin.<sup>21-23</sup> By consensus, arrived at by polling thromboembolism experts who planned to participate, it was decided that the study needed to have a 95% probability of detecting a higher frequency of recurrent thrombosis in the unfractionated heparin group (1-sided  $\alpha = .05$ ) if the

unfractionated heparin regimen was truly associated with a 5% absolute increase in venous thromboembolism. In addition, the study was required to have a 90% power of concluding that unfractionated heparin was not less effective than low-molecular-weight heparin if the 2 treatments were truly equally effective. A study of 824 patients satisfies these requirements.<sup>24</sup> When, in conjunction with a slow rate of enrollment, a blinded interim analysis

**Figure.** Patient Flow



\*Patients could have more than 1 reason for exclusion.

†Among the 11 patients who were not eligible for the analysis of efficacy, no follow-up was performed for 7 patients in the unfractionated heparin group (none known to have had recurrent venous thromboembolism or bleeding), follow-up was completed and was negative for venous thromboembolism and bleeding in the other 3 patients in the unfractionated heparin group, and no follow-up was performed for the 1 patient in the low-molecular-weight heparin group (not known to have had recurrent venous thromboembolism or bleeding).

‡All patients who were not analyzed for safety were also patients who were not analyzed for efficacy.

**Table 1.** Baseline Patient Characteristics\*

Characteristics	Unfractionated Heparin (n = 355)	Low-Molecular-Weight Heparin (n = 353)	Total (N = 708)
Age, mean (SD), y	60 (17)	60 (16)	60 (17)
Weight, mean (SD), kg	82 (19)	84 (19)	83 (19)
Women	173 (49)	147 (42)	320 (45)
Active cancer†	59 (17)	53 (15)	112 (16)
Previous venous thromboembolism†	38 (11)	36 (10)	74 (10)
Qualifying thrombotic event			
Deep vein thrombosis alone	285 (81)	286 (81)	571 (81)
Symptomatic proximal	276	269	545
Symptomatic isolated distal	8	10	18
Asymptomatic proximal or distal	1	7	8
Pulmonary embolism, symptomatic	68 (19)	66 (19)	134 (19)
Location when qualifying event diagnosed			
Outpatient	249 (71)	232 (66)	481 (68)
Inpatient	104 (29)	120 (34)	224 (32)

\*Of the randomized patients, 2 who were allocated to the unfractionated heparin group and 1 who was allocated to the low-molecular-weight heparin group did not have baseline data recorded that could be included in these estimates; none of these 3 patients was included in either the efficacy or safety analyses (see Figure and text). Data are expressed as No. (%) unless otherwise indicated.

†Previous venous thromboembolism or active malignancy was noted for these patients; because this information was not specified for all patients, this number may be an underestimate.

**Table 2.** Treatment Characteristics by Study Group

Characteristics	Unfractionated Heparin (n = 351)*	Low-Molecular-Weight Heparin (n = 352)*†
First dose of study drug, mean (SD)		
Units	26 080 (6640)	8290 (1930)
Units/kg	320 (33)	99 (10)
Second and subsequent doses of study drug, mean (SD)		
Units	20 260 (4570)	8290 (1930)
Units/kg	249 (11)	99 (10)
Days receiving study drug, mean (SD)	6.3 (2.1)	7.1 (2.4)
Location of treatment with study drug, No. (%)		
All patients		
Outpatient entirely	251 (72)	238 (68)
Inpatient entirely	67 (19)	81 (23)
Patients with symptoms of deep vein thrombosis only		
Outpatient entirely	222 (78)	215 (75)
Inpatient entirely	44 (15)	54 (19)
Patients with symptoms of pulmonary embolism		
Outpatient entirely	29 (43)	23 (35)
Inpatient entirely	23 (34)	27 (41)
Days receiving study drug as an outpatient, mean (SD)		
All patients	5.1 (3.0)	5.4 (3.7)
Patients with symptoms of deep vein thrombosis only	5.3 (2.8)	5.8 (3.6)
Patients with symptoms of pulmonary embolism	4.1 (3.6)	3.7 (3.6)
Percentage of time with INR in given range, mean (SD)‡		
INR <2.0	28 (23)	25 (20)
INR 2.0-3.0	55 (22)	56 (21)
INR >3.0	17 (18)	19 (19)

\*Four patients randomized to unfractionated heparin and 1 patient randomized to low-molecular-weight heparin did not receive any study drug.

†The low-molecular-weight heparin was dalteparin in 261 patients and enoxaparin in 91 patients.

‡The percentage of time spent in each international normalized ratio (INR) category while receiving warfarin during 3 months of follow-up was calculated for each patient by linear interpolation.

revealed a lower-than-expected frequency of recurrent venous thromboembolism in all randomized patients combined, a decision was made by the steering committee to stop the study after 700 patients were enrolled.

