Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis

Paloma López-Beret, MD,[a] Antonio Orgaz, MD,[a] Juan Fontcuberta, MD,[a] Manuel Doblas, MD,[a] Adela Martinez, RVT,[a] Gloria Lozano, RVT,[a] and **Arturo Romero, MD,[b]** *Toledo, Spain*

Purpose: **The purpose of this study was to evaluate whether low molecular weight heparin (LMWH) could be equal or more effective than conventional oral anticoagulants (OAs) in the long-term treatment of deep venous thrombosis (DVT).**
Methods: **One hundred fifty-eight patients with symptomatic DVT of the lower limbs confirmed by means of duplex ultrasound scan were randomized to receive 3 to 6 months' treatment with nadroparine calcium or acenocoumarol. Quantitative and qualitative duplex scan scoring systems were used to study the evolution of thrombosis in both groups at 1, 3, 6, and 12 months.**
Results: **During the 12-month surveillance period, two (2.5%) of the 81 patients who received LMWH and seven (9%) of the 77 patients who received OAs had recurrence of venous thrombosis (not significant). In the LMWH group no cases of major bleeding were found, and four cases (5.2%) occurred in the OA group (not significant). The mortality rate was nine (11.1%) in the LMWH group and 7.8% in the OA group (not significant). The quantitative mean duplex scan score decreased in both groups during the follow-up and had statistical significance after long-term LMWH treatment on iliofemoral DVT (1, 3, 6, and 12 months), femoropopliteal DVT (1-3 months), and infrapopliteal DVT (first month). Duplex scan evaluation showed that the rate of venous recanalization significantly increased in the common femoral vein at 6 and at 12 months and during each point of follow-up in the superficial and popliteal veins in the LMWH group. Reflux was significantly less frequent in communicating veins after LMWH treatment (17.9% vs 32.2% in the OA group). The reflux rates in the superficial (22.4% in the LMWH group, 30.6% in OA group) and deep (13.4% vs 17.7%) venous system showed no significant differences between groups.**
Conclusions: **The unmonitored subcutaneous administration of nadroparine in fixed daily doses was more effective than oral acenocoumarol with laboratory control adjustment in achieving recanalization of leg thrombi. With nadroparine, there was less late valvular communicating vein insufficiency, and it was at least as efficacious and safe as oral anticoagulants after long-term administration. These results suggest that LMWHs may therefore represent a real therapeutic advance in the long-term management of DVT. (J Vasc Surg 2001;33:77-90.)**

The standard treatment for acute deep venous thrombosis (DVT) has been a short course of intravenous unfractioned heparin (UFH) followed by oral anticoagulants (OAs) for at least 3 months.[1,2] Although this treatment has been effective in decreasing mortality and thromboembolic events, there is a significant risk of hemorrhage, and the patient receiving this therapy requires hospitalization and continuous laboratory monitoring during initial and long-term treatment. Moreover, it does not prevent the development of long-term venous insufficiency and post-thrombotic syndrome (PTS).[2] Recent studies have shown that initial treatment with low molecular weight heparins (LMWHs) is equally or more effective and safer than UFH,[3,4] and LMWHs are now used in several countries as the initial treatment of choice for most patients with DVT.[5-7]

The pharmacologic lysis of a thrombus located in the deep venous system is an attractive therapeutic option, because removal of this mass could prevent post-thrombotic symptoms if lysis occurs before valves are destroyed.[8,9] Fibrinolytic therapy was introduced because of this, although the risk of acute major bleeding outweighed the potential benefit of a diminished risk for PTS. Therefore, the routine use of fibrinolytic therapy is currently not defendable.[3] The direct or indirect thrombolytic effect of LMWH has been observed in several experimental studies[10-13] and is likely to occur in humans,[14-17] which would lead to a reduction of thrombus size, thereby preventing venous dysfunction with a low risk of bleeding.[18]

Long-term administration of LMWH in the secondary prophylaxis of thromboembolic events has been used in

From the Unit of Vascular Surgery, Cardiovascular Institute,[a] and the Admissions and Medical Documentation Department, Hospital Virgen de la Salud.[b]
Competition of interest: nil.
Reprint requests: Paloma López-Beret, Unit of Vascular Surgery, Cardiovascular Institute, Virgen de la Salud Hospital, Avenida de Barber, 30, 45004, Toledo, Spain (e-mail: aromero@cht.es).

