Low-molecular-weight heparin (nadroparin) and very low doses of warfarin in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters: a pilot randomized trial

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Background and Objectives. Upper extremity thrombosis is a major complication of central venous catheters implanted for chemotherapy in cancer patients. Vitamin K antagonists and low-molecular-weight heparins have been recommended in this setting, but their relative benefit-to-risk ratios have never been compared.

Design and Methods. A prospective, randomized, open, parallel-group, multicenter trial was performed comparing the antithrombotic efficacy and safety of warfarin and the low-molecular-weight heparin, nadroparin, in cancer patients who had undergone central venous catheter implantation. Warfarin was given orally at a fixed daily dose of 1 mg and nadroparin was injected subcutaneously at a fixed daily dose of 2,850 IU for 90 days, or until venographically-confirmed thrombosis occurred. The primary efficacy outcome was the occurrence of upper extremity thrombosis confirmed by venography performed 90 days after insertion of the catheter, or earlier if symptoms of thrombosis had appeared. Safety end-points were bleeding and thrombocytopenia.

Results. Fifty-nine patients were included in the study. A total of 21 and 24 patients in the nadroparin and warfarin groups, respectively, were evaluable for primary efficacy. Six out of the 21 patients in the nadroparin group (28.6%) and 4 out of the 24 patients in the warfarin group (16.7%) had venographically-documented upper extremity thrombosis at day 90 (p=0.48). Safety was satisfactory and similar with both treatments.

Interpretation and Conclusions. Warfarin at a fixed, very low dose and nadroparin at a fixed, prophylactic dose had comparable benefit-to-risk ratios in the prevention of thrombosis associated with central venous catheters in cancer patients.

Key words: central venous catheter, upper extremity thrombosis, warfarin, low-molecular-weight heparin, prevention.

Haematologica 2003;88:67-73
http://www.haematologica.org/2003_01/88067.htm

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Infusion chemotherapy for cancer treatment requires reliable venous access for which indwelling long-term central venous catheters have been developed.[1] A major complication of catheter placement is the occurrence of thrombotic events. This thrombotic risk varies between 17% and 62%, depending notably on the type of catheter and the nature of the cancer.[1-3] Thrombosis of the axillary/subclavian veins is a serious adverse event which results in loss of the central venous access for infusion chemotherapy, favors sepsis and may be complicated by pulmonary embolism and post-thrombotic syndrome.[4-7] Systemic treatments to prevent thrombosis are, therefore, needed.

Only two randomized open clinical trials examining different antithrombotic strategies in cancer patients with central venous catheters have been performed.[2,3] In the first study comprising 82 patients, the vitamin K antagonist, warfarin, administered at a fixed, very low dose of 1 mg once daily for three months, significantly reduced the incidence of thrombosis associated with a central venous catheter from 37.5% in the non-treated control group to 9.5%.[2] A second, smaller trial on 29 patients showed that the low-molecular-weight heparin, dalteparin, injected at a daily dose of 2,500 IU, reduced this incidence from 61.5% to 6.2%.[3] Based on these trials, these two antithrombotic stategies have been recommended in cancer patients with central venous catheters.[8] However, the optimal treatment has not yet been determined as the relative benefit-to-risk ratios of warfarin and low-molecular-weight heparins in this setting have never been compared in a single trial.

The aim of the present study was to compare the antithrombotic efficacy and safety of warfarin and the low-molecular-weight heparin, nadroparin, in cancer patients with a central venous catheter. Since the rate of upper extremity thrombosis varied widely in the previous studies,[1-3] we conducted a pilot trial in 60 cancer patients to establish the feasibility of a further larger trial.

Design and Methods

This study was a prospective, randomized, open, parallel-group, multicenter trial comparing oral warfarin and subcutaneous nadroparin.