The primary analysis for efficacy was the absolute difference in the proportion of eligible patients who had recurrent venous thromboembolism at 3 months. The primary analysis for safety was the absolute difference in the proportion of patients who received at least 1 dose of study drug who had an episode of major bleeding within 10 days of randomization. A small number of patients who underwent automated telephone randomization were not included in the analysis, mostly because they did not meet eligibility criteria (Figure). The decision to exclude these patients from the safety and efficacy analyses was made by the steering committee without knowledge of patients' treatment allocations or their subsequent clinical course, and all such patients are described in this report. The Fisher exact test was used to compare proportions. Data were analyzed using SAS software, version 9.1 (SAS Institute Inc, Cary, NC) and StatXact software, version 7.0 (Cytel Corp, Boston, Mass).

### Laboratory Assay

When feasible, a single blood sample was obtained from each patient 6 hours (between 3.0 and 9.9 hours was acceptable) after injection of unfractionated heparin on the third day (the second through sixth days were acceptable) of treatment for measurement of APTT using Thrombosil (Instrumentation Laboratory, Lexington, Mass) and an STA Compact coagulometer (Diagnostica Stago, Asnières sur Seine, France). All APTT measurements were performed in a centralized laboratory in Hamilton, Ontario, by technologists who were blinded to clinical information. Assays were performed after the study was completed, and the results were categorized as low if APTT was shorter than 60 seconds and high if APTT was longer than 85 seconds; these values corre-

spond to antifactor Xa heparin levels of 0.35 U/mL and 0.7 U/mL, respectively (ie, the therapeutic range for intravenous heparin in Hamilton, Ontario). The APTT results were not available to the clinical centers or to the central adjudication committee.

## RESULTS

### Study Patients and Treatment

Patients were enrolled at 6 clinical centers between September 1, 1998, and February 29, 2004. A total of 2430 patients were initially assessed as meeting the inclusion criteria, of whom 1140 had at least 1 exclusion criterion and 582 others were eligible but refused to participate (Figure). The remaining 708 patients were registered and randomized to receive unfractionated heparin (355 patients) or low-molecular-weight heparin (353 patients) (TABLE 1). Patients in the 2 groups had similar baseline characteristics (Table 1). Eighty percent of the patients had symptomatic deep vein thrombosis without symptoms of pulmonary embolism, 19% had symptomatic pulmonary embolism, and 1% had asymptomatic deep vein thrombosis; 68% were outpatients and 32% were inpatients at diagnosis.

For unfractionated heparin, a mean first dose corresponding to 320 U/kg of body weight was given; subsequent doses were a mean of 249 U/kg (TABLE 2). For low-molecular-weight heparin (dalteparin in 74% and enoxaparin in 26% of patients), the mean dose corresponded to 99 IU/kg (Table 2). Study drug was given for a mean of 6.3 days in the unfractionated heparin group and 7.1 days in the low-molecular-weight heparin group (Table 2) and was stopped before the fifth day of treatment in 84 unfractionated heparin group patients and 44 low-molecular-weight heparin group patients, most commonly because the international normalized ratio was greater than 3.0. One patient stopped study drug prematurely because of thrombocytopenia (low-molecular-weight heparin group); heparin-induced thrombocytopenia was not sus-

**Table 3.** Clinical Outcomes During the Study Period

Outcomes	Unfractionated Heparin, No. (%)	Low-Molecular-Weight Heparin, No. (%)	Risk Difference (95% Confidence Interval)
<b>Efficacy analysis</b>			
n = 345 (Unfractionated), n = 352 (Low-Molecular-Weight)			
Recurrent venous thromboembolism			
First 10 d	1 (0.3)	2 (0.6)*	-0.3 (-1.8 to 1.1)
Entire 3 mo	13 (3.8)	12 (3.4)*	0.4 (-2.6 to 3.3)
Type of recurrence			
Pulmonary embolism	2	4	
Deep vein thrombosis	11	8	
<b>Safety analysis</b>			
n = 348 (Unfractionated), n = 352 (Low-Molecular-Weight)			
Major bleeding			
First 10 d	4 (1.1)	5 (1.4)†	-0.3 (-2.3 to 1.7)
Entire 3 mo	6 (1.7)	12 (3.4)†	-1.7 (-4.3 to 0.8)
Major or minor bleeding			
First 10 d	16 (4.6)	8 (2.3)	2.3 (-0.4 to 5.3)
Entire 3 mo	29 (8.3)	30 (8.5)	-0.2 (-4.4 to 4.0)
Deaths			
First 10 d	0 (0)	2 (0.6)	-0.6 (-2.0 to 6.0)
Entire 3 mo	18 (5.2)	22 (6.3)	-1.1 (-4.6 to 2.5)

\*Recurrent venous thromboembolism in the first 10 days and in the entire 3 months occurred in 2 (0.7%) and 9 (3.4%) who received dalteparin and in 0 and 3 (3.3%) who received enoxaparin, respectively.