0741-5214/2001/$35.00 + 0 **24/1/109336**
doi:10.1067/mva.2001.109336

patients who have a high risk of bleeding, in those who present with complications from OAs, or in those whose OA therapy could not be monitored easily.[18-23] LMWH has a less-activating effect on osteoclasts than the UFH, which thereby reduces osteoporosis as a result of long-term administration.[20,24,25] This effectiveness of LMWH therapy raises the important practical question of whether LMWH can be used to treat all patients with DVT over the long term.

The aim of the current study was to evaluate if LMWH administration can be used as an alternative to long-term OAs in patients with DVT, to minimize the prevalence and severity of early-medium complications (recurrent thromboembolic events, death, and major bleeding) and later sequelae (PTS), and to further facilitate the outpatient management of DVT.

MATERIALS AND METHODS

Patients. Consecutive symptomatic patients who were referred to the vascular laboratory in our hospital in whom lower limb DVT was objectively documented with duplex scan examination were considered for entry into the study. Patients were excluded if they were younger than 18 years, were pregnant, had previous episodes of DVT in the same limb, had a past complication due to heparin or acenocoumarol, received full doses of anticoagulants at the time of referral, had surgery within the last 5 days, or refused to give their informed consent. All exclusions were documented.

The study protocol was approved by the Hospital Ethics Committee. All patients gave their written consent for participation in the study according to the Helsinki declaration.

Regimens of treatment. Prefilled syringes were used containing 10.25 AXa IU/mL of nadroparine calcium (Fraxiparina; Sanofi Winthrop, Paris, France). As soon as the patients were included in the study, a subcutaneous dose of nadroparine adjusted to body weight (0.1 mL/10 kg) was administered. Because of methodologic requirements of the study, all patients were hospitalized during the initial course of treatment, and a set dose of nadroparine was subcutaneously administered every 12 hours. Whenever possible, patients were allowed to walk on the third day; they wore elastic graduated compression stockings or bandages. After informed consent for the study was obtained, patients were allocated at random on the third day to receive an LMWH or an OA. In view of the nature of the treatments, it was not possible to use a double-blind design for the study.

In those patients allocated to the LMWH group, fixed subcutaneous doses of nadroparine twice a day were continued at home and were usually administered by the patients themselves, by relatives, or occasionally by nurses from the local primary care centers. In patients randomized to OA, acenocoumarol (Sintrom; Novartis, Basel, Switzerland) was administered once a day beginning on the third day with an initial dose of 4 mg. Further doses were adjusted to obtain an international normalized ratio (INR) between 2 and 3. LMWH was given to overlap with OA and was discontinued when the INR was 2.0 or more in two consecutive measurements 24 hours apart after at least 5 days of initial treatment.[26] After discharge, those patients attended the hematologic unit for routine monitoring of OA therapy to maintain the INR between 2 and 3. The intensity of oral anticoagulation was expressed as the percentage of laboratory determinations at the hematologic unit in which a patient had an INR less than 2, from 2 to 3, or more than 3 with this period calculated with lineal interpolation.[26]

Both treatments continued for 3 months and were prolonged for 6 months when the DVT affected the iliac or femoral veins and if the patient had persistent risk factors for thrombosis or an idiopathic DVT.[27] After the third month, nadroparine was administered once a day at fixed doses of 0.1 mL/10 kg, whereas the dosage of acenocoumarol was set to maintain the INR between 2 and 3.

