Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer


BACKGROUND
Patients with cancer have a substantial risk of recurrent thrombosis despite the use of oral anticoagulant therapy. We compared the efficacy of a low-molecular-weight heparin with that of an oral anticoagulant agent in preventing recurrent thrombosis in patients with cancer.

METHODS
Patients with cancer who had acute, symptomatic proximal deep-vein thrombosis, pulmonary embolism, or both were randomly assigned to receive low-molecular-weight heparin (dalteparin) at a dose of 200 IU per kilogram of body weight subcutaneously once daily for five to seven days and a coumarin derivative for six months (target international normalized ratio, 2.5) or dalteparin alone for six months (200 IU per kilogram once daily for one month, followed by a daily dose of approximately 150 IU per kilogram for five months).

RESULTS
During the six-month study period, 27 of 336 patients in the dalteparin group had recurrent venous thromboembolism, as compared with 53 of 336 patients in the oral-anticoagulant group (hazard ratio, 0.48; P=0.002). The probability of recurrent thromboembolism at six months was 17 percent in the oral-anticoagulant group and 9 percent in the dalteparin group. No significant difference between the dalteparin group and the oral-anticoagulant group was detected in the rate of major bleeding (6 percent and 4 percent, respectively) or any bleeding (14 percent and 19 percent, respectively). The mortality rate at six months was 39 percent in the dalteparin group and 41 percent in the oral-anticoagulant group.

CONCLUSIONS
In patients with cancer and acute venous thromboembolism, dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.
The standard treatment for acute venous thromboembolism consists of initial therapy with low-molecular-weight heparin or unfractionated heparin followed by long-term therapy with an oral anticoagulant. This approach is highly effective in most patients, but patients with cancer have a substantial risk of recurrent thromboembolism and hemorrhagic complications. Furthermore, oral anticoagulant therapy is problematic in patients with cancer. Drug interactions, malnutrition, vomiting, and liver dysfunction can lead to unpredictable levels of anticoagulation. Invasive procedures and thrombocytopenia caused by chemotherapy often require interruption of anticoagulant therapy, and poor venous access can make laboratory monitoring difficult. These limitations may contribute to the higher risk of recurrent thromboembolism and bleeding in patients with cancer than in patients without cancer.

Secondary prophylaxis with low-molecular-weight heparin may be a more effective and practical alternative to oral anticoagulant therapy. Unlike vitamin K antagonists, low-molecular-weight heparins have predictable pharmacokinetic properties and drug interactions, and they can be effective in patients with cancer who have recurrent thromboembolism while receiving warfarin. Poor gastrointestinal absorption is not a concern with subcutaneously injected low-molecular-weight heparins. The therapeutic dosage is based on the patient’s weight, and laboratory monitoring is not routinely required. With a rapid onset of action and predictable clearance, they are also convenient for patients who require frequent interruptions of anticoagulant therapy.

We performed a multicenter, randomized, open-label clinical trial to investigate whether the low-molecular-weight heparin dalteparin (Fragmin, Pharmacia), initially for five to seven days and a vitamin K antagonist for six months. Dalteparin was supplied in 3.8-ml multidose vials containing 25,000 IU of dalteparin per milliliter. A dose of 200 IU per kilogram of body weight (maximal daily dose, 18,000 IU) was administered once daily. Within 24 hours after randomization, patients in this group also began taking warfarin or acenocoumarol. Warfarin was used in all participating centers except those in the Netherlands and Spain. All doses were adjusted to achieve treatment for cancer within the previous six months, or recurrent or metastatic cancer. Proximal deep-vein thrombosis was diagnosed on the basis of evidence of thrombus in the popliteal or more proximal veins on compression ultrasonography or contrast venography. A diagnosis of pulmonary embolism required verification by ventilation–perfusion lung scanning, helical computed tomography, or pulmonary angiography.