Patients

Consecutive patients aged at least 18 years with non-hematologic cancer scheduled to undergo placement of a long-term subclavian venous catheter and having an expected survival of over three months, were considered for

inclusion. Patients were excluded if they had had central catheters implanted previously, if they required long-term anticoagulant treatment for a chronic co-morbid condition, if they had had a stroke within the previous two months, or if they had active bleeding, bacterial endocarditis, a platelet count below 100 $\times 10^9$/L, a prothrombin time > 15 s (normal reference range, 11 to 14 s), an activated partial thromboplastin time > 10 s the normal reference time (32 s), a prior history of allergy to heparin or heparin-induced thrombocytopenia, a hypersensitivity to iodinated contrast medium, or impaired renal or liver function.

Placement of catheters

All types of totally implantable port-system catheter could be used (DistriCath®, Districlass Medical S.A., France; Port-A-Cath®, Deltec Inc., USA; B Braun's central venous catheter, B Braun Medical, Germany). Catheters were implanted in an operating room by a surgeon experienced in percutaneous techniques. The subclavian route was recommended, correct placement of the catheter tip in the superior vena cava being confirmed by chest X-ray. The implantation of central venous catheters ipsilateral to a tumor likely to be treated with radiotherapy was prohibited.

It was recommended that catheter maintenance was performed according to a standardized procedure: the catheter lumen was flushed with 10 mL of saline solution and 5 mL of heparinized saline solution (500 IU of heparin) after catheter insertion, after each blood collection, after each infusion chemotherapy, and otherwise at least once a week.

Study design

Three days before catheter placement, eligible patients were randomly assigned to receive a dose of either 2,850 IU of nadroparin (Sanofi-Synthelabo, Paris, France) administered subcutaneously, once daily, starting 2 h before insertion of the catheter, or a low fixed dose (1 mg) of warfarin (Aventis, Bridgewater, NJ, USA) given orally, once daily, starting three days before insertion of the catheter. Randomization was stratified by center. Concealment of randomization was achieved through centralized distant randomization. A computer-derived treatment schedule was used to assign treatment regimens. To obtain a continuing balance of treatments, the randomization list was divided into consecutive blocks.

The day of catheter placement was defined as day 0. The treatments were scheduled to last for 90±5 days, or until venographically-confirmed thrombosis occurred. Patients' appointments were scheduled at one-monthly intervals during the 90-day study treatment period. Patients were then followed-up at six months. At each appointment, a clinical examination, assessing notably the absence of catheter occlusion and compliance with study treatments, and biological assays (blood cell count and international normalized ratio - INR) were performed. All clinical signs of thrombosis of the upper extremity ipsilateral to the catheter were carefully sought. Prothrombin times (Neoplastine, Stago, Asnières, France), measured using an automatic analyzer (BCS, Dade Behring, Paris, France) and converted into INR were assayed on days 0, 3, 7, 30, 60 and 90. Platelet counts were performed twice a week during the first three weeks of the treatment period, and weekly thereafter.

The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by the local Ethics Committee (*Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale de la région Rhône-Alpes, Loire, France*). Written informed consent was obtained from eligible patients before randomization.

Medications

Study medications were packaged in boxes. Each patient was given a box holding 108 prefilled, single-dose syringes containing 2,850 IU of nadroparin in 0.3 mL of water for injectable preparations (a concentration of 9,500 IU/mL) or three bottles of 20 scored tablets containing 2 mg of warfarin, breakable into two parts each containing 1 mg of warfarin. Throughout the treatment period, any other anticoagulant agents, high-dose aspirin (>500 mg/day), ticlopidine, pyrazolone, and miconazole, were prohibited. The use of low-dose aspirin (<500 mg/day), other non-steroidal anti-inflammatory drugs and corticosteroids was discouraged. In addition, centers were advised to avoid chloramphenicol, diflunisal and latamoxef in patients receiving warfarin. Finally, all decisions on chemotherapy drugs or radiotherapy were left to the discretion of the care-giving oncologists.