Duplex scan evaluation. All DVTs were confirmed by combining B-mode color imaging and Doppler scan measurements. Venous duplex scan examinations were performed with a Philips P-700 scanner (Philips, Einthoven, The Netherlands) and a 5- or 7.5-MHz probe, depending on the depth of the veins. We examined deep veins: common and external iliac veins, the common femoral vein (CFV), the superficial femoral vein (SFV) along the thigh, the popliteal vein (PV), and the infrapopliteal vein. Also, the superficial long and lesser saphenous veins were examined. The standard findings of partial or complete venous incompressibility and absent or diminished Doppler flow signals were analyzed.[28]

For the evaluation of DVT at diagnosis and at 1, 3, 6, and 12 months of follow-up, an objective and reproducible *quantitative* duplex scan score was obtained with the addition of degrees of thrombi present in the CFV, the SFV, and the PV with five grades at each segment: 4 points for *complete* occlusion (100%), 3 for *severe* occlusion (61%-99%), 2 for *intermediate* occlusion (31%-60%), 1 for *slight* thrombosis (1%-30%) and 0 for *patency* (0%).[29] Maximum value for this score was 12 points (4 × 3). The iliac vein segment was routinely explored; however, because of the limitations of duplex scan examinations for establishing the exact degree of thrombosis into the venous lumen at this level,[30,31] it was not used for calculations of overall scores.

Because measurements of lumen occupation of the infrapopliteal veins were imprecise, thrombosis at this level was scored according to location alone; a ½ point value was applied for each thrombosed vein: double tibial (anterior tibial, posterior tibial, peroneal) and muscular veins (soleal, gastrocnemius). The maximum possible value for this score was 4 points (½ × 8).

The evolution of thrombosis was *qualitatively* scored during follow-up with duplex scan examination of the residual thrombus in the CFV, the SFV, and the PV. Thrombus scores for both groups at 1, 3, 6, and 12 months were compared with baseline scores, which reflected *recanalization* (complete lysis or improvement > 90%), *substantial* regression (improvement of 60%-90%), *moderate* regression (30%-60%), *slight* regression (< 30%), unchanged, and

propagation.[32] A repeat duplex scan was performed 24 to 48 hours after standard examination when proximal or distal thrombus extension (thrombosis in a previously unaffected venous segment) or worsening (increased degree of thrombosis in a previously affected venous segment) was found.

Additionally, at 6 and 12 months, the duplex scan follow-up examination included checks on the presence of venous flow and reflux in deep veins, superficial veins, and communicating veins. Reflux was defined as reversed flow with a velocity of more than 10 cm/s[33] or valve closure lasting more than 2 seconds[34] during proximal or distal compression, which was confirmed with cuff compression. The duplex scan examinations (diagnosis and follow-up) were interpreted independently, without knowledge of allocation to groups to prevent bias.

Surveillance and follow-up. All patients were carefully examined daily during initial LMWH therapy, with special emphasis on signs of bleeding or recurrence of DTV. The following parameters were measured at admission: red blood cell (RBC) count, hematocrit, hemoglobin level, white blood cell (WBC) count, platelet count, activated partial thromboplastin time, prothrombin time, and thrombin time. Measurements were repeated on days 3 and 7.

During surveillance all patients were seen routinely in our vascular clinic 1, 3, 6, and 12 months after diagnosis and were instructed to report at once if symptoms or signs suggestive of recurrent DVT, pulmonary thromboembolism, bleeding, or other complications developed. At these visits, patients underwent clinical examination; their limbs were evaluated for tenderness, edema, varicose veins, hyperpigmentation, or ulceration. The presence of local complications was documented, and their diameters were measured. The circumferences of both limbs were recorded, and duplex scan examination was performed. RBC count, WBC count, platelet count, activated partial thromboplastin time, prothrombin time, INR, and thrombin time were determined at 1, 3, and 6 months. Patient compliance was monitored in both groups.

Information was obtained on every subsequent hospital admission, and the cause of death was documented for patients who died. The efficacy of treatment was assessed in terms of the absence or decrease of complications of DVT or treatment and improvement in clot size.