†Major bleeding in the first 10 days and in the entire 3 months occurred in 5 (1.9%) and 10 (3.8%) who received dalteparin and in 0 and 2 (2.2%) who received enoxaparin.

pected. Only 1 patient who prematurely stopped study drug was subsequently given the alternative therapy (unfractionated heparin group). Treatment was administered entirely in the outpatient setting in 72% of the unfractionated heparin group and 68% of the low-molecular-weight heparin group ( $P=.29$ ) (Table 2).

### Recurrent Venous Thromboembolism

Recurrent venous thromboembolism occurred in 13 (3.8%) of 345 patients in the unfractionated heparin group and 12 (3.4%) of 352 patients in the low-molecular-weight heparin group (difference, 0.4%; 95% confidence interval, -2.6% to 3.3%; hypothesis supporting assumptions for noninferiority,  $P=.002$ ) (TABLE 3). The recurrent episode of venous thromboembolism was a pulmonary embolism in 2 patients in the unfractionated heparin group (neither was fatal) and in 4 patients in the low-molecular-weight heparin group (1 was fatal; a sudden unexplained death 81 days after enrollment); the remaining episodes were deep vein thrombosis. An addi-

tional 41 patients in the unfractionated heparin group and 40 patients in the low-molecular-weight heparin group had investigation for and exclusion of suspected venous thromboembolism during follow-up.

### Bleeding

During the first 10 days, major bleeding occurred in 4 (1.1%) of 348 patients in the unfractionated heparin group and 5 (1.4%) of 352 patients in the low-molecular-weight heparin group (difference, -0.3%; 95% confidence interval, -2.3% to 1.7%). During 3 months of follow-up, major bleeding occurred in 6 patients (1.7%) in the unfractionated heparin group and 12 patients (3.4%) in the low-molecular-weight heparin group (difference, -1.7%; 95% confidence interval, -4.3% to 0.8%). Of the major bleeding events, 1 in the unfractionated heparin group (a subdural hematoma associated with trauma 68 days after enrollment) and 1 in the low-molecular-weight heparin group (an epidural hematoma 3 days after enrollment) were fatal. There was 1 other nonfatal intracranial bleed in the low-molecular-weight heparin group (intracerebral

bleeding associated with a fall 26 days after enrollment). Only 1 patient had both a major bleeding event (15 days after enrollment) and recurrent venous thromboembolism (27 days after enrollment, while receiving warfarin). Total bleeding, which included major and minor bleeding, was not significantly different between the 2 groups at 10 days or at 3 months (Table 3).

### Deaths

There were 18 deaths in the unfractionated heparin group and 22 deaths in the low-molecular-weight heparin group. Causes of death in the unfractionated heparin group were bleeding in 1, cancer in 13, and other causes in 4 and in the low-molecular-weight heparin group were pulmonary embolism in 3 (2 occurred after diagnosis of recurrent nonfatal venous thromboembolism), bleeding in 1, cancer in 16, and other causes in 2.

### APTT Values and Clinical Outcomes in the Unfractionated Heparin Group

The APTT was measured midway between injections (a mean of 6.0 hours after the morning dose) a mean of 2.8 days after starting therapy in 197 of the unfractionated heparin patients. The APTT values were shorter than 60 seconds in 39 patients, 60 to 85 seconds in 37 patients, and longer than 85 seconds in 121 patients. Recurrent venous thromboembolism during 3 months of follow-up occurred in none of the 39 patients who had an APTT of shorter than 60 seconds compared with 5 of 158 (3.2%) who had an APTT of 60 seconds or longer ( $P = .58$ ). Major bleeding within 10 days of enrollment occurred in none of 121 patients who had an APTT of longer than 85 seconds compared with none of 76 who had an APTT of 85 seconds or shorter ( $P > .99$ ).

### COMMENT

This study demonstrates that fixed-dose, unmonitored, subcutaneous unfractionated heparin is as effective and safe as fixed-dose, unmonitored, subcutaneous low-molecular-weight heparin in patients with acute venous

thromboembolism. Lack of an association between low APTT results and recurrent venous thromboembolism or between high APTT results and bleeding in the unfractionated heparin group provides additional evidence that APTT monitoring is not required with this dosing regimen. More than 75% of patients in each group, including a substantial proportion of patients with pulmonary embolism, were treated either partially or entirely as outpatients, indicating that this unfractionated heparin regimen is suitable for out-of-hospital use. Because unfractionated heparin costs less than low-molecular-weight heparin, the unfractionated heparin regimen is attractive for clinical practice.<sup>2,25</sup> For example, based on a US average wholesale price of \$7.42 per 1000 IU of enoxaparin<sup>26</sup> (100 IU corresponds to 1 mg) and \$0.15 per 1000 U of unfractionated heparin,<sup>26</sup> drug costs for a 6-day course of treatment for a patient weighing 80 kg would be \$712 for low-molecular-weight heparin and \$37 for unfractionated heparin. These calculations assume that both drugs are administered in the regimens used in this study (ie, twice daily, with use of multidose vials).

