Comparison of Low-Molecular-Weight Heparin and Warfarin for the Secondary Prevention of Venous Thromboembolism in Patients With Cancer

A Randomized Controlled Study

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Background: The use of warfarin sodium for treating venous thromboembolism in patients with cancer is associated with a significant risk of recurrence and bleeding. The use of low-molecular-weight heparin sodium for secondary prevention of venous thromboembolism in cancer patients may reduce the complication rate.

Objective: To determine whether a fixed dose of subcutaneous low-molecular-weight heparin is superior to oral warfarin for the secondary prophylaxis of venous thromboembolism in patients with cancer and venous thromboembolism.

Methods: In a randomized, open-label multicenter trial performed between April 1995 and March 1999, we compared subcutaneous enoxaparin sodium (1.5 mg/kg once a day) with warfarin given for 3 months in 146 patients with venous thromboembolism and cancer.

Main Outcome Measure: A combined outcome event defined as major bleeding or recurrent venous thromboembolism within 3 months.

Results: Of the 71 evaluable patients assigned to receive warfarin, 15 (21.1%; 95% confidence interval [CI], 12.3%-32.4%) experienced one major outcome event compared with 7 (10.5%) of the 67 evaluable patients assigned to receive enoxaparin (95% CI, 4.3%-20.3%; $P=.09$). There were 6 deaths owing to hemorrhage in the warfarin group compared with none in the enoxaparin group. In the warfarin group, 17 patients (22.7%) died (95% CI, 13.8%-33.8%) compared with 8 (11.3%) in the enoxaparin group (95% CI, 5.0%-21.0%; $P=.07$). No difference was observed regarding the progression of the underlying cancer or cancer-related death.

Conclusions: These results confirm that warfarin is associated with a high bleeding rate in patients with venous thromboembolism and cancer. Prolonged treatment with low-molecular-weight heparin may be as effective as oral anticoagulants and may be safer in these cancer patients.

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VENOUS THROMBOEMBOLISM is a frequent complication of active malignancy and has been repeatedly identified as a marker of poor outcome in patients with cancer.[1-3] Patients with cancer and venous thromboembolism have a 3-fold lower survival at 1 year than patients with cancer who do not have venous thromboembolism.[3] The increased mortality rate observed in cancer patients with venous thromboembolism may result from a more advanced cancer state[3] but can also be related to venous thromboembolism itself, which is difficult to treat in these patients. In patients receiving warfarin sodium for venous thromboembolism, underlying malignancy is associated with both an increased risk of recurrent thromboembo-

lism and bleeding.[4-6] In patients receiving oral anticoagulants for venous thromboembolism, underlying malignancy is associated with a 3.0 rate ratio of recurrent thromboembolism and with a 6.2 rate ratio of major bleeding compared with patients free of cancer.[7] These findings strongly call for alternative treatments that should be evaluated in cancer patients with venous thromboembolism.

A recent meta-analysis[8] of the studies comparing unfractionated heparin with low-molecular-weight heparin sodium for the initial treatment of deep venous thrombosis showed a significant 40% reduction in the mortality rate among the patients with cancer who were receiving low-molecular-weight heparin. It has also been suggested that low-molecular-weight heparin may safely

PATIENTS AND METHODS

DESIGN

This study was a multicenter, open-label, randomized trial performed between April 2, 1995, and March 31, 1999, comparing warfarin with once-daily subcutaneous enoxaparin sodium in patients with acute venous thromboembolism and cancer. The study was conducted in 25 centers in France. The ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of Saint-Louis Hospital in Paris approved the study protocol.

PATIENTS

Consecutive patients older than 18 years with cancer of any type and pulmonary embolism and/or deep venous thrombosis were considered for enrollment in the study. Diagnosis of deep vein thrombosis was confirmed by venography or compression ultrasonography. Pulmonary embolism was confirmed by pulmonary angiography or ventilation-perfusion lung scanning that indicated a high probability of pulmonary embolism or a nonnormal lung scan finding coinciding with objectively confirmed deep vein thrombosis. Cancer was defined as solid tumor with or without distant localization or hematologic malignancy. All malignancies were active or in remission but with ongoing antitumor treatment.