Complications. The primary outcome was symptomatic recurrence or progression of venous thromboembolism documented by duplex scan examination at regular intervals or earlier if there was any increase in pain, tenderness, or edema of the limbs. Recurrence was defined as the appearance of thrombosis in a previously unaffected venous segment of the ipsilateral or contralateral leg. In asymptomatic patients, recurrent DVT was diagnosed in duplex scan examination follow-up. In patients with clinically suspected pulmonary thromboembolism, the diagnosis was confirmed by the presence of a constant intraluminal filling defect in spiral computed tomography or conventional angiography.

Bleeding during the study was the second outcome event. Bleeding was classified as major if it was overt and was associated with a decrease of 2 g/dL or more in the hemoglobin level, if it required a blood transfusion of 2 units or more, if it was intracranial or retroperitoneal, or if the treatment had to be permanently discontinued.[26,35,36] All other episodes of bleeding were defined as minor. Thrombocytopenia was defined as a platelet count below 100,000/μL or a minimum decrease of 40% compared with the baseline value.[35]

The final allocation of all potential outcome events, including deaths, was made by an independent panel of physicians. The panel included a member of our team who was not directly involved in the execution of the trial.

Statistical analysis. Analysis was performed with the SPSS 8.0 statistical package (SPSS, Inc, Chicago, Ill) for Windows 95 and Microsoft Excel. A P value less than .05 was considered significant. The tests used were difference of means, the Fisher exact test, and tests for contrast of proportions. Comparisons for nonparametric distributions were performed with the Mann-Whitney U test.

RESULTS

Patients. From January 1996 to March 1998, 201 consecutive symptomatic patients with confirmed DVT were considered to enter the trial. Of these, 43 were excluded because of age younger than 18 years (1), pregnancy (6), previous ipsilateral DVT (10), history of heparin-induced thrombocytopenia (2), previous treatment with UFH for more than 24 hours (17), lack of staff (2), surgery within the last 5 days (4), and the refusal of informed consent (1). Therefore, 158 patients were included in the study: 81 (51.3%) were assigned to receive nadroparine, and 77 (48.7%) received acenocoumarol.

There were 69 men and 89 women; ages ranged from 18 to 92 years (mean, 65.7 years). The incidence of various predisposing factors did not vary significantly between the two groups (Table I). The average length of stay was 4.0 days (range, 3-5 days) in the LMWH group and 8.5 days (range, 6-15 days) in the OA group.

For 10 patients (6%), two in the LMWH group and eight in the OA group, the medication under study was interrupted before an end point was reached. Nadroparine was withdrawn in a 66-year-old man immobilized in a wheelchair with iliofemoral thrombosis after 30 days of treatment and in an 88-year-old woman with iliofemoral DVT after 2 months of treatment, because of family and another physician's decision. In the OA group, reasons for treatment interruption were rethrombosis (four patients) and major bleeding (four patients). Seventy-eight patients continued treatment for 6 months: 34 in the LMWH group and 44 in the OA group.

Clinical evaluation. During the study period nearly all patients showed improvement in clinical DVT symptoms. At 12-month follow-up, edema was the most frequent sign found; it was found in 38.3% of the LMWH group and in 36.4% of the OA group. No clinical evidence of pathologic fractures or back pain was found during treatment or follow-up.