Outcome measures

The primary end-point, with respect to efficacy, was upper extremity thrombosis by day 90 confirmed by bilateral venography performed routinely 90±5 days after insertion of the catheter, or earlier if symptoms of thrombosis had appeared. Upper extremity thrombosis included both asymptomatic and symptomatic deep-vein thrombosis, as well as non-occlusive thrombosis around the catheter. Secondary efficacy end-points were any thromboembolic events (deep-vein thrombosis or pulmonary embolism confirmed by venography of the upper extremities, Doppler ultrasonography and/or venography of the lower limbs, ventilation-perfusion lung scanning, pulmonary angiogram, helical computed tomography or autopsy), and catheter complications (infection, removal and obstructions). Catheter-related infec-

tion was defined as clinical manifestations of infection, at least one positive blood culture obtained from a peripheral vein, and no other apparent source for the bloodstream infection other than the catheter.

Venograms were performed via both the antecubital arm vein ipsilateral to the catheter and the contralateral antecubital arm vein. In breast cancer patients, due to the risk of lymphedema and in order to avoid any infectious complications, only unilateral venography ipsilateral to the catheter was performed. When necessary for clarification, a selective catheterization of the superior vena cava, the proximate innominate vein or the subclavian veins was performed. Contrast medium was systematically injected via the catheter in order to determine whether thrombi were present in the catheter. All venograms were reviewed by an independent reading committee, the members of which were unaware of the patients' treatment allocation.

Catheter obstruction was considered if infusion through the catheter became impossible after all the following procedures of permeabilization: when the catheter was not patent, the catheter lumen was first flushed with saline and heparin; if this was unsuccessful, 5,000 units of urokinase were injected through the catheter; the study was continued according to the protocol if the catheter became patent again; if the catheter was still not patent, venography of the upper extremity was performed to determine whether the inability to infuse through the catheter was due to thrombosis; if no thrombus was present and in the absence of international recommendations, 75,000 units of urokinase, a dose commonly used in the various investigating centers, were injected over three hours; if this treatment was unsuccessful, catheter obstruction was recorded and catheter removal was left to the investigator's discretion, but the patient continued the study according to the protocol.

Safety end-points were death, episodes of major bleeding and laboratory-confirmed heparin-induced thrombocytopenia. Major bleeding included fatal bleeding, bleeding that was intracranial, retroperitoneal, or involved another critical organ (e.g. eyes or adrenal glands), or bleeding associated with a need for transfusion of two or more units of packed red blood cells.

All outcome events were reviewed by a central adjudication committee, the members of which were unaware of the patients' treatment allocation.

Statistical analysis

This pilot study was conducted to determine the rate of upper extremity deep-vein thromboses and thromboses in the catheter, and assess the feasibility of a further larger study comparing these treatments in preventing catheter-induced deep-vein thrombosis. In the absence of any knowledge about this complication rate, the number of patients was empirically set at 30 patients per group. Efficacy and safety analyses were by intention-to-treat. Data were processed and analyzed by the SAS-Windows™ software (version 8.2). Analysis of categorical variables was performed using a χ^2 test, or Fisher's exact test, when appropriate. Continuous variables were analyzed using Student's t-test. A p value of less than 0.05 (two-tailed) was considered to indicate statistical significance.

Results

Between May 1998 and March 2000, 60 patients were randomized in five French centers (*see Appendix*). Thirty patients were allocated to the nadroparin group and 30 to the warfarin group. One patient from the nadroparin group withdrew consent just prior to placement of the catheter, leaving 29 patients in this group. The baseline characteristics of the 59 patients who completed the study are shown in Table 1. There were more lymph node tumefactions in the patients of the warfarin group than among those of the nadroparin group (p=0.027). No other statistically detectable differences in the baseline characteristics between the two treatment groups were observed. The description of the indwelling long-term central venous catheters is presented in Table 2.

