

## ORIGINAL ARTICLE

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

Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc.,  
for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators\*

## ABSTRACT

**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.

From the Departments of Medicine (A.Y.Y.L., M.N.L.) and Clinical Epidemiology and Biostatistics (M.N.L., J.A.J., S.H., M.G.), McMaster University, Hamilton, Ont., Canada; Henderson Research Centre, Hamilton Health Sciences and McMaster University, Hamilton, Ont., Canada (M.N.L., J.A.J., S.H., M.G.); the Department of Medicine, University of Western Australia, Perth, Australia (R.I.B.); Pharmacia Corporation, Peapack, N.J. (C.B.); the Department of Surgical Oncology and Technology, Imperial College, London (A.K.K.); Academic Hospital Maastricht, Maastricht, the Netherlands (M.P.); the Department of Medicine and Pediatrics, George Washington University, Washington, D.C. (F.R.R.); and the Department of Medicine, University of Western Ontario, London, Ont., Canada (M.J.K.). Address reprint requests to Dr. Levine at Hamilton Health Sciences, Henderson Hospital, Rm. 9, 90 Wing, 711 Concession St., Hamilton, ON L8V 1C3, Canada.

\*Participating investigators and institutions are listed in the Appendix.

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**T**HE 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.<sup>1</sup> This approach is highly effective in most patients, but patients with cancer have a substantial risk of recurrent thromboembolism and hemorrhagic complications.<sup>2,3</sup> 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.<sup>2,3</sup>

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,<sup>4</sup> and they can be effective in patients with cancer who have recurrent thromboembolism while receiving warfarin.<sup>5-7</sup> 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 is more effective and safer than oral anticoagulant therapy in preventing recurrent thromboembolism in patients with cancer who have acute venous thromboembolism.

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## METHODS

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### STUDY POPULATION

Adult patients with active cancer and newly diagnosed, symptomatic proximal deep-vein thrombosis, pulmonary embolism, or both were eligible. Active cancer was defined as a diagnosis of cancer, other than basal-cell or squamous-cell carcinoma of the skin, within six months before enrollment, any

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.<sup>8</sup> A diagnosis of pulmonary embolism required verification by ventilation-perfusion lung scanning, helical computed tomography, or pulmonary angiography.<sup>9-11</sup>

Patients were excluded if they weighed 40 kg or less, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 3 or 4,<sup>12</sup> 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 discontinued after a minimum of five days and once the INR had remained above 2.0 for two consecutive days. The INR was measured at least once every two weeks thereafter.

The patients assigned to the dalteparin group received 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 significant 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 dalteparin 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 included a history taking, physical examination, assessment of compliance, and blood drawing for the calculation of a complete blood count and measurement of liver enzymes and creatinine. Scheduled calls and visits included a standardized assessment

of the signs and symptoms of recurrent thromboembolism, bleeding episodes, and adverse reactions. Patients were instructed to report to the clinic immediately if they had any bleeding or symptoms of recurrent deep-vein thrombosis, pulmonary embolism, or both. All suspected episodes of recurrent thrombosis were investigated with the use of objective tests, according to prespecified diagnostic algorithms.<sup>13</sup> 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 episode of objectively documented, symptomatic, recurrent deep-vein thrombosis, pulmonary embolism, 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 ultrasonography or if there were constant intraluminal filling defects in two or more projections on venography. Unequivocal extension of the thrombus was required for the diagnosis of recurrence if the results were abnormal on previous testing.<sup>8,14,15</sup> Venography was required to confirm distal deep-vein thrombosis. Pulmonary embolism was diagnosed on the basis of a lung scan indicating a high probability of its presence, as indicated by the presence of new or enlarged areas of segmental perfusion defects with ventilation-perfusion mismatch; an abnormal perfusion scan with documentation of new or recurrent deep-vein thrombosis; the presence of nonenhancing filling defects in the central pulmonary vasculature on helical computed tomography; a finding of intraluminal filling defects on pulmonary angiography; or evidence of fresh pulmonary embolism at autopsy.<sup>9,14,15</sup>