Patients were excluded if they weighed 40 kg or less, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or 4, had received therapeutic doses of any heparin for more than 48 hours before randomization, were already receiving oral anticoagulant therapy, had had active or serious bleeding within the previous two weeks, had conditions associated with a high risk of serious bleeding (e.g., active peptic ulcer or recent neurosurgery), had a platelet count of less than 75,000 per cubic millimeter; had contraindications to heparin therapy (e.g., heparin-induced thrombocytopenia) or the use of contrast medium, had a creatinine level that was at least three times the upper limit of the normal range, were pregnant, or could not return to the clinical center for follow-up.

At base line, a complete blood count was obtained and the prothrombin time, activated partial-thromboplastin time, and serum creatinine and liver enzyme levels were measured. The study protocol was reviewed and approved by the institutional review boards of each participating center. Written informed consent was obtained from all patients.

**Treatment Regimens**

Patients were assigned to receive subcutaneous dalteparin or an oral anticoagulant. Randomization was stratified according to the clinical center and centralized at the coordinating and methods center at the Henderson Research Centre, Hamilton, Ontario, Canada. The patients assigned to the oral-anticoagulant group received a low-molecular-weight heparin, dalteparin (Fragmin, Pharmacia), initially for five to seven days and a vitamin K antagonist for six months. Dalteparin was supplied in 3.8-ml multidose vials containing 25,000 IU of dalteparin per milliliter. A dose of 200 IU per kilogram of body weight (maximal daily dose, 18,000 IU) was administered once daily. Within 24 hours after randomization, patients in this group also began taking warfarin or acenocoumarol. Warfarin was used in all participating centers except those in the Netherlands and Spain. All doses were adjusted to achieve
a target international normalized ratio (INR) of 2.5 (therapeutic range, 2.0 to 3.0). Dalteparin was dis-
continued after a minimum of five days and once
the INR had remained above 2.0 for two consecu-
tive days. The INR was measured at least once every
two weeks thereafter.

The patients assigned to the dalteparin group re-
ceived 200 IU of dalteparin per kilogram (maximal
daily dose, 18,000 IU) from multidose vials once
daily for the first month. For the remaining five
months, patients were treated with 75 to 83 percent
of the full dose (approximately 150 IU per kilogram)
with the use of prefilled syringes. These syringes
were supplied according to the patient’s weight:
7500 IU for those weighing 56 kg or less, 10,000 IU
for those weighing 57 to 68 kg, 12,500 IU for those
weighing 69 to 82 kg, 15,000 IU for those weighing
83 to 98 kg, and 18,000 IU for those weighing 99 kg
or more. Patients were instructed to inject the entire
contents of one syringe once daily. The practice of
measuring the anticoagulant effect against activated
factor X was discouraged. The only exception was
in the cases of patients in whom clinically signifi-
cant renal insufficiency developed.

Dose adjustment was recommended for patients
with thrombocytopenia. Study drug was withheld
from patients with a platelet count of less than
50,000 per cubic millimeter and was resumed at
the scheduled dose when the count was 100,000 per
cubic millimeter or higher. When the platelet count
was 50,000 to 99,000 per cubic millimeter, the next
lower dose of prefilled syringe was used in the dal-
teparin group, whereas the target INR was reduced
to 2.0 (range, 1.5 to 2.5) in the oral-anticoagulant
group.

The assigned study treatment was administered
at home whenever possible, and it was continued
during hospitalization. Patients, family members,
or both were taught how to inject the medication,
but home care or equivalent nursing services were
arranged if necessary.

FOLLOW-UP

During the six-month study period, patients were
contacted by telephone every two weeks and were
seen in the clinic one week and one, three, and six
months after randomization. Each clinic visit in-
cluded a history taking, physical examination, as-
essment of compliance, and blood drawing for the
calculation of a complete blood count and measure-
ment of liver enzymes and creatinine. Scheduled
calls and visits included a standardized assessment
of the signs and symptoms of recurrent thrombo-
embolism, bleeding episodes, and adverse reac-
tions. Patients were instructed to report to the clinic
immediately if they had any bleeding or symptoms
of recurrent deep-vein thrombosis, pulmonary em-
bolism, or both. All suspected episodes of recurrent
thrombosis were investigated with the use of objec-
tive tests, according to prespecified diagnostic al-
gorithms.13 All patients were followed until the
six-month visit, death, or withdrawal of consent,
whichever came first.