Patients were excluded from the study if they had any of the following conditions: previous history of heparin-induced thrombocytopenia, known allergy to iodine, pregnancy, fibrinolytic treatment within 3 days, oral anticoagulant use for more than 5 days, treatment with full-dose heparin for this episode of venous thromboembolism, major pulmonary embolism with shock, less than a 3-month life expectancy, contraindication to anticoagulant treatment (active bleeding, diastolic blood pressure above 120 mm Hg, platelet count lower than $30 \times 10^3/\mu L$), severe hepatic failure (ie, prothrombin time of less than 17 seconds) or severe renal failure (ie, serum creatinine level of 2.04 mg/dL [>180 µmol/L]), major surgery planned within 3 months, and chemotherapy known to induce severe thrombocytopenia (ie, platelet count below $30 \times 10^3/\mu L$) planned within 3 months. After the patients had given written informed consent, randomization was performed using presealed treatment boxes. Treatment allocation was balanced at each center in blocks of 4.

TREATMENT REGIMENS

All patients were given a fixed dose of 1.5 mg/kg of body weight of enoxaparin (Bellon Laboratories, Neuilly sur Seine, France) subcutaneously once daily. The patients randomized to enoxaparin received this regimen for 3 months without dosage adjustment. The patients randomized to warfarin were given 6 to 10 mg of warfarin sodium orally, subsequently adjusted to achieve an international normalized ratio (INR) between 2.0 and 3.0 for 3 months. In these patients, enoxaparin was given until the INR reached at least 2.0 on 2 consecutive measurements taken 24 hours apart after at least 4 days of enoxaparin treatment. The continuation and nature of anticoagulant treatment after the 3-month treatment period were left to the attending physician.

FOLLOW-UP AND SURVEILLANCE

In the patients randomized to the enoxaparin group, anti–factor Xa activity was measured at day 2, day 10, day 30, day 60, and day 90, but no dosage adjustments were performed. Platelet count was monitored twice a week during the first month, then once a week until day 90. In the patients randomized to the warfarin group, INR was

be used for 3 months in patients with venous thromboembolism.[9] Low-molecular-weight heparin may thus represent a promising tool for the secondary prophylaxis of venous thromboembolism in patients with cancer, but data to support this hypothesis are lacking. We report herein the results of an open-label, randomized trial designed to determine whether a fixed dose of subcutaneous low-molecular-weight heparin is superior to oral warfarin for the secondary prophylaxis of venous thromboembolism in patients with cancer and venous thromboembolism.

RESULTS

STUDY POPULATION

There were 147 patients randomized in the study, and 146 received at least one dose of the study medication. Noninclusion registries were not available, but the hospital discharge summaries were analyzed in the 4 main study centers where 56% of the study patients were included. During the study period, 248 patients with cancer and venous thromboembolism were admitted to these centers and 82 (33%) were included. The causes of noninclusion were extracted from the medical records of 78 (47%) of the 166 nonincluded patients: 15 (19%) had more than 5 days of anticoagulant treatment, usually because the cancer was discovered after the thromboembolic episode; 13 (17%) had contraindications to anticoagulant therapy; 13 (17%) refused or were unable to give informed consent; 8 (10%) were in a terminal condition and were judged ineligible by the responsible physician; 7 (9%) had massive pulmonary embolism and received thrombolytic treatment; 7 (9%) had upper extremity venous thrombosis; 5 (6%) had previous heparin-induced thrombocytopenia; 5 (6%) had planned surgery; and 5 (6%) were younger than 18 years.

