

# A Randomized Trial Comparing 2 Low-Molecular-Weight Heparins for the Outpatient Treatment of Deep Vein Thrombosis and Pulmonary Embolism

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**Background:** Low-molecular-weight heparins (LMWHs) are now standard therapy for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). No published trials have compared LMWHs, and few studies have examined outpatient therapy for PE. Only tinzaparin sodium has demonstrated superiority to unfractionated heparin in a clinical trial.

**Methods:** We compared 2 LMWH products, tinzaparin and dalteparin sodium, for the treatment of acute DVT and PE in a randomized, controlled clinical trial of consecutive outpatients presenting to a venous thromboembolism service at 4 tertiary-care hospitals. Patients were treated with subcutaneous tinzaparin sodium, 175 IU/kg every 24 hours, or subcutaneous dalteparin sodium, 200 IU/kg every 24 hours, for at least 5 days. Warfarin sodium therapy was started simultaneously and continued for 90 days. The primary end point was efficacy (recurrence of venous thromboembolism); safety (bleeding) was a composite end point.

**Results:** Two hundred fifty-four patients received tinzaparin (39 with PE and 215 with DVT) and 251 received dalteparin (51 with PE and 200 with DVT). Most patients had an active malignancy or idiopathic DVT/PE. The outcome events occurred in 11 (4.4%; 95% confidence interval [CI], 2.2%-7.7%) and 15 patients (5.9%; 95% CI, 3.3%-9.5%) in the dalteparin and tinzaparin groups, respectively, including 9 and 10 recurrences, respectively, and 2 and 5 major hemorrhages, respectively ( $P = .44$ ). The 95% CI on the difference of  $-1.5\%$  was  $-5.3\%$  to  $2.4\%$ .

**Conclusions:** Tinzaparin and dalteparin are safe and effective for the outpatient treatment of DVT or PE. Our finding of no differences between the LMWHs based on major clinical end points means that practical issues can be the deciding factor on which drug to use.

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**M**ANY RECENT STUDIES have demonstrated that the safety and efficacy of subcutaneously administered low-molecular-weight heparin (LMWH) are at least equivalent to those of intravenous unfractionated heparin for the treatment of deep vein thrombosis (DVT).<sup>1,2</sup> However, only 1 LMWH, tinzaparin sodium, has demonstrated statistical superiority to unfractionated heparin in individuals trials.<sup>3</sup> Three randomized trials have been published in which LMWH was used for the treatment of pulmonary embolism (PE).<sup>4-6</sup> None of these studies assessed outpatient therapy. To our knowledge, no randomized trial has treated patients entirely on an outpatient basis, and no randomized trial has compared 2 different LMWHs for the treatment of acute DVT or PE.

There are almost no head-to-head studies that guide physicians in choosing among various drugs in any particular class. Most decisions are made on the basis of formulary, physician comfort, and

cost. It is widely debated whether there are clinically important differences between LMWHs. Some authors have suggested that dalteparin sodium may be associated with fewer major hemorrhages but higher recurrence rates.<sup>7</sup> Differences in antifactor Xa-antifactor IIa ratios, methods of drug preparation, recommended dosages, molecular weights, and drug half-

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lives have been cited as evidence that LMWHs may not be equivalent. Some clinical data suggest that not all LMWHs are the same. In studies comparing LMWHs to unfractionated heparin in patients with angina at rest or with non-Q-wave myocardial infarction, a statistically significant result in favor of enoxaparin so-

dium was demonstrated in terms of a reduction in rates of death, myocardial infarction, and recurrent angina, but there was no difference between unfractionated heparin and dalteparin in a similar study.<sup>8,9</sup> At the time we started our trial, the 2 LMWH preparations approved in Canada for the treatment of DVT were dalteparin and tinzaparin. These drugs, given once daily, differ in the recommended dosage, in mean molecular weight (6000 for dalteparin and 4500 for tinzaparin), and in their antifactor Xa–antifactor-IIa ratios (1.9 and 2.7, respectively). However, despite a lack of head-to-head comparisons, many physicians use LMWHs interchangeably. Ideally, to assume a class effect, randomized clinical trials should be conducted to compare drugs within a class.<sup>10</sup>

The objective of this study was to compare the effectiveness and safety of 2 LMWH preparations for the treatment of acute DVT and PE.