OUTCOME MEASURES

The primary efficacy outcome was the first epi-
sode of objectively documented, symptomatic, re-
current deep-vein thrombosis, pulmonary embo-
lism, or both during the six-month study period.
Recurrent deep-vein thrombosis was diagnosed if
a previously compressible proximal venous segment
or segments could no longer be compressed on ul-
tasonography or if there were constant intralumi-
nal filling defects in two or more projections on ve-
nography. Unequivocal extension of the thrombus
was required for the diagnosis of recurrence if the
results were abnormal on previous testing.9,14,15 Ve-
nography was required to confirm distal deep-vein
thrombosis. Pulmonary embolism was diagnosed
on the basis of a lung scan indicating a high proba-
bility of its presence, as indicated by the presence
of new or enlarged areas of segmental perfusion de-
fects with ventilation–perfusion mismatch; an ab-
normal perfusion scan with documentation of new
or recurrent deep-vein thrombosis; the presence of
nonenhancing filling defects in the central pulmo-
nary vasculature on helical computed tomography;
a finding of intraluminal filling defects on pulmo-
nary angiography; or evidence of fresh pulmonary
embolism at autopsy.9,14,15

Secondary outcome events included clinically
overt bleeding (both major bleeding and any bleed-
ing) and death. A bleeding event was classified as
major if it was associated with death, occurred at a
critical site (intracranial, intraspinal, intraocular,
retroperitoneal, or pericardial area), resulted in a
need for a transfusion of at least 2 units of blood,
or led to a drop in hemoglobin of at least 2.0 g per
deciliter.

All suspected events were reviewed by a central
adjudication committee whose members were un-
aware of the patients’ treatment assignments. Sup-
porting documents, including clinical notes, imag-
ing studies, and the results of laboratory tests, were
forwarded to the coordinating and methods center for adjudication. All reported episodes that were suggestive of recurrent thrombosis were evaluated and confirmed or rejected as representing recurrence, overt bleeding events were classified as major or minor, and all reported deaths were reviewed to determine the cause of death.

**Statistical Analysis**

The initial calculation of the sample size was based on an estimated risk of recurrent thrombosis of 20 percent at six months among patients treated with oral anticoagulant therapy. In order to detect a 50 percent reduction in risk with a power of 0.85 and a two-sided alpha of 0.05, it was determined that 70 primary efficacy outcome events were required. In order to adjust for the loss to follow-up from early death, the sample size was increased by 20 percent. A blinded reassessment of the sample size that was specified in the protocol led us to increase the targeted enrollment by an additional 90 patients. Accordingly, we determined that 676 patients would be required.

An analysis of efficacy end points was performed according to the intention-to-treat principle and included all randomized patients who had a confirmed, qualifying thrombotic event and active cancer. The primary analysis of efficacy was based on the time from randomization to the first recurrent thromboembolic event. Data on patients without events were censored at the time of the six-month visit or death, whichever occurred first. The risk of recurrence over time was estimated according to the Kaplan–Meier method and the treatment groups were compared with use of the two-sided log-rank test. A Cox proportional-hazards regression model was used to examine the influence of potentially prognostic base-line factors (e.g., age, ECOG status, type of qualifying thrombotic event, and presence or absence of metastases) on the risk of recurrent thromboembolism. Interactions between treatment group and covariates were assessed in the model.