Laboratory findings. No significant alterations in

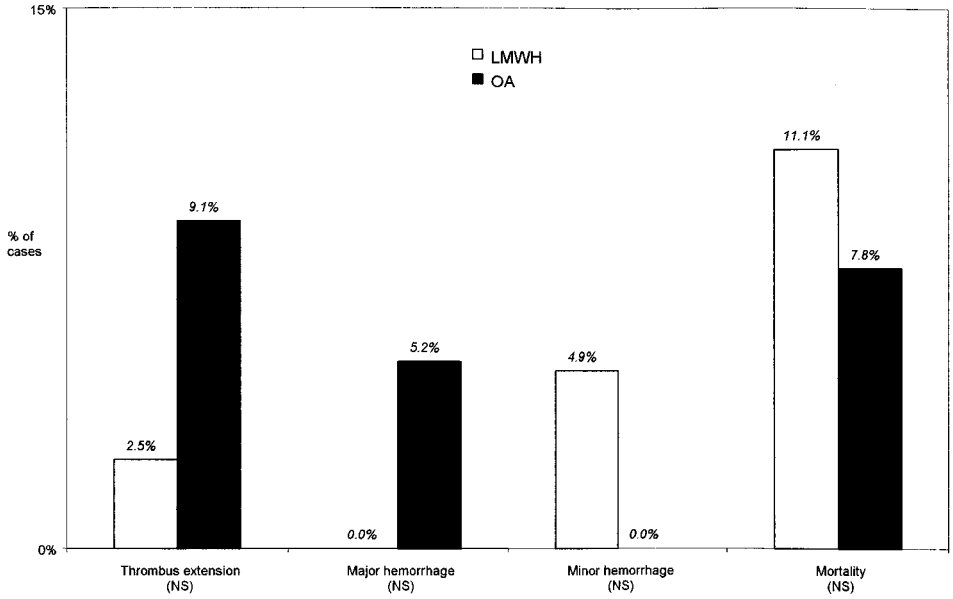

Fig 1. Complications after long-term treatment of DVT. *LMWH,* Low molecular weight heparin; *NS,* not statistically significant; *OA,* oral anticoagulant.

Table I. Baseline clinical characteristics of patients

	Nadroparine (n = 81)	*Acenocoumarol (n = 77)*	P *value*
Age—y (mean)	65 (95% CI, 62-69)	66 (95% CI, 63-70)	ns
No. < 40 y, 40-70 y, > 70 y	10/34/37	6/31/40	ns
Sex: male/female	31/50	38/39	ns
Side: left/right	46/35	41/36	ns
DVT level:			
Iliofemoral DVT	45	39	ns
Femoropopliteal DVT	9	13	ns
Popliteal DVT	13	14	ns
Infrapopliteal DVT	14	11	ns
Relevant associate conditions:			
Recent surgery	23 (28.3%)*	19 (24.6%)*	ns
Known malignancy	17 (20.9%)*	18(23.3%)*	ns
Oral contraceptives	2 (8.3%)†	1 (5.5%)†	ns
Hypercoagulability	9 (21.9%)‡	6 (13.9%)‡	

*Total of patients in each group.
†Total of premenopausal women.
‡Total of patients younger than 60 years with idiopathic DVT or younger than 50 years without known permanent risk factors.
DVT, Deep venous thrombosis; *ns,* not statistically significant.

RBC count and WBC count were found. No thrombocytopenia was observed during treatment or follow-up. The mean platelet count in the two groups showed an increase on the third and seventh days of treatment; it returned to initial values during the surveillance period. In the hematologic unit, control INR values found were less than 2 in 22.8%, 2 to 3 in 67.8%, and more than 3 in 9.4% of the OA group.

Complications. The complications observed in both treatment groups have been summarized in Fig 1 and Table II.

Recurrent venous thromboembolism. Nine patients, two (2.5%) of 81 in the LMWH group and seven (9.1%) of 77 in the OA group, had recurrence of DVT; differences were not significant. DVT recurrence involving the limb initially affected was found in two patients (22%), and DVT recurrence in the contralateral limb was found in seven patients (78%) ($P = .0023$). No isolated recurrences of thrombosis were found in duplex scan examinations without clinical signs.

During different phases of the study, thoracic pain episodes appeared in three patients: a 37-year-old man with