Thromboembolic events

Twenty-one patients in the nadroparin group and 24 patients in the warfarin group were evaluable for the primary end-point (Table 3). Missing data were equally distributed between the two treatment groups. Overall, ten patients died before completing the study, six in the nadroparin group and four in the warfarin group. Due to technical difficulties or patients' refusal, venograms of the upper extremities could not be performed in four patients, two in each treatment group. None of these patients had clinical evidence of thrombosis.

Table 3 shows the distribution of the upper extremity thromboses (symptomatic and asymptomatic deep-vein thrombosis and thrombosis in the catheter) observed in the two treatment groups at day 90. Six out of the 21 (28.6%) patients in the nadroparin group and four out of the 24 (16.7%) patients in the warfarin group had venographically-documented upper extremity thrombosis at day 90 (p=0.48). Thrombosis occurred in the arm ipsilateral to the catheter in all patients but one in the nadroparin group. One episode of thrombosis was controlateral. Neither the type of catheter, nor the presence of lymph node tumefactions significantly affected the incidence of thrombosis; for example, six patients out of 10 presenting a thromboembol-

Table 1. Baseline characteristics of patients who completed the study.

Baseline values	*Nadroparin Group (n=29)*	*Warfarin Group (n=30)*
Male sex, n (%)	19 (65.5)	15 (50.0)
Age, years, mean ± SD	60.3 ± 9.5	57.1 ± 9.0
Previous history of thrombotic events, n (%)	8 (27.6)	6 (20.0)
Cancer duration, months, median (1st and 3rd quartiles)	1.6 (1.3-5.4)	2.2 (1.5-17.6)
Cancer location, n (%)		
gastrointestinal tract	15 (51.7)	15 (50.0)
breast, ovary, uterus	6 (20.7)	8 (26.7)
lung	2 (6.9)	3 (10.0)
head and neck	2 (6.9)	1 (3.3)
testis	0 (0.0)	1 (3.3)
others	4 (13.8)	2 (6.7)
Metastases, n (%)	23 (79.3)	26 (86.7)
lymph node tumefaction	10 (34.5)	19 (63.3)†
liver	9 (31.0)	8 (26.7)
lung, peritoneum	8 (27.6)	6 (20.0)
bone	2 (6.9)	7 (23.3)
brain	0 (0.0)	1 (3.3)
Prior chemotherapy	4 (13.8)	5 (16.7)
Prior chest radiotherapy	4 (13.8)	7 (23.3)
Baseline platelet count, $\times 10^9$/L, mean ± SD	322 ± 120	334 ± 125

†*p=0.027 warfarin versus nadroparin.*

Table 2. Description of the indwelling long-term central venous catheters used.

Baseline Values	*Nadroparin Group (n=29)*	*Warfarin Group (n=30)*
Type of central venous catheter, n		
single	28	29
double	1	1
Type of central lines, n		
silicone	28	28
polyurethane	1	2
Insertion procedure, n		
subclavian route	28	28
jugular route	1	2
Side insertion, n		
right	22	19
left	7	11

ic event had lymph node tumefactions compared to 17 patients out of 35 without any thromboembolic event. However the incidence seemed to be higher in patients with a history of venous thromboembolism than in those without such a history (36.4% and 17.6%, respectively). The overall number of total thromboembolic events did not differ significantly between the nadroparin group (31.8%) and the warfarin group (16.7%) (p=0.23, Table 3). One patient in the nadroparin group developed a symptomatic deep-vein thrombosis in a lower limb by day 90 and was not available for the analysis of the primary end-point because he died at day 50 before systematic venography had been performed.

Catheter complications

By day 90, there had been one catheter removal in each treatment group due to catheter-related infection. In one patient in the warfarin group, the catheter was not patent at day 90, but as it became patent after the administration of urokinase and remained functional throughout the study period, no catheter obstruction was recorded.

Safety results

By day 90, six patients in the nadroparin group and four patients in the warfarin group had died (Table 4). One episode of major bleeding (fatal hemoptysis in a patient with lung cancer) occurred in the nadroparin group compared with none in the warfarin group. Severe thrombocytopenia (<50 $\times 10^9$/L) occurred in two patients in the nadroparin group and one patient in the warfarin group, but no laboratory-confirmed heparin-induced thrombocytopenia was reported.