Death from all causes was also calculated and compared with use of the Kaplan–Meier method and the two-sided log-rank test, respectively. Patients who received at least one dose of the study drug were included in the safety analyses. The proportions of patients in each group who had a major bleeding event after the first dose and up to 48 hours after the permanent discontinuation of the study drug were compared with use of a two-sided Fishcer’s exact test. Similarly, the proportions of patients in each group with any bleeding were compared.

Two investigators designed and developed the original protocol, which was revised and approved by the steering committee. This committee, composed of seven academic members and one representative of the sponsor, was responsible for overseeing the conduct of the study, formulating the statistical-analysis plan, reviewing and interpreting the data, and preparing the manuscript. The central adjudication committee and data-monitoring committee operated independently of the sponsor. The Clinical Trials Methodology Group at the Henderson Research Centre, Hamilton Health Sciences, was responsible for study coordination, data management, statistical analyses, and administrative support.

### Table 1. Base-Line Characteristics of the Patients.†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dalteparin (N=338)</th>
<th>Oral Anticoagulant (N=338)</th>
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<tbody>
<tr>
<td>Mean age (yr)</td>
<td>62±12</td>
<td>63±13</td>
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<tr>
<td>Female sex (no. of patients)</td>
<td>179</td>
<td>169</td>
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<td>ECOG performance score (no. of patients)</td>
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<tr>
<td>0</td>
<td>80</td>
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<td>1</td>
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<tr>
<td>2</td>
<td>118</td>
<td>122</td>
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<tr>
<td>3†</td>
<td>5</td>
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<td>Hospitalization status (no. of patients)</td>
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<td>Outpatient</td>
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<tr>
<td>Inpatient</td>
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<td>Solid tumor (no. of patients)</td>
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<tr>
<td>No clinical evidence of disease</td>
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<td>33</td>
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<tr>
<td>Localized disease</td>
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<td>43</td>
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<tr>
<td>Metastatic disease</td>
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<td>232</td>
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<td>Antineoplastic treatment (no. of patients)‡</td>
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<td>259</td>
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<tr>
<td>Current smoker (no. of patients)</td>
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<td>42</td>
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<tr>
<td>History of DVT or PE (no. of patients)</td>
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<td>36</td>
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<tr>
<td>Recent major surgery (no. of patients)</td>
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<tr>
<td>Central venous catheter (no. of patients)</td>
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<tr>
<td>Qualifying thrombotic event (no. of patients)‡</td>
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<td></td>
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<tr>
<td>DVT alone</td>
<td>235</td>
<td>230</td>
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<tr>
<td>PE, with or without DVT</td>
<td>103</td>
<td>108</td>
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</table>

† Antineoplastic treatment included chemotherapy, radiation, and surgery.
activities. Pharmacia provided funding and the study drug.

**RESULTS**

**STUDY POPULATION**

Forty-eight clinical centers in eight countries participated (see the Appendix). Recruitment began in May 1999 and was completed in October 2001. Of the 1303 patients who met the inclusion criteria, 439 also met one or more of the exclusion criteria and were not considered eligible. The three most frequent reasons for exclusion were an ECOG score of 3 or 4 (169 patients), treatment with any heparin for more than 48 hours (107), and an inability to reach the clinical center easily (43). Of the remaining 864 eligible patients, 676 provided written informed consent. Eight patients with an ECOG score of 3 were enrolled before the protocol was amended to exclude patients with such a score.

Of the 676 consenting patients, 338 were allocated to receive dalteparin and 338 were assigned to oral anticoagulant therapy, each for six months. Patients in the two groups had similar base-line characteristics (Table 1). Ninety percent of the patients had solid tumors (Table 2), and 67 percent had metastatic disease at the time of randomization.

**ANTICOAGULANT THERAPY**

The mean duration of study treatment was 125 days in the dalteparin group and 115 days in the oral-anticoagulant group. For patients who did not have an outcome event throughout the study period, the mean duration of study treatment was 170 days in both groups.

In the oral-anticoagulant group, the mean (±SD) INR was 2.5±0.75. Using linear interpolation over time, we estimated that the INR was in the therapeutic range 46 percent of the time, below the range 30 percent of the time, and above the range 24 percent of the time.