Among the 146 included patients, 75 were randomized to warfarin and 71 were randomized to enoxaparin. There was no imbalance in baseline characteristics between the 2 groups (**Table 1** and **Table 2**). All but 2 patients received anticoagulant treatment before randomization for a mean time of 3.0±1.7 days in the warfarin group and 2.9±1.5 days in the enoxaparin group. In the warfarin group, 29 patients (38.7%) received unfractionated heparin and 46 (61.3%) received low-molecular-weight heparin. In the enoxaparin group, 27 patients (38.0%) received unfractionated heparin before randomization, 42 (59.1%) received low-molecular-

measured daily until 2 consecutive measurements between 2.0 and 3.0 were obtained and was then monitored at least once a week until day 90. In addition, the local investigator or the primary care physician was free to implement more intensive monitoring when the INR was above or below the therapeutic levels. All patients were examined daily during initial hospitalization. Follow-up visits were scheduled at day 30, day 60, day 90, and day 180. All patients were asked to report any symptoms of recurrent venous thromboembolism or bleeding to the investigator.

Bleeding was defined as major if it was overt and associated with a decrease in hemoglobin concentration by at least 2.0 g/dL or with the need for transfusion of 2 or more units of blood or if bleeding was retroperitoneal, intracranial, intraocular, or associated with death. Minor bleeding was defined as any overt bleeding not fulfilling the definition for major bleeding.

Patients with suspected new or recurrent pulmonary embolism underwent ventilation-perfusion lung scan and/or angiography. Recurrent pulmonary embolism was diagnosed if there was a new segmental or larger perfusion defect with normal ventilation on the lung scan or when a new intraluminal filling defect or a new sudden cutoff was observed in an arterial branch on angiography. Patients with suspected new or recurrent deep vein thrombosis underwent compression ultrasonography or venography, whichever test had been performed on inclusion. Recurrent deep venous thrombosis was defined as a lack of compressibility in a previously compressible venous segment on ultrasonography or as a new intraluminal filling defect on venography.

OUTCOME MEASURES

The primary end point was a combined outcome event of treatment failure defined as symptomatic and objectively confirmed recurrent venous thromboembolism and/or major bleeding within the 3-month treatment period. All potential outcome events were assessed by an independent adjudication committee whose members were unaware of treatment assignment. Secondary end points were 3- and 6-month mortality, evolution of the underlying cancer at 6 months, major and minor bleeding, heparin-induced thrombocytopenia, and recurrent thromboembolism during the 6-month study period.

STATISTICAL ANALYSIS

The incidence of major bleeding or recurrent thromboembolic event in patients with venous thromboembolism and cancer treated with warfarin was estimated to be approximately 30%.[10-12] A sample size of 120 evaluable patients in each group was needed to detect a reduction from 30% to 15% in the primary end point (recurrence of venous thromboembolism and/or major hemorrhage) with enoxaparin using a 2-tailed test, an 80% power, and an α error of .05. However, the steering committee, which was independent from the organization in charge of the data management and unaware of the results, decided to interrupt the study once 146 patients had been enrolled over 4 years because the slow recruitment rate was not compatible with the continuation of the study.

The analysis was performed on an intention-to-treat basis. The χ^2 test (or Fisher exact test when appropriate) and the t test (or Wilcoxon rank sum test) were used for comparisons between the groups. The cumulative incidence of outcome events and deaths was described according to the Kaplan-Meier method, and rates were compared with the use of the log-rank test. Results are given as mean (SD) or as a percentage with 95% confidence intervals (CIs).

weight heparin, and 2 patients did not receive any treatment before randomization and were included as soon as the diagnosis of venous thromboembolism was obtained.

MAIN END POINT

The principal analysis of the primary outcome was conducted on 138 patients because 8 patients (4 in each group) were considered not evaluable by the outcome adjudication committee. Among them, 2 were lost to follow-up; 3 withdrew their consent but did not have any outcome event before; 1 died of septic shock (autopsy was not performed and the adjudication committee was unable to exclude pulmonary embolism as the cause of death); 1 died at home after an acute onset of dyspnea and fever (autopsy was not performed and the adjudication committee was unable to confirm or exclude pulmonary embolism as the cause of death); and 1 was clinically suspected of having recurrent deep vein thrombosis but the adjudication committee judged the venous compression ultrasonography noninformative.