Laboratory results

At day 7 (i.e. 10 days after the start of warfarin treatment), the INR was more than 1.5 in three patients of the warfarin group (INR equal to 1.77, 1.95 and 3.78). It exceeded 1.5 at least once within the 90-day study period in four patients of the warfarin group.

Follow-up results

From day 90 to 6 months, patients no longer received their respective antithrombotic agent according to the protocol. Two patients in the nadroparin group who experienced deep-vein thrombosis of an upper extremity between day 0 and day 90 had one additional symptomatic vein thrombosis, one in an upper extremity (day 120), and one in a lower limb (day 142) (Table 4). Neither patient had been treated for the first event because it was asymptomatic and diagnosed subsequently by the central reading committee. One further patient in the nadroparin group experienced a symptomatic deep-vein thrombosis in a lower limb on day 133 (Table 4). During this period, all catheters remained functional, none was removed and there were no episodes of catheter-related infection. There were two episodes of major bleeding and two episodes of severe thrombocytopenia, all occurring in the warfarin group. Finally, five additional deaths

occurred, four in the nadroparin group and one in the warfarin group.

Discussion

This pilot, randomized study did not demonstrate that a fixed, low dose of warfarin and a fixed, prophylactic dose of the low-molecular-weight heparin, nadroparin, had statistically different efficacies in preventing upper extremity thrombosis in cancer patients with indwelling long-term central venous catheters. Safety was satisfactory with both treatments.

Our study population, limited to patients with solid tumors, was representative of cancer patients who undergo catheter placement for infusion chemotherapy. The baseline characteristics of the two treatment groups differed only in the number of lymph node tumefactions, but this parameter did not affect the incidence of thrombosis. Other clinical or biological parameters reported to be risk factors for the development of upper extremity thrombosis, such as previous episodes of thrombotic events[9] or blood platelet count,[3] were similar between the two groups.

The overall incidence of upper extremity thrombosis including thrombosis within the catheter (symptomatic and asymptomatic), occurring by day 90 remained relatively high with both treatments (16.7% and 28.6% with warfarin and nadroparin, respectively). However, these incidences are lower than those reported in previous trials in patients receiving no antithrombotic treatment, which were 37.5%[2] and 61.5%,[3] indirectly highlighting the need for such a treatment in cancer patients with a long-term indwelling central venous catheter.

The antithrombotic efficacy of warfarin in our trial was comparable to that observed in a previous study performed in 60 patients receiving warfarin according to the same dosage regimen.[2] In that study, the incidence of upper extremity deep-vein thrombosis (excluding thrombosis within the catheter, which was not recorded) was 9.5% (95% confidence interval: 0.5-18%), compared to 11.5% in our study. The incidence of upper extremity thrombosis in patients treated with nadroparin was higher than that observed in a previous smaller study (on 29 patients) using a prophylactic dose (2500 IU once daily) of dalteparin, another low-molecular-weight heparin.[3] In that study, the incidence of upper extremity thrombosis in the 16 patients treated with dalteparin was 6.2% (95% confidence interval: 0-18%) compared to 28.6% in the nadroparin group of the study reported here. It should be noted, however, that the rates of symptomatic thrombosis between these two studies were similar, 6.2% and 4.8%, respectively. Furthermore, in our trial, when thrombosis in the catheter was excluded, the incidences of upper extremity deep-vein thrombosis in the warfarin and nadroparin groups were close (12.5% and 14.3%, respectively). Different venographic procedures may explain the relatively high rate of asymptomatic thrombosis observed in our trial: in contrast to Monreal *et al*.,[3] we systematically performed bilateral venography of the upper extremities, and systematically inject-

Table 3. Results of the efficacy end-point analysis at day 90.