Table II. Complications during thrombosis treatment in both groups

Group	*No. of cases*	*Complications*	*Sex*	*Age (y)*	*Initial DVT*	*Time (d)*	*Predisposing factors*
Nadroparine	Recurrent DVT (2)	Contralateral P-DVT	F	88	Iliofemoral	270	Uterine cancer, hormonal therapy
		Ipsilateral FP-DVT	M	34	Calf	270	AIDS, hepatitis
	Minor bleeding (4)	Hematuria	M	68	Iliofemoral	8	Prostatectomy
		Hematuria	M	80	Iliofemoral	60	Carcinoma of bladder
		Hematuria	F	75	Iliofemoral	8	Carcinomatosis
		Blood in stools	F	30	Iliofemoral	120	Hemorrhoids, granulomatosis colitis
	Deaths (9)		F	90	Iliofemoral	60	Heart failure
			F	78	Iliofemoral	15	Carcinomatosis, ovarian cancer
			F	75	Iliofemoral	20	Carcinomatosis, uterine cancer
			F	81	Iliofemoral	45	Carcinomatosis, vaginal cancer
			F	92	Iliofemoral	50	Heart failure
			F	75	Iliofemoral	180	Carcinomatosis, ovarian cancer
			M	69	Iliofemoral	60	Prostate cancer
			M	80	Iliofemoral	120	Bladder cancer, lung metastasis
			F	50	Femoropopliteal	90	Breast cancer, uterine cancer, lung metastasis
Acenocoumarol	Recurrent DVT (7)	Contralateral IF-DVT	M	52	Iliofemoral	270	Unknown for DVT, epilepsy
		Contralateral IF-DVT	F	78	Iliofemoral	60	Ovarian cancer, carcinomatosis
		Contralateral FP-DV	F	56	Iliofemoral	105	Uterine cancer
		Contralateral IF-DVT	F	78	Iliofemoral	45	Carcinomatosis
		Contralateral IP-DVT	M	32	Femoropopliteal	180	Activated protein C resistance
		Contralateral P-DVT	F	59	Popliteal	180	Breast cancer, chemotherapy
		Ipsilateral FP-DVT	M	64	Popliteal	60	Stroke, common iliac artery occlusion
	Major bleeding (4)	Hematuria	M	66	Iliofemoral	120	Carcinoma of bladder
		Hematuria	M	68	Infrapopliteal	8	Partial prostatectomy
		Rectorrhage	F	70	Iliofemoral	6	Colon cancer
		Epistaxis	F	56	Iliofemoral	6	Degeneration and destruction of turbinates
	Deaths (6)		F	78	Iliofemoral	90	Carcinomatosis, ovarian cancer*
			F	76	Iliofemoral	180	Breast cancer, lung metastasis
			F	70	Iliofemoral	90	Carcinomatosis, colon cancer
			M	69	Iliofemoral	180	Lung cancer, cerebral metastasis
			M	78	Iliofemoral	45	Carcinomatosis, colon cancer
			F	75	Infrapopliteal	150	Breast cancer, lung metastasis

*Rethrombosis the second month since randomization, 1 month before death.
DVT, Deep vein thrombosis; *F,* female; *FP,* femoropopliteal; *IF,* iliofemoral; *IP,* infrapopliteal; *M,* male; *P,* popliteal.

iliofemoral DVT (on the second day after initial treatment), a 48-year-old obese woman with popliteal DVT (on the 30th day of LMWH treatment), and a 56-year-old man with iliofemoral DVT (during the surveillance period, 1 month after the OA therapy was discontinued). Pulmonary thromboembolism could not be confirmed by means of computed tomography or pulmonary angiography.

Bleeding complications. No fatal bleeding complications were found. Major bleeding occurred in four patients who received OA therapy (5.2%), but did not occur in the LMWH group. There were four cases of minor bleeding (4.9%) during long-term LMWH treatment versus none in the OA group. No significant difference was present.

Local complications. After 3 months of nadroparine treatment, nearly all patients had small hematomas, sub-