**RECURRENT VENOUS THROMBOEMBOLISM**

Two patients in each group were excluded from the efficacy analysis because they did not have a qualifying thrombotic event: one patient had a thrombosis in an arm vein, one had an asymptomatic thrombus in the leg, and the other two did not have a confirmed pulmonary embolism. Symptomatic, recurrent deep-vein thrombosis, pulmonary embolism, or both occurred in 27 of 336 patients in the dalteparin group and 53 of 336 patients in the oral-anticoagulant group (Table 3). The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002) over the six-month study period (Fig. 1). The Kaplan–Meier estimate of the probability of recurrent thrombosis at six months was 9 percent in the dalteparin group, as compared with 17 percent in the oral-anticoagulant group. All recurrent deep-vein thromboses were proximal. No significant interactions between treatment group and risk factors were detected. Of the 53 thrombotic events in the oral-anticoagulant group, 20 occurred when the INR was below 2.0.

**BLEEDING**

Three patients assigned to oral anticoagulant therapy did not receive the study drug and were exclud-

<table>
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<tr>
<th>Tumor Site</th>
<th>Dalteparin (N=298)</th>
<th>Oral Anticoagulant (N=308)</th>
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<tbody>
<tr>
<td>no. of patients</td>
<td></td>
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<tr>
<td>Breast</td>
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<td>Pancreas</td>
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<td>16</td>
</tr>
<tr>
<td>Brain</td>
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<td>13</td>
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<tr>
<td>Other</td>
<td>41</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Dalteparin (N=336)</th>
<th>Oral Anticoagulant (N=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep-vein thrombosis alone</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>Nonfatal pulmonary embolism</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>53</td>
</tr>
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</table>
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In the dalteparin group, one patient died from massive hemoptysis related to metastatic lung cancer and three patients bled at a critical site: one patient with a brain tumor had intracranial bleeding, one patient with prostate cancer had retroperitoneal bleeding, and one patient with lung cancer had pericardial bleeding. In the oral-anticoagulant group, there were no fatal bleeding events and four patients bled at a critical site: two patients, one with breast cancer and one with prostate cancer, had intracranial bleeding, and two patients, one with a brain tumor and one with prostate cancer, had retroperitoneal bleeding.

Mortality
During the six-month study period, 130 patients died in the dalteparin group and 136 patients died in the oral-anticoagulant group. The respective mortality rates at six months were 39 percent and 41 percent (P=0.53) (Fig. 2). Ninety percent of the deaths in each group were due to progressive cancer.

Discussion
In patients with cancer, recurrent thromboembolism complicates management and diminishes the patients’ quality of life. Our study shows that the risk of symptomatic, recurrent thromboembolism among patients with active cancer is significantly lower with dalteparin therapy than with oral anticoagulant therapy. Although previous trials comparing low-molecular-weight heparins with warfarin for the secondary prophylaxis of venous thromboembolism did not find a difference in the risk of recurrent thrombosis, most of the trials were small and conducted primarily in patients without cancer.18-24

We did not detect a significant difference in the rates of major bleeding or any bleeding between the treatment groups. Given the limitations of cross-study comparisons, the rates of bleeding in the oral-anticoagulant group are consistent with those in previous studies.2,25 However, our rates of major bleeding from the safety analyses. Nineteen of 338 patients in the dalteparin group (6 percent) and 12 of 335 patients who received oral anticoagulant therapy (4 percent) had major bleeding (P=0.27). The respective rates of any bleeding were 14 percent and 19 percent (P=0.09). At the time of a major bleeding event, two patients in the dalteparin group had thrombocytopenia. Major bleeding was associated with an INR of more than 3.0 in six patients in the oral-anticoagulant group.