Number of patients	*Nadroparin Group (n=29)*	*Warfarin group (n=30)*	*p value*
Available for the primary end-point analysis*	21	24	
with symptomatic upper extremity DVT	1	2	
with asymptomatic upper extremity DVT	2	1	
with symptomatic thrombosis in the catheter	0	0	
with asymptomatic thrombosis in the catheter	3	1	
Total upper extremity thromboses	6	4	
[95% confidence interval]°	28.6% [9-48]	16.7% [2-32]	0.48
Available for the secondary efficacy end-points#	22	24	
with upper extremity thrombosis	6	4	
with lower limb DVT	1	0	
with PE	0	0	
Total thromboembolic events	7	4	
[95% confidence interval]	31.8 % [12-51]	16.7 % [2-32]	0.23

*DVT denotes deep-vein thrombosis and PE, pulmonary embolism. *Systematic venography was not performed at day 90 in 14 patients because of death before day 90 in 10 patients (six in the nadroparin group and four in the warfarin group) and because of technical difficulties or the patients' refusal in four patients, two in each treatment group. None of these 14 patients had clinical evidence of thrombosis. °Thrombosis occurred in the arm ipsilateral to the catheter in all patients but one in the nadroparin group. #One patient in the nadroparin group developed a symptomatic deep-vein thrombosis in a lower limb by day 90; this patient was not available for the analysis of primary efficacy (n=21) because he died at day 50 before systematic venography had been performed, but was included in the analysis of secondary efficacy (n=22).*

Table 4. Thromboembolic events and deaths at six months.

Number of patients	*Nadroparin group (n=29)*	*Warfarin group (n=30)*	*p*
With thromboembolic event			
day 0 to day 90	7	4	
day 90 to 6 months	3	0	
Total thromboembolic events at 6 months	8/22†	4/24	
[95% Confidence Interval]	(36.4%) [16-56]	(16.7%) [2-32]	0.13
Deaths:			
day 0 to day 90	6	4	
day 90 to 6 months	4	1	
Total deaths at 6 months			
[95% Confidence Interval]	10/29 (34.5%) [17-52]	5/30 (16.7%) [3-30]	0.12

†Two patients in the nadroparin group each experienced two thromboembolic events within six months.

ed contrast medium via the catheter in order to determine whether thrombi were present in the catheter. Differences in the population of cancer patients, type of central venous catheter or type of chemotherapy infusion, all factors known to contribute to the development of catheter-associated thrombosis[1,5] could also explain our findings. Nevertheless, asymptomatic upper extremity deep-vein thromboses, which appear to be relatively frequent, should not be neglected because they may progress to superior vena cava syndrome, pulmonary embolism, and chronic edema.[7]

Both antithrombotic treatments were administered at low doses. The use of very low, fixed doses of warfarin makes this treatment practical and attractive in already heavily-monitored cancer patients since the cumbersome laboratory monitoring required by standard warfarin treatment is avoided. However, while such a dose regimen has been shown to be effective in preventing upper extremity thrombosis in cancer patients[2] and deep-vein thrombosis in patients undergoing gynecologic surgery,[10] other trials found it ineffective in preventing post-operative venous thrombosis in patients undergoing major orthopedic surgery.[11-13] Likewise, the optimal dose of low-molecular-weight heparins in cancer patients with a central venous catheter is not known. While the dose regimen of nadroparin used in the present trial was found to be effective for thromboprophylaxis in general surgery,[14,15] higher doses are required in situations involving a high risk of thromboembolism, such as orthopedic surgery.[16,17] Thus, the efficacy of prophylactic treatments in cancer patients with a central venous catheter might be improved with a higher prophylactic dose regimen of low-molecular-weight heparin. A recent cohort study suggested that a 7,500 IU/day dose of nadroparin, 2- to 3-times higher than the dose studied in our trial, virtually abolished catheter-related thrombosis in cancer patients since the thrombosis rate decreased from 28.3% in patients without heparin prophylaxis to 2.2% in those given low-molecular-weight heparin.[18] However, the benefit-to-risk ratio of such regimens remains to be determined and they cannot be recommended at this time.