## METHODS

### STUDY PARTICIPANTS

All patients presenting to our thrombosis consultation and outpatient services with objectively proved upper or lower extremity DVT or PE were potentially eligible. Objectively proved DVT and PE were defined as follows:

- In patients with suspected DVT and no history of DVT or PE, (1) noncompressibility of the deep veins in a portion from the common femoral to the popliteal veins, including the calf trifurcation on ultrasonography findings; (2) noncompressibility or color flow–demonstrated intraluminal thrombus in a portion of the deep veins from the axillary vein to brachiocephalic veins on ultrasonography findings; or (3) an intraluminal filling defect on contrast dye venography findings.
- In patients with suspected DVT and a history of DVT, (1) a new area of noncompressibility on ultrasonography findings (ie, compared with prior studies) or (2) an intraluminal filling defect on contrast dye venography findings.
- In patients with suspected PE and no history, (1) a high-probability finding on a ventilation-perfusion scan and moderate or high pretest clinical probability; (2) a constant intraluminal filling defect or an abrupt cutoff of vessels greater than 2.5 mm in diameter on contrast dye pulmonary angiography findings; or (3) an intraluminal filling defect in segmental or larger vessels on spiral computed tomography findings.
- In patients with a history of PE, the ventilation-perfusion scan criteria were the same provided the defects were not present on the previous scan. Computed tomography and pulmonary angiography, as defined herein, were also allowed to diagnose recurrent PE.<sup>11</sup>

Exclusion criteria were as follows: (1) active bleeding or a very high risk for major bleeding (patients who had had a stroke in the preceding 10 days, gastrointestinal tract bleeding in the preceding 14 days, or thrombocytopenia defined as a platelet count less than  $75 \times 10^3/\mu\text{L}$ ), (2) asymptomatic DVT detected by screening test results, (3) age younger than 18 years, (4) no fixed address, (5) previously documented heparin-induced thrombocytopenia, (6) renal failure defined as creatinine level of greater than 2.3 mg/dL ( $>200 \mu\text{mol/L}$ ), (7) use of unfractionated heparin or LMWH for more than 36 hours, (8) PE with associated hypotension, hypoxia on room air, or severe pain requiring intravenous narcotic analgesia, (9) necessary continued hospitalization for another comorbidity, and (10) failure to sign informed consent.

## SETTING AND LOCATIONS

Four Canadian academic centers participated. Patients were recruited from the thrombosis units of our respective institutions. Referrals came from the community, our local emergency departments, and the inpatient wards.

## INTERVENTIONS

Patients were randomized to treatment with subcutaneous tinzaparin sodium (Leo Pharma Inc, Thornhill, Ontario), 175 IU/kg every 24 hours, or subcutaneous dalteparin sodium (Pharmacia and Upjohn, Mississauga, Ontario), 200 IU/kg every 24 hours. Patients had to receive therapy on an outpatient basis. All patients started oral anticoagulation therapy with warfarin sodium on the day of randomization or within 24 hours of the first dose of LMWH. Initial warfarin dosage adjustments were made using a standardized nomogram.<sup>12</sup> The LMWH preparations were given for a minimum of 5 days and until the international normalized ratio was 2.0 or greater on 2 consecutive days. All patients continued warfarin therapy for 3 months.

## SURVEILLANCE AND FOLLOW-UP

During the initial week of therapy, patients underwent review at 24- to 48-hour intervals by telephone or in person by the study coordinator at each center. All patients received an emergency contact number on a pocket card outlining the symptoms suggestive of recurrent DVT or PE. Patients were seen in the clinic 1 week and 90 days after the initial visit. All other visits were on the basis of need. Patients were asked to report to the study center as soon as possible if symptoms of recurrent venous thromboembolism or bleeding occurred. All efforts were made to document causes of death. Events were determined, and patients were followed up for a period of 90 days from the day of randomization.