Secondary outcome events included clinically overt bleeding (both major bleeding and any bleeding) 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.<sup>14,15</sup>

All suspected events were reviewed by a central adjudication committee whose members were unaware of the patients' treatment assignments. Supporting documents, including clinical notes, imaging 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.<sup>16,17</sup> 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 Fish-

**Table 1. Base-Line Characteristics of the Patients.\***

Characteristic	Dalteparin (N=338)	Oral Anticoagulant (N=338)
Mean age (yr)	62±12	63±13
Female sex (no. of patients)	179	169
ECOG performance score (no. of patients)		
0	80	63
1	135	150
2	118	122
3†	5	3
Hospitalization status (no. of patients)		
Outpatient	169	156
Inpatient	169	182
Hematologic cancer (no. of patients)	40	30
Solid tumor (no. of patients)		
No clinical evidence of disease	36	33
Localized disease	39	43
Metastatic disease	223	232
Antineoplastic treatment (no. of patients)‡	266	259
Current smoker (no. of patients)	33	42
History of DVT or PE (no. of patients)	39	36
Recent major surgery (no. of patients)	62	67
Central venous catheter (no. of patients)	46	40
Qualifying thrombotic event (no. of patients)		
DVT alone	235	230
PE, with or without DVT	103	108

\* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group, DVT deep-vein thrombosis, and PE pulmonary embolism.

† Eight patients were included in the study before the protocol was amended to exclude patients with an ECOG score of 3 or 4.

‡ Antineoplastic treatment included chemotherapy, radiation, and surgery.

er'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

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 ( $\pm$ SD) INR was  $2.5\pm 0.75$ . 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-

**Table 2. Sites of Solid Tumors.**

Tumor Site	Dalteparin (N=298)	Oral Anticoagulant (N=308)
	<i>no. of patients</i>	
Breast	59	49
Colorectal area	54	54
Lung	40	50
Genitourinary tract	39	47
Gynecologic system	38	30
Pancreas	13	16
Brain	14	13
Other	41	49

**Table 3. Primary Efficacy Outcome Events.**

Event	Dalteparin (N=336)	Oral Anticoagulant (N=336)
	<i>no. of patients</i>	
Deep-vein thrombosis alone	14	37
Nonfatal pulmonary embolism	8	9
Fatal pulmonary embolism	5	7
Total	27	53

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-

ed 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.

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.