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Discussion
In patients with cancer, recurrent thromboembolism complicates management and diminishes the patients’ quality of life. Our study shows that the risk of symptomatic, recurrent thromboembolism among patients with active cancer is significantly lower with dalteparin therapy than with oral anticoagulant therapy. Although previous trials comparing low-molecular-weight heparins with warfarin for the secondary prophylaxis of venous thromboembolism did not find a difference in the risk of recurrent thrombosis, most of the trials were small and conducted primarily in patients without cancer.18-24

We did not detect a significant difference in the rates of major bleeding or any bleeding between the treatment groups. Given the limitations of cross-study comparisons, the rates of bleeding in the oral-anticoagulant group are consistent with those in previous studies.2,25 However, our rates of major
bleeding were lower than those reported in another randomized trial involving patients with cancer; in that study, 7 percent of patients who received low-molecular-weight heparin and 16 percent of those who received warfarin had major bleeding over a three-month period. Differences in the patient population, the INR control, and outcome assessment may explain some of the variations in these results.

The open-label design could be a potential source of bias in our trial. We believed that a double-blind design would not be logistically feasible or safe in patients with cancer who had many other serious conditions and who were taking multiple drugs, potentially increasing the risk of drug interactions. We tried to minimize reporting and diagnostic bias by contacting patients in both groups at frequent and regular intervals, using standardized follow-up procedures, using objective tests to evaluate suspected events, and having all suspected outcomes evaluated by a central committee whose members were unaware of the patients’ treatment assignments. Also, substantial bias related to treatment management is unlikely because the level of INR control achieved was similar to that in other studies and showed that patients who received oral anticoagulant therapy were treated adequately. In addition, the mean duration of treatment in patients who did not have any outcome event was the same in the two groups.

When we planned the study, there was little information on the optimal dose of low-molecular-weight heparin for secondary prophylaxis. We designed a regimen that would provide intensive anticoagulation initially and potentially reduce the risk of anticoagulant-related bleeding over the long term. Practical issues regarding the long-term use of low-molecular-weight heparin include the cost of the drug and the feasibility of self-injection. Long-term self-injection of dalteparin was acceptable to our patients, and it significantly reduced the risk of recurrent venous thromboembolism without increasing the risk of bleeding.

Funded by Pharmacia, Peapack, N.J., which also supplied the study drug. Dr. Lee is the recipient of a New Investigator Award from the Canadian Institutes of Health Research. Drug Research and Development Program; Dr. Levine is the Buffett Taylor Chair in Breast Cancer Research, McMaster University, Hamilton, Ont., Canada; and Dr. Kovacs is an Internal Scholar of the Department of Medicine, University of Western Ontario, London, Ont., Canada.