During the 3-month treatment period, 15 patients (21.1%) assigned to receive warfarin experienced major hemorrhage or recurrent thromboembolism (95% CI, 12.3%-32.4%) compared with 7 patients (10.5%) assigned to receive enoxaparin (95% CI, 4.3%-20.3%; P=.09) (relative risk, 2.02; 95% CI, 0.88-4.65). When time to event of primary outcome was analyzed, enoxaparin was more effective than warfarin (P=.04 by the log-rank test) (**Figure 1**).

During the 3-month treatment period, 21 patients (29.6%) randomized to receive warfarin (95% CI, 19.3%-41.6%) experienced major hemorrhage or recurrent thromboembolism or died compared with 13 patients (19.4%) randomized to receive enoxaparin (95% CI, 10.8%-30.9%; P=.17).

MORTALITY

During the 3-month study treatment period, 17 patients (22.7%) receiving warfarin died (95% CI, 13.8%-33.8%) compared with 8 patients (11.3%) receiving enoxaparin (95% CI, 5.0%-21.0%; P=.07) (**Figure 2**). Death was related to progression of the underlying cancer in 14 of the 25 patients who died (9 in the warfarin group and 5 in the enoxaparin group), to bleeding in 6 patients (all in the warfarin group), to sepsis in 4 patients, and to aspiration pneumonia in 1 patient. At the end of the 3-month follow-up period, progression of the un-

Table 1. Baseline Clinical and Biological Characteristics of Study Patients*

Characteristic	Warfarin Sodium Group (n = 75)	Enoxaparin Sodium Group (n = 71)
Male, No. (%)	37 (49.3)	28 (39.4)
Age, y		
Mean ± SD	66 ± 11	65 ± 13
Range	39-86	25-91
Weight, kg		
Mean ± SD	68 ± 14	70 ± 15
Range	40-100	40-106
Venous thromboembolism, No. (%)		
Isolated DVT	25 (33.3)	19 (26.8)
Isolated PE	11 (14.7)	8 (11.3)
DVT and PE	39 (52.0)	44 (62.0)
Risk factors, No. (%)		
Immobilization	20 (26.7)	21 (29.6)
Previous VTE	23 (30.7)	13 (18.7)
Recent surgery	12 (16.0)	18 (25.4)
Varicose veins	13 (17.3)	11 (15.7)
Congestive heart failure	4 (5.3)	5 (7.0)
BMI >30 kg/m^2, No. (%)	8 (10.7)	8 (11.3)
Blood urea nitrogen, mean ± SD, mg/dL (mmol/L)	17 ± 8 (6.0 ± 3.0)	16 ± 9 (5.6 ± 3.2)
Platelet count, mean ± SD, ×10^3/µL	218 ± 101	225 ± 83
Creatinine, mean ± SD, mg/dL (µmol/L)	0.99 ± 0.26 (87.2 ± 23.1)	0.95 ± 0.26 (84.4 ± 22.9)
Hemoglobin, mean ± SD, g/dL	11.4 ± 2.1	10.9 ± 1.7

*DVT indicates deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; and BMI, body mass index.

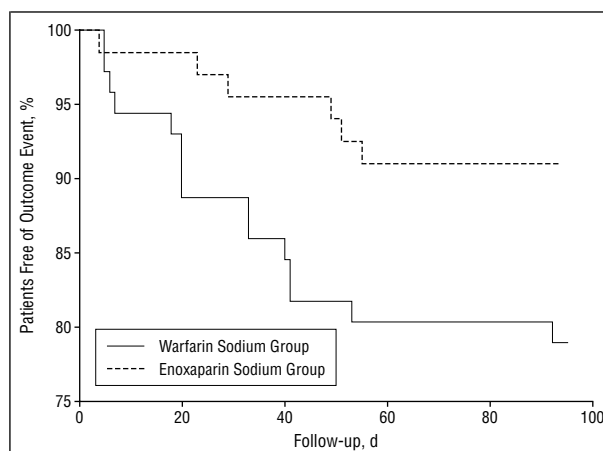**Table 2. Characteristics of the Underlying Cancer at Inclusion in 146 Patients With Venous Thromboembolism***