## OBJECTIVES AND HYPOTHESIS

The primary objective was to compare the efficacy (recurrence of venous thrombosis) and safety (bleeding), as a composite end point, of tinzaparin and dalteparin as therapy for acute DVT of the upper or lower extremity or PE for a 90-day treatment period. By combining event rates in the 2 randomized trials evaluating tinzaparin, we determined that treatment of DVT and PE with tinzaparin should result in at least a 4% lower incidence of the combined end point of major bleeding and recurrent venous thrombosis compared with treatment with dalteparin.<sup>3,5,13-15</sup>

## OUTCOMES

All suspected outcome events were adjudicated by a panel of physicians unaware of patient assignment. They applied the criteria that follows.

For DVT, new sites of noncompressibility (eg, extension to a more proximal site, a previously uninvolved site, or a different limb) or an increase in clot diameter by 4 mm or greater were used to diagnose recurrent DVT.<sup>16</sup> If the change in vein diameter was 1 mm or less, recurrence was excluded. If the vein diameter had increased by 1.1 to 3.9 mm, serial testing or venography was used. Recurrent PE was documented by performing a ventilation-perfusion scan or pulmonary angiography for comparison with previous scans. Only new defects were interpreted, according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis.<sup>17</sup> Patients who did not have high-probability findings on lung scans (ie, intermediate or low-probability finding) underwent further investigations in the form

of leg vein ultrasonography, venography, or angiography as per our previously published protocol.<sup>11</sup>

A diagnosis of PE was excluded in patients with no new defects or with normal findings on lung scans/angiography.

Documentation of clinically suspected bleeding events included the recording of the clinical event and objective imaging tests. Bleeding was defined as major if it was clinically overt and associated with a fall in hemoglobin level of 2 g/dL or a need for transfusion of at least 2 U of red blood cells, if it was intracranial or retroperitoneal, or if it warranted the permanent discontinuation of anticoagulation therapy. We also evaluated the risk of bleeding according to an index derived by Nieuwenhuis et al<sup>18</sup> (hereafter referred to as the Nieuwenhuis index). Deaths were classified as due to PE, possibly due to PE, or unrelated to PE (for which the exact cause of death was recorded).

## SAMPLE SIZE

The published literature describes combined recurrence and major bleeding rates for tinzaparin of 3.3% (0.5% for major bleeding and a 2.8% recurrence rate) and for dalteparin of 7.0% (2.0% for major bleeding and a 5.0% recurrence rate).<sup>3,5,13-15</sup> Therefore, our goal was to perform a study designed to detect a difference in event rates of 4%, which is a reasonable minimal clinically important difference and is the difference supported by the literature.<sup>3,5,13-15</sup> Detecting this difference with a power of 80%, at a significance level of .05 (2 sided), a sample of 465 patients per group was required based on the uncorrected  $\chi^2$  test of proportions. Given that there had been only 2 studies using tinzaparin, it was possible that the projected event rates would be incorrect, so we planned an interim analysis after enrolling half the expected sample size.

## RANDOMIZATION

Randomization was performed in computer-generated blocks, with the block size unknown to the investigators but ranging from 4 to 8. Stratification was performed according to the presence of malignancy and by center. Randomization assignments were concealed in opaque envelopes. Envelopes were opened sequentially and only after the patient consent form was signed. All physicians and nurses who were involved in the patient's care were blinded except for the nurse who provided the initial care to the patient. In all cases, 2 prescriptions were written for the patient, and the physician was unaware which drug was ultimately assigned. The nurse who was initially involved with the patient was not involved in follow-up assessment for recurrence or bleeding. This was the responsibility of the physician.