In cancer patients requiring a central venous catheter, prophylactic anticoagulant treatment should be administered for long periods since thrombotic complications may occur long after catheter insertion.[1] The duration of treatment chosen in our study was, therefore, 90 days and the primary outcome was measured at the end of the treatment period, as in two other trials.[2,3] Our results are in agreement with previous findings[1-3] in that the majority of the upper extremity deep-vein thromboses were observed between one and three months after catheter insertion.

In conclusion, although it cannot be excluded that a difference in efficacy between the two study drugs might have been observed if the study population had been larger, no difference in efficacy between warfarin- and nadroparin-treated patients was detected in this pilot trial. Therefore, we cannot recommend the use of one antithrombotic strategy rather than the other purely on the grounds of efficacy. Vitamin K antagonists are attractive because they are effective, safe, easy to administer and inexpensive. However, oncologists are reluctant to give them to many cancer patients due to an unpredictable anticoagulant effect, even with such a low dose as 1 mg of warfarin. In the present study, the INR was more than 1.5 at least once during the study period in 4 warfarin-treated patients, and in another previous trial, warfarin was discontinued in 10% of the patients because the prothrombin time became too long.[2] In addition, some patients are resistant to vitamin K antagonists, especially at such low doses.[19] In contrast, low-molecular-weight heparins are more expensive and have to be administered by the subcutaneous route, but they are both effective and safe, and may therefore be given to patients in whom vitamin K antagonists are contraindicated.

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Appendix

The CIP Study Group: participating centers. Oncology Unit of the University Hospital Saint-Etienne (Prof. B. Perpoint, Dr. D. Mille, Dr A. Guyot): 42 patients; Oncology Unit of the Clinique Mutualiste de La Digonnière, Saint-Etienne (Dr. J.P. Jacquin): 7 patients; Pneumology Department of the University Hospital of Saint-Etienne (Dr. P. Fournel): 6 patients; ORL Unit of the University Hospital of Saint-Etienne (Prof. J.M. Prades): 3 patients; and Gynecology Department of the General Hospital of Firminy (Dr. R. Reynaud): 1 patient. *Project Director*. Dr. P. Mismetti.

Monitoring center

Thrombosis Research Group: Prof. H. Decousus, Drs. V. Charlet, A. Buchmüller-Cordier. *Radiologists responsible for the venography procedures*: Prof. F-G. Barral, Dr R. Mohammedi. *Surgeons responsible for implanting the infusion systems*: Prof. J. Porcheron, Dr. O. Tiffet. *Central adjudication committee*: Drs. Ph. Girard, F. Parent and B. Tardy. *Independent reading committee for venograms*: Profs. P. Lacombe, M. Sapoval. *Data management and analysis*: S. Laporte, S. Quenet, C. Chauvet, I. Michel. *Sanofi-Synthelabo data monitoring*: Mrs C. Chabert, V. Farvacque.

Pre-publication Report & Outcomes of Peer Review

Contributions

PM, VC, CD-D, HD: conception and design, draft, final approval. PM: primary responsibility for the paper; SL: analysis of data, revising and final approval; DM, AB-C, JPJ, PF: revising and final approval; SL: Tables 1-4.

This paper is dedicated to our friend Bruno Perpoint, who helped us to initiate and conduct this study. He left us two years ago.

Funding

Sanofi-Synthelabo.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received July 17, 2002; accepted November 26, 2002. In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

What is already known on this topic

Both vitamin K antagonists and low-molecular-weight heparins have been recommended in the prevention of upper extremity thrombosis in cancer patients with indwelling long-term central venous catheter. Their relative benefit-to-risk ratios, however, have never been compared.

What this study adds

Warfarin at a fixed, very low dose and nadroparin at a fixed, prophylactic dose have comparable benefit-to-risk ratios in the prevention of thrombosis in the above setting.