Characteristic	Warfarin Sodium Group (n = 75)	Enoxaparin Sodium Group (n = 71)
Cancer localization		
Breast	13 (17.3)	19 (26.8)
Digestive tract	11 (14.7)	11 (15.5)
Bronchial	8 (10.7)	8 (11.3)
Hematologic	7 (9.3)	9 (12.7)
Urologic	15 (20.0)	9 (12.7)
Genital	8 (10.7)	8 (11.3)
Unknown origin	7 (9.3)	3 (4.2)
Other	6 (8.0)	4 (5.6)
Cancer duration, mean ± SD, mo	30.3 ± 38.3	25.9 ± 37.6
Metastatic cancer	39 (52.0)	38 (53.5)
Ongoing cancer treatment	52 (69.3)	54 (76.0)

*Data are presented as number (percentage) of patients unless otherwise indicated. No significant difference was observed between the groups.

Figure 1. Recurrent venous thromboembolism or major hemorrhage during the 3-month treatment period in 138 patients with cancer and venous thromboembolism treated with warfarin and enoxaparin. *P*=.04 by the log-rank test.

derlying cancer was observed in 10 patients receiving warfarin (13.3%; 95% CI, 6.6%-23.2%) and in 12 patients receiving enoxaparin (16.9%; 95% CI, 9.0%-27.7%).

BLEEDINGS

Major hemorrhage occurred in 12 patients (16.0%) randomized to receive warfarin (95% CI, 8.6%-26.3%) compared with 5 patients (7.0%) randomized to receive enoxaparin (95% CI, 2.3%-15.7%; *P*=.09). No fatal bleeding was observed in the patients assigned to receive enoxaparin (95% CI, 0%-5.1%), whereas 6 patients (8.0%) in the warfarin group died of bleeding (95% CI, 3.0%-

16.6%; *P*=.03); only 1 of these patients was considered a do-not-resuscitate case. All 5 patients randomly assigned to receive enoxaparin who experienced major bleeding had a creatinine clearance between 30 and 111 mL/min (0.50 and 1.85 mL/s).

The sites and study day of all major bleedings are given in **Table 3**. In the enoxaparin group, mean anti–factor Xa activity was 0.80±0.36 IU/mL at day 30, 0.72±0.31 IU/mL at day 60, and 0.68±0.35 IU/mL at day 90. The mean number of INR measurements in the warfarin group was 2.4 per week during the 3-month treatment period, and patients were within the therapeutic range for 41% of the treatment period.
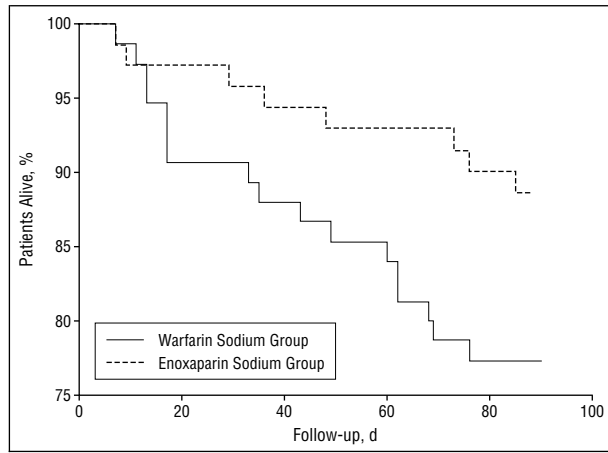
Figure 2. Overall mortality during the 3-month treatment period in 146 patients with cancer and venous thromboembolism treated with warfarin and enoxaparin. *P*=.07 by the log-rank test.

SIX-MONTH FOLLOW-UP

One hundred twenty-one patients were alive at the end of the 3-month treatment period and were followed up for an additional 3 months. During this additional period, 50 received warfarin, 25 received low-molecular-weight heparin, 5 were given unfractionated heparin, and 41 did not receive any anticoagulant treatment. From day 90 to day 180, 3 episodes of recurrent venous thromboembolism occurred in 3 patients who did not receive any anticoagulant treatment after the 3-month study treatment (all in patients from the enoxaparin group).