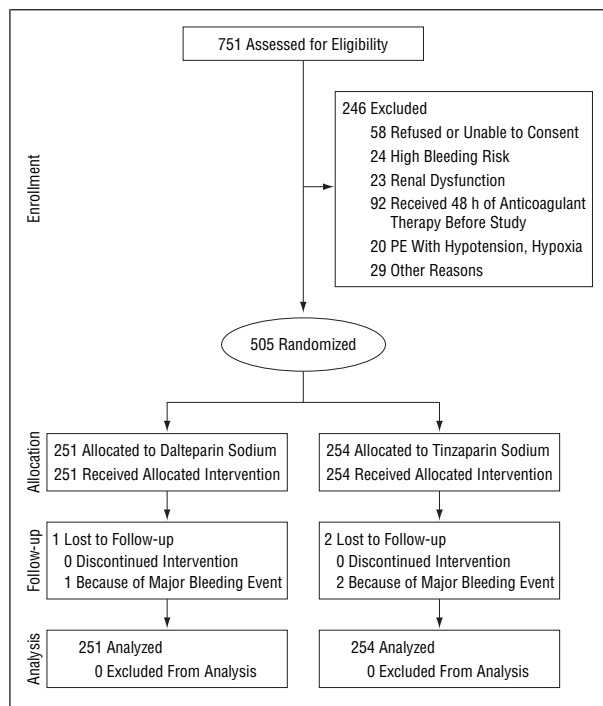
## STATISTICAL ANALYSIS

The treatment groups were compared on the basis of the rates of recurrence and bleeding by using the uncorrected  $\chi^2$  test procedure. The primary analysis was intention to treat. We determined 95% confidence intervals (CIs) for all reported proportions by using the binomial distribution. We used SPSS version 10.0 for Windows (SPSS Inc, Chicago, Ill) and SAS version 8.1 for the Unix platform (SAS Institute, Cary, NC) for statistical analysis.

## RESULTS

### STUDY PATIENTS

A total of 751 patients with acute DVT or PE were approached for study eligibility. The 188 patients ex-



**Figure.** Trial profile from enrollment to analysis. PE indicates pulmonary embolism.

cluded are outlined in the **Figure**. Of the remaining 563 patients, 44 refused informed consent and 14 were unable to provide consent. The remaining 505 patients were eligible, provided informed consent, and were randomized. No patients were lost to follow-up. Patients were enrolled from February 1, 1999, through March 31, 2001.

Of the consenting patients, 251 were treated with dalteparin and 254 with tinzaparin. The baseline characteristics of the 2 treatment groups demonstrated no statistical differences with respect to risk factors, age, and sex (**Table 1**). We enrolled 374 patients with lower extremity DVT, (349 proximal and 25 isolated to the calf trifurcation), 41 with upper extremity DVT, and 90 with PE, 23 of whom also had DVT. Overall, 260 patients (51.5%) had idiopathic PE or DVT, 94 (18.6%) had prior venous thromboembolic events, 113 (22.4%) had active malignancy, and 62 (12.3%) had recent surgery or immobilization as a risk factor. Three hundred ninety-nine patients had a score of 2 or less by the Nieuwenhuis index (ie, low risk for major bleeding), 98 had a score of 3 or 4 (moderate risk), and 8 had a score of 5 or greater (high risk).<sup>12</sup> The mean duration of therapy with LMWH was 6.04 days (SD, 1.4 days) in the dalteparin group and 6.14 days (SD, 2.1 days) in the tinzaparin group. The median duration of therapy was 6 days (range, 3-26 days) for dalteparin and 6 days (range, 3-31 days) for tinzaparin.

Outcome events are presented in **Table 2**. Eleven (4.4%; 95% CI, 2.2%-7.7%) of 251 patients treated with dalteparin had 1 of the composite end points (2 major hemorrhages and 9 recurrent venous thromboembolic events [in 5 patients with DVT and 4 with PE]). Fifteen (5.9%; 95% CI, 3.3%-9.5%) of 254 treated with tinzaparin had 1 of the events in the composite end point (5 major hemorrhages and 10 recurrent venous thromboem-