This study has a number of potential weaknesses that need to be considered. First, the open-label design could have led to a biased assessment of outcomes during follow-up. This is unlikely because a central adjudication committee that was blinded to treatment allocation assessed all outcomes using standardized criteria. In addition, because a similar number of patients in each group had a negative evaluation for venous thromboembolism during follow-up, there is no evidence to suggest that the clinical centers had different thresholds for investigating patients for recurrent thrombosis in the 2 groups.

Second, the total number of patients included in the study was lower than originally planned because of slow enrollment. Although the smaller sample size reduces the precision of the findings, we still are able to confirm our

hypothesis that the unfractionated heparin regimen is not inferior to low-molecular-weight heparin ( $P = .002$  for noninferiority). Furthermore, our data show that it is very unlikely that there is as much as a 3.3% higher frequency of recurrent venous thromboembolism with unfractionated heparin (Table 3), thereby satisfying the criteria recently used to conclude that fondaparinux and ximelagatran were not inferior to standard therapy for treatment of acute venous thromboembolism.<sup>27-29</sup> A power calculation was performed after the study results were known. For this calculation, we assumed that there were 348 patients in each treatment group. Using the observed recurrent venous thromboembolism proportion of 3.6% as expected in each group, a 1-sided  $\alpha$  level of .05, and a power of 90%, the noninferiority margin is 4.1%. That is, a frequency of recurrent venous thromboembolism in the unfractionated heparin group during follow-up of 7.7% (3.6% plus 4.1%) or greater can be excluded under the noninferiority hypothesis. Therefore, because the proportion of patients who developed recurrent venous thromboembolism was lower than expected (ie, 3.6% vs 6.0%) despite reduced enrollment (ie, 697 vs 824 patients), the study has greater power (ie, 97%) to detect an absolute increase of recurrent venous thromboembolism of 5% in the unfractionated heparin group. However, with the expression of the noninferiority margin in relative terms, the reduced sample size and lower recurrent venous thromboembolism proportion produces a larger noninferiority risk ratio of 2.14 (7.7%/3.6%) instead of the 1.83 ratio associated with the original parameters (11%/6%).

A third potential limitation is that there were more postrandomization exclusions in the unfractionated heparin group than in the low-molecular-weight heparin group (10 vs 1) and that the decision to exclude these patients may have been influenced by the open-label study design. However, as the decision to exclude randomized patients

from the final analysis was made by the steering committee without knowledge of treatment allocation, and as only 2 of the 11 postrandomization exclusions (Figure) were due to patient or physician preference (both patients were allocated to the unfractionated heparin group), it is unlikely that post-randomization exclusions biased the study results.

Strengths of this study include that the method of random allocation ensured that clinical centers could not anticipate or influence the group to which patients were allocated (ie, there was effective concealment),<sup>30</sup> that there was no loss to follow-up of patients who were eligible for the analysis of efficacy, that suspected episodes of recurrent venous thromboembolism were investigated in a standardized manner, and that all outcomes were evaluated by an independent central adjudication committee.

Two changes in clinical practice occurred in the course of the study that made it more difficult to enroll patients. First, once-daily low-molecular-weight heparin became acceptable for treatment of acute venous thromboembolism,<sup>31</sup> and second, low-molecular-weight heparin became preferred over warfarin therapy for long-term treatment of venous thromboembolism in patients with cancer.<sup>32</sup>

We conclude that fixed-dose subcutaneous unfractionated heparin is as effective and safe as low-molecular-weight heparin for initial treatment of patients with venous thromboembolism and is suitable for treatment at home. In addition, the results of this study question the value of APTT monitoring in patients who are treated with currently recommended doses of unfractionated heparin.

**Author Contributions:** Drs Kearon and Julian had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Kearon, Ginsberg, Julian, Hirsh, Gent.

**Acquisition of data:** Kearon, Ginsberg, Douketis, Solymoss, Ockelford, Jackson, Turpie.

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**Drafting of the manuscript:** Kearon, Ginsberg, Hirsh.

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The writer's problem is, how to strike the balance between the uncommon and the ordinary so as on the one to hand to give interest, on the other to give reality.

—Thomas Hardy (1840-1928)