APPENDIX

The following investigators and institutions participated in the CLOT Trial: Steering Committee: M. Levine (chair), R. Baker, C. Bowden, M. Gent, A. Kakkar, A. Lee, M. Prins, F. Riches; External Safety and Efficacy Monitoring Committee: J. Pater (chair), H. Bülter, S. Goldhaber; Central Adjudication Committee: J. Ginsberg, J. Hirsh, C. Kearon, G. Thomson, J. Weitz; Coordinating and Methods Center: Clinical Trials Methodology Group, Henderson Research Centre, Hamilton, Ont., Canada — I. Julian, S. Haley, A. Ling, B. Rush, T. Finch, L. Bonilla-Escobedo, L. Matthews, J. Windsor, C. Tavormina, H. Nelson, G. Lewis, J. Sicurella; Clinical Centers (the numbers of patients enrolled in each country are given in parentheses) — Canada (255): Hamilton Health Sciences, Henderson Hospital, Hamilton, Ont. — A. Lee, N. Booker, S. Schmidt; London Health Sciences Centre, London, Ont. — M. Kovacs, B. Morrow; Queen Elizabeth II Health Sciences Centre, Halifax, N.S. — B. McCarron, S. Pleasance; Toronto General Hospital, Toronto — W.F. Brien, S. Boross-Harmer; St. Joseph’s Hospital, Hamilton, Ont. — J.D. Douketis, T. Schnurr; Montreal General Hospital, Montreal — S. Solymoss, B. St. Jacques; Sunnybrook and Women’s College Health Sciences Centre, Toronto — W. Geerts, K. Code; British Columbia Cancer Agency, Vancouver Cancer Centre, Vancouver, B.C. — S. Chia, S. Monkman; Hamilton Health Sciences, Hamilton General Hospital, Hamilton, Ont., A.G.G. Turpie, J. Johnson; Kelowna General Hospital, Kelowna, B.C. — J. Sutherland, S. Shori; Australia (144) and New Zealand (16): Australasian Society of Thrombosis and Haemostasis: Royal Perth Hospital, Perth, W.A. — R. Baker, J. Smith; Flinders Medical Centre, Bedford Park, S.A. — D.W. Goghan, J.M. Osmond; Prince of Wales Hospital, Randwick, N.S.W. — S. Dunkley, B. Chong; Box Hill Hospital, Monash University, Box Hill, Victoria — H. Salem, L. Poulton; Westmead Hospital, Westmead, N.S.W. — M. Levine (chair), R. Baker, C. Bowden, M. Levine; Catholic Health System, Suburban Hospital, Springfield, Victoria — J. Lamb, S. Corrigan; Royal North Shore Hospital, University of Sydney, Sydney, N.S.W. — C.M. Ward, K. Sheather; Royal Adelaide Hospital, Adelaide, S.A. — I.N. Oliver, T. Marzafoni; St. Vincent’s Hospital, Sydney, N.S.W. — D. Ma; Monash Medical Centre, Clayton, Victoria — T.E. Gan, A. Cummins; Royal Melbourne Hospital, Parkville, Victoria — A. Grigg, E. Cine; United States (118): University of Southern California, Keck School of Medicine, Los Angeles — S.M. Smorenburg, C.P. W. Klerk; University Hospital, Maastricht, The Netherlands (21): Academic Medical Center of the University of Amsterdam, Amsterdam — M. Levine (chair), R. Baker, C. Bowden, M. Levine; Cleveland Clinic, Cleveland, Ohio — S.B. Deitcher; Mt. Sinai Medical Center, New York — L. Lipsey; St. Joseph Mercy Oakland, Pontiac, Mich. — A. Brady, R. Krishnan; University of Vermont and Fletcher Allen Health Care, Burlington — M. Cushman, L. Chassereau; University of Virginia Health System, Charlottesville — B.G. Maskin, L. Newton; Lovelace Health System, Albuquerque, N.M. — A. Tarnower, R.J. Weiler; Newark Beth Israel Medical Center, Newark, N.J. — A.J. Cohen, E. White; University of Connecticut, Farmington — R. Bona, K. Jennings; Italy (67): Ospedali Riuniti, Bergamo — A. Palanga, R. Labianca; Clinica Medica II, University of Padua, Padua — F. Prandoni, A. Labianca; University of Milan and National Cancer Institute of Milan, Milan — A.B. Federici, G. Pizzocaro; the Netherlands (41): Academic Medical Center of the University of Amsterdam, Amsterdam — M.S. Smorenburg, C.W. Klerk; University Hospital Nymegen, Nymegen — E. Berkemot, D.J.T. Wagener; Maasland Hospital, Sittard — F.L.G. Erdkamp; St. Elisabeth Hospital, Tilburg — C. van der Heul, C. Post; St. Antonius Hospital, Nieuwegein — D.H. Biessma; Van Weel Bethesda Hospital, Dinkelsbühl — C. Kroon, M. Kampius van der Poel; Spain (33): Hospital Universitari Germans Trias i Pujol, Badalona — E. Darant, M. Monsalve; United Kingdom (2): Oldchurch Hospital, Romford — M. Quigley; Mount Vernon Cancer Centre, Northwood — G.J.S. Rastin, J. Boxall.
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