**Table 1. Patient Characteristics and Risk Factors\***

Characteristic	Treatment Groups	
	Dalteparin Sodium (n = 251)	Tinzaparin Sodium (n = 254)
Age, mean (SD), y	58.5 (17.2)	57.1 (17.2)
Age, median (range), y	6 (3-26)	6 (3-31)
Weight, mean (SD), kg	84.1 (20.2)	83.9 (21.4)
No. male/female	140/111	133/121
Risks		
Previous venous thromboembolism	53 (21.1)	41 (16.1)
Cancer	54 (21.5)	59 (23.2)
Surgery/immobilization	28 (11.2)	34 (13.4)
≥2 Risks	9 (3.6)	15 (5.9)
Idiopathic disease	125 (49.8)	135 (53.1)
Proximal DVT	163 (64.9)	186 (73.2)
Calf trifurcation DVT	16 (6.4)	9 (3.5)
Upper extremity DVT	21 (8.4)	20 (7.9)
PE	51 (20.3)	39 (15.4)

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolism.

\*Unless otherwise indicated, data are expressed as number (percentage) of patients.

**Table 2. Outcome Events**

Outcome Events	Study Group, No. (%) of Patients	
	Dalteparin Sodium (n = 251)	Tinzaparin Sodium (n = 254)
Recurrent venous thromboembolism		
Days 1-7	3 (1.2)	1 (0.4)
Days 8-45	5 (2.0)	8 (3.1)
Days 46-90	1 (0.4)	1 (0.4)
Entire study	9 (3.6)*	10 (3.9)*
Major hemorrhage		
Days 1-7	1 (0.4)	3 (1.2)
Days 8-45	0	1 (0.4)
Days 46-90	1 (0.4)	1 (0.4)
Entire study	2 (0.8)	5 (2.0)
Death		
Days 1-7	0	1 (0.4)
Days 8-45	4 (1.6)	6 (2.4)
Days 46-90	8 (3.2)	7 (2.8)
Entire study	12 (4.8)	14 (5.5)

\*Four and 2 of the recurrent events in the dalteparin and tinzaparin groups, respectively, were pulmonary emboli.

bolic events [in 8 patients with DVT and 2 with PE]). The different composite end-point rates between tinzaparin and dalteparin treatments were not statistically significant ( $P = .44$ ). Twenty-six patients died, 12 in the dalteparin group and 14 in the tinzaparin group. No deaths were secondary to hemorrhage or recurrent PE. The cause of death was metastatic cancer in 21, sepsis in 2, cerebrovascular event in 2, and amyotrophic lateral sclerosis in 1. In 1 patient in the tinzaparin group, a sudden neurological event on day 4 of therapy resulted in death. This was adjudicated as a cerebrovascular event and not

a major hemorrhage, but without an autopsy we cannot be sure the event was not secondary to an intracranial hemorrhage.

In the 90 patients treated for acute PE, only 2 had a recurrent thromboembolic event (1 patient with DVT and 1 with PE). Major hemorrhage did not develop in any patient with PE. Three patients with PE died of causes other than PE, on days 35, 50, and 60. These results are similar to the overall outcome event rates in the patients with DVT only.

After the first 470 patients, we conducted the planned interim analysis.<sup>19</sup> At this point there were 11 combined outcome events in the 231 patients who received dalteparin and 13 in the 239 patients who had received tinzaparin. At this point, the event rates were 4.8% in the dalteparin group and 5.4% in the tinzaparin group. The difference was 0.68% (95% CI, -3.30% to 4.66%). We determined that we would need 16 433 patients per group to achieve a statistically significant difference.<sup>20</sup> Also, if 465 patients were enrolled per group, as per our original plan and sample size calculation, and if rates stayed the same, then at the completion of the study we would have a power of only 7% to find the minimally clinically important difference of 4%. We therefore chose to close the study early, because it was determined that we would be unlikely to reach our study objective.

The 95% CI on the absolute difference in the primary composite end point (1.5% at study termination) was -5.3% to 2.4%. This suggests that dalteparin is not inferior to tinzaparin, but given our minimally clinically important difference of 4%, it is possible that dalteparin is superior to tinzaparin and our study is underpowered to detect this difference. Subgroup analysis by center did not reveal significant differences in the outcomes.