During the total 6-month follow-up, 29 patients (38.7%) randomized in the warfarin group (95% CI, 27.6%-50.6%) died compared with 22 patients (31.0%) randomly assigned to enoxaparin (95% CI, 20.5%-43.1%; *P*=.25 by the log-rank test). During the same period, cancer progressed in 27 patients (36.0%) who received warfarin (95% CI, 25.2%-47.9%) compared with 24 patients (33.8%) given enoxaparin (95% CI, 23.0%-46.0%).

ADDITIONAL FINDINGS

During the 6-month study period, minor hemorrhage occurred in 9 patients from the warfarin group and in 5 patients from the enoxaparin group. Eighteen patients randomly assigned to warfarin (24%) experienced 1 or more episodes of thrombocytopenia compared with 16 patients randomly assigned to enoxaparin (32.4%). There was no episode of heparin-induced thrombocytopenia in either group. No vertebral fracture was observed in either group during the 6-month follow-up period.

COMMENT

The results of the present study confirm that patients with cancer are at high risk of adverse events during anticoagulant treatment for venous thromboembolism. They also support that major bleeding is the main concern, at least when warfarin is used for secondary prophylactic

Table 3. Major Bleeding During the 3-Month Treatment Period With Warfarin (n = 75) or Enoxaparin Sodium (n = 71) in 146 Patients With Cancer and Venous Thromboembolism*

Site of Bleeding	Time of Bleeding	Last INR or Anti–Factor Xa Value Before Bleeding, IU/mL (Date)
Warfarin sodium group		
Cerebral metastases	D 17	1.0 (D 16)
Upper gastrointestinal tract	D 41	6.5 (D 41)
Epistaxis (tumor)	D 31	4.0 (D 31)
Hematuria†	D 13	3.0 (D 13)
Hematuria (tumor)†	D 4	4.5 (D 4)
Upper gastrointestinal tract†	D 6	4.0 (D 4)
Rectal tumor†	D 2	1.4 (D 2)
Rectal tumor	D 19	3.7 (D 16)
Subdural hematoma	D 74	1.2 (D 74)
Upper gastrointestinal tract†	D 47	2.7 (D 47)
Upper gastrointestinal tract (tumor)†	D 18	4.0 (D 18)
Upper gastrointestinal tract	D 53	8.0 (D 53)
Enoxaparin sodium group		
Pancreatic tumor	D 23	ND
Lower gastrointestinal tract	D 55	0.34 (D 38)
Hematuria	D 48	0.97 (D 4)
Postoperative wound hematoma	D 13	ND
Upper gastrointestinal tract	D 68	0.59 (D 57)

*INR indicates international normalized ratio; D, day after inclusion; and ND, not done.
†Fatal bleeding occurred.

treatment of venous thromboembolism, whereas enoxaparin may reduce the overall major complication rate in these patients. However, such results are not applicable to all patients with cancer and venous thromboembolism, since only about 33% of the patients admitted to the main study centers were included. Patients with massive pulmonary embolism requiring thrombolytic treatment and those with a high risk of bleeding were not included. The study was designed as an open-label trial to avoid the use of a daily subcutaneous placebo injection in the patients randomized to warfarin. As a result, the difference we observed concerning major bleeding may be driven by bias, although all potential outcome events reported by the local investigators were assessed by an outcome adjudication committee unaware of treatment assignment.