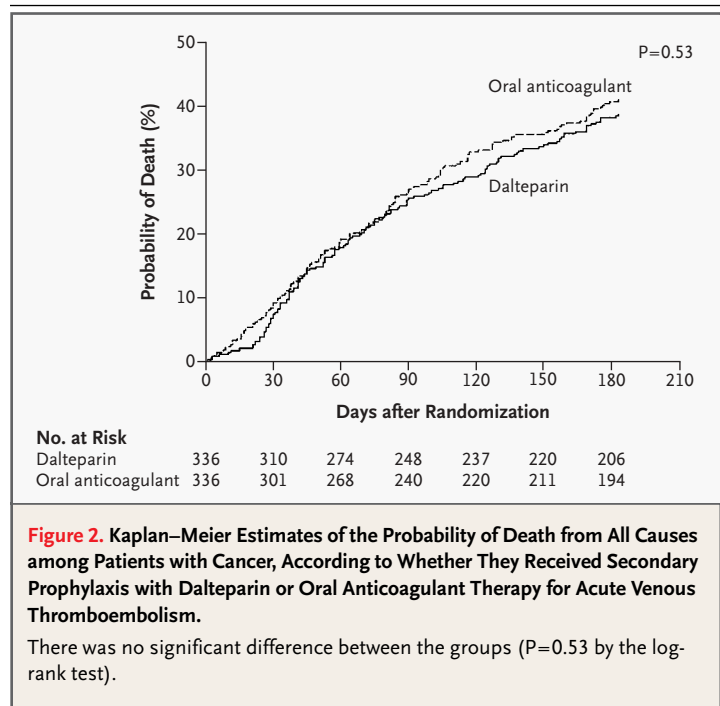
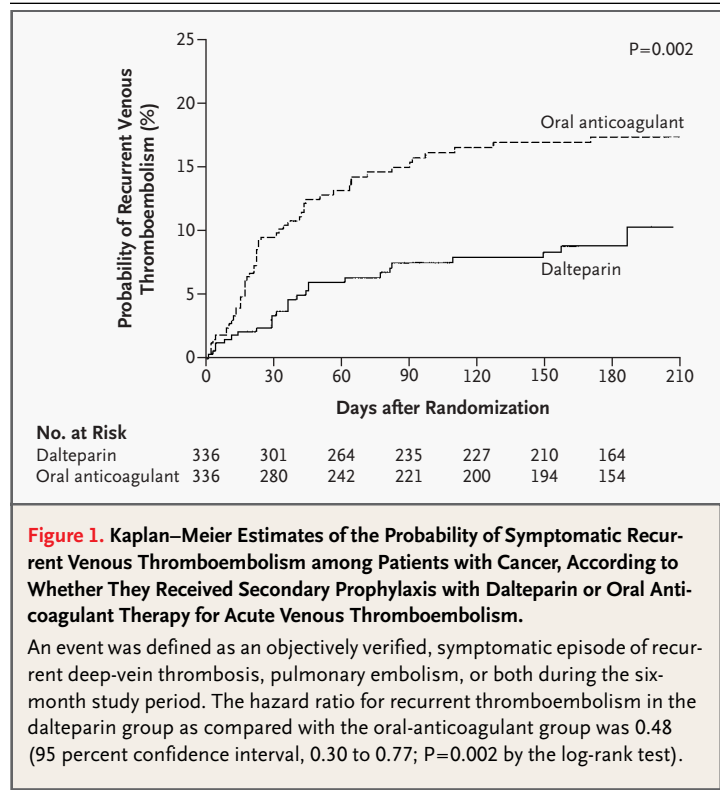
#### MORTALITY

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.<sup>18-24</sup>

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.<sup>2,25</sup> 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.<sup>18</sup> 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.<sup>2,18</sup> 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. Rickles; **External Safety and Efficacy Monitoring Committee:** J. Pater (chair), H. Büller, 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 — J. 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. Coghlan, 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. Hertzberg, P. Stavros; Auckland Hospital, Auckland — P. Ockelford, V. Rolfe-Vyson; St. George Hospital, Kogarah, N.S.W. — T.A. Brighton, R. Ristuccia; Royal North Shore Hospital, University of Sydney, Sydney, N.S.W. — C.M. Ward, K. Sheather; Royal Adelaide Hospital, Adelaide, S.A. — I.N. Olver, T. Marafioti; 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. Cinc; **United States (118):** University of Southern California, Keck School of Medicine, Los Angeles — H. Liebman, I. Weitz; University of Texas, M.D. Anderson Cancer Center, Houston — C.P. Escalante, P. Horace; Northwestern University, Chicago — D. Green, M. Calimaran; University of North Carolina at Chapel Hill, Chapel Hill — S. Moll, S.K. Jones; Arizona Cancer Center, University of Arizona, Tucson — A. Stopeck, K. Glennie; Atlanta Veterans Affairs Medical Center—Emory University, Atlanta — M. Ribeiro, L. Starke; Cleveland Clinic Foundation, Cleveland — S.R. 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. Macik, 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. Falanga, R. Labianca; Clinica Medica II, University of Padua, Padua — P. Prandoni, A. Piccioli, E. Zanon; Angelo Bianchi Bonomi Hemophilia Thrombosis Center, 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 — S.M. Smorenburg, C.P.W. Klerk; University Hospital Nymegen, Nymegen — F. Berkmortel, 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. Biesma; Van Weel Bethesda Hospital, Dirksland — C. Kroon, M. Kamphuis van der Poel; **Spain (33):** Hospital Universitari Germans Trias i Pujol, Badalona — E. Davant, M. Monreal; **United Kingdom (2):** Oldchurch Hospital, Romford — M. Quigley; Mount Vernon Cancer Centre, Northwood — G.J.S. Rustin, J. Boxall.

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