Six (1.5%; 95% CI, 0.6%-3.3%) of 399 patients at low risk of bleeding by the Nieuwenhuis index had a major bleeding event, as did 1 (1.0%; 95% CI, 0.03%-5.5%) of 98 at moderate risk and 0 of 7 at high risk. The differences between those at low and moderate risk were not statistically significant ( $P = .72$ ).

#### COMMENT

We performed a randomized single-blind study of 2 LMWH preparations in patients with DVT or PE who were eligible by our previously published criteria for home treatment. We found no evidence that tinzaparin was superior to dalteparin. Both medications provided safe and effective care for the treatment of DVT or PE. The upper boundary of the 95% CI on the difference of 1.5% in favor of dalteparin did not exceed our a priori minimal clinically important difference of 4%. We combined the end points of bleeding and recurrence, because recent data suggest that the risk of death with a major hemorrhage exceeds the risk of death with recurrent thrombosis. The risk of death with a major hemorrhage has been estimated as 21%, and the risk of death with recurrent thrombosis as 15%.<sup>21</sup>

To our knowledge, our study is the largest study of LMWH in which treatment was administered entirely to outpatients, and it is the only study to compare LMWH

preparations, the only randomized outpatient study to enroll a broad spectrum of patients, and the first randomized outpatient study of patients with PE. We believed it was justified to include patients with a diagnosis of PE, given the safety and effectiveness that we and others have demonstrated.<sup>5,6,22</sup> The outcomes in the patients with PE were similar to those in the patients with DVT. No patient died of recurrent PE. We believe our results are generalizable to other centers that treat patients who present in an ambulatory setting (emergency departments or outpatient clinics), because we enrolled more than 80% of the patients who presented with PE and most of the patients with DVT. The recurrence and bleeding event rates in our study were similar to those in other publications.<sup>2</sup> We enrolled only symptomatic patients (asymptomatic patients have a better prognosis), and most of our patients had idiopathic disease or cancer, thus constituting the 2 groups known to have the highest risk of recurrence, and in the case of cancer, bleeding.<sup>23-26</sup>

Our study could be criticized for the fact that it was single blind, ie, only the physicians were blinded. The single-blind design was performed for 2 reasons. First, the study was unfunded, and a double-blind design would have been prohibitively expensive, especially given the different concentrations of the products. Second, a failure to blind the patient would be unlikely to influence outcomes, because we gave the patients no reason to suspect that one drug was better than the other. Although the physicians in the study did not state a preference for either drug, if a preference existed, diagnostic suspicion bias in the case of suspected recurrence could be an issue during patient follow-up. However, we ensured bias was limited in the evaluation of suspected recurrent events and major hemorrhage by performing blinded adjudication of all suspected outcomes and by following well-accepted, objective guidelines. The expected event rates used to determine the sample size were based on the only available published data, and the literature clearly supported a directional hypothesis. We used a combined end point of recurrence and major hemorrhage, which is in contrast to previously published treatment studies in patients with venous thromboembolism. We believe the combined end point is the most appropriate, because both end points have similar clinical importance and this is a prerequisite for combined end points.<sup>21,27</sup> We stopped our study prematurely after a planned interim analysis was performed that demonstrated that the outcome event rates were almost identical in the 2 groups. We subsequently performed a futility analysis on the initial 470 patients, which suggested that there would be only a remote possibility that recruitment of the 930 patients we had originally planned would be adequate to demonstrate our hypothesis.<sup>19</sup> The futility analysis was performed by the study statisticians (G.W. and K.O.) without knowledge of patient assignment. The 3 trials comparing LMWH (with some outpatient care provided) with intravenous unfractionated heparin for treatment of DVT, even when combined and analyzed by the Mantel-Haenszel procedure (data not shown), did not demonstrate superiority to intravenous unfractionated heparin.<sup>6,28,29</sup> Despite lack of superiority, outpatient therapy is becoming the standard in many centers around the world, at least for DVT.

In conclusion, our study suggests that both tinzaparin and dalteparin provide effective and safe outpatient treatment of DVT or PE. Because there are no differences based on major clinical end points, the choice of agent can be based on practical issues such as price, drug delivery systems, and availability.

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