The rate of recurrent venous thromboembolism in the patients who received warfarin is in agreement with previously reported data in patients with venous thromboembolism and cancer. In the Columbus study,[6] in which patients with venous thromboembolism were treated with either unfractionated heparin or low-molecular-weight heparin followed by oral anticoagulants, the 3-month recurrence rate was 8.6% in the subgroup of 232 patients with cancer at baseline compared with 5.3% in the present study. The 22.7% mortality rate in the patients assigned to receive warfarin is also in accordance with results previously reported in cancer patients receiving oral anticoagulants.[6,13] Indeed, the 3-month mortality rate in cancer patients treated with warfarin for venous thromboembolism was 20.3% in the Columbus study[6] and 21.5% in a recent meta-analysis on low-molecular-weight heparin for the initial treatment of deep venous thrombo-

sis.[13] The 16% major bleeding rate observed in our study among the patients allocated to receive warfarin for 3 months was higher than the 13.3 major bleeding per 100 patient-years reported in a recent analysis of 264 patients with cancer included in the Columbus or Tasman trials,[7] but was close to the figures reported by others.[14] Although patients assigned to receive warfarin underwent weekly INR monitoring during the study, these patients had therapeutic INRs during 41% of the treatment time only. This poor anticoagulant control was, at least in part, responsible for the high bleeding rate observed in our patients receiving warfarin as suggested by the high INR values observed at time of bleeding in 8 of the 12 patients receiving warfarin who experienced a major bleeding episode. In the present study, the patients did not have their oral anticoagulant treatment managed in an anticoagulant clinic, the warfarin dosing had been managed by either the local investigator or the primary care physician according to standard practice in our country, and this may in part explain the poor anticoagulant control we observed in the patients randomized to warfarin. However, such poor anticoagulant control has been previously reported in patients with cancer who were followed up in an anticoagulation clinic[15] and may be related to hepatic dysfunction induced by chemotherapy and/or by interaction between the oral anticoagulant treatment and other medications in these patients. Difficulties encountered to achieve stable oral anticoagulation may explain why cancer is considered an independent risk factor for major bleeding in patients receiving anticoagulant therapy for venous thromboembolism.[5,16] The lower incidence of major bleeding and fatal bleeding episodes in the patients receiving low-molecular-weight heparin may be owing to better anticoagulation control in this group of patients as suggested by the anti–factor Xa levels.

The high failure rate of long-term oral anticoagulant treatment in patients with venous thromboembolism and cancer suggests that alternative treatments should be evaluated, and it has been suggested that long-term low-molecular-weight heparin use may be superior to oral anticoagulants in these patients.[2,17] The results of the present study support this hypothesis, suggesting that a full dose of enoxaparin is at least as effective as and may be safer than warfarin for the long-term treatment of venous thromboembolism in cancer patients. Since initial anticoagulant treatment was short and did not differ between the 2 groups, the results may not be explained by differences in the initial prestudy treatment or by the site and extension of the underlying cancer, which were also well balanced between the 2 groups. However, since the number of patients recruited in the study is relatively small, the difference observed between the 2 treatment groups should be interpreted with caution due to a lack of power.

We did not observe a reduction in the mortality rate owing to cancer in the patients receiving enoxaparin compared with those assigned to receive warfarin. This observation was reinforced by the lack of difference between the 2 treatments concerning progression of the underlying malignancy at 3 and 6 months. This result contrasts with the conclusions from a recent analysis of 629 patients with cancer who received low-molecular-weight heparin or unfractionated heparin for the initial treatment of deep vein thrombosis.[8] The authors concluded that 5- to 10-day low-molecular-weight heparin treatment was associated with a reduced 3-month mortality rate, which was not explained by a reduction in major bleeding or recurrent thromboembolism. They therefore suggested that low-molecular-weight heparin could have an antitumorigenic effect. In our study, the potential antimetastatic effect of low-molecular-weight heparin could be of little help due to the large number (53%) of patients with disseminated cancer at inclusion. Conversely, it has been recently suggested that long-term use of warfarin was associated with a lower risk of newly diagnosed cancer[18]; according to this finding, the lack of difference concerning cancer spread between the 2 study groups could also be owing to an antitumorigenic effect of warfarin, but our study was neither designed nor powerful enough to address this issue.

In conclusion, the results of the present study suggest that the long-term use of enoxaparin may be an effective and safe treatment for secondary prevention of venous thromboembolism in patients with cancer and venous thromboembolism. These results were obtained in patients with malignancies with various origins and various degrees of dissemination. However, larger studies are required to confirm these findings.

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