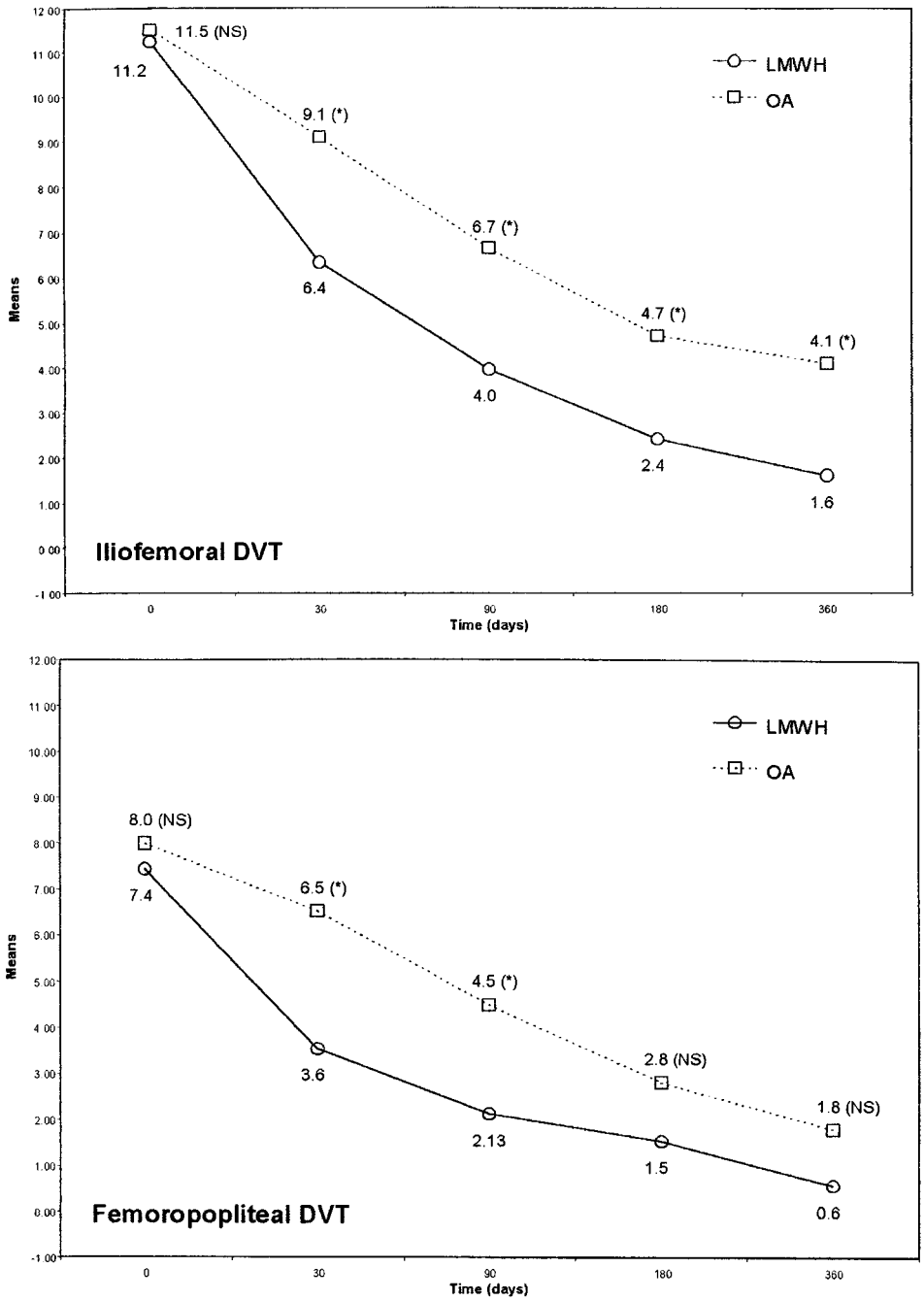

Fig 2. Effect of both treatments on the evaluation of thrombosis expressed by quantitative duplex scan score according to DVT level. *DVT,* Deep venous thrombosis; *LMWH,* low molecular weight heparin; *NS,* not significant; *OA,* oral anticoagulant; *statistically significant.

cutaneous nodes, or both at injection sites. A 56-year-old woman also had local erythema and pruritus after 40 days of nadroparine administration.

Mortality. Fifteen patients died during the combined period of treatment and surveillance: nine in the LMWH group (11.1%) and six in the OA group (7.8%). This difference was not significant. No episodes of sudden death occurred. Thirteen patients with cancer at an advanced stage died because of the progression of their neoplastic disease: seven (41.2%) of 17 patients with malignancy in the LMWH group and six (33.3%) of 18 with cancer in the OA group.

Evolution of thrombi. During the surveillance period 556 duplex scan examination were made, 289 in the LMWH group and 267 in the OA group. Three venous segments were routinely explored in each limb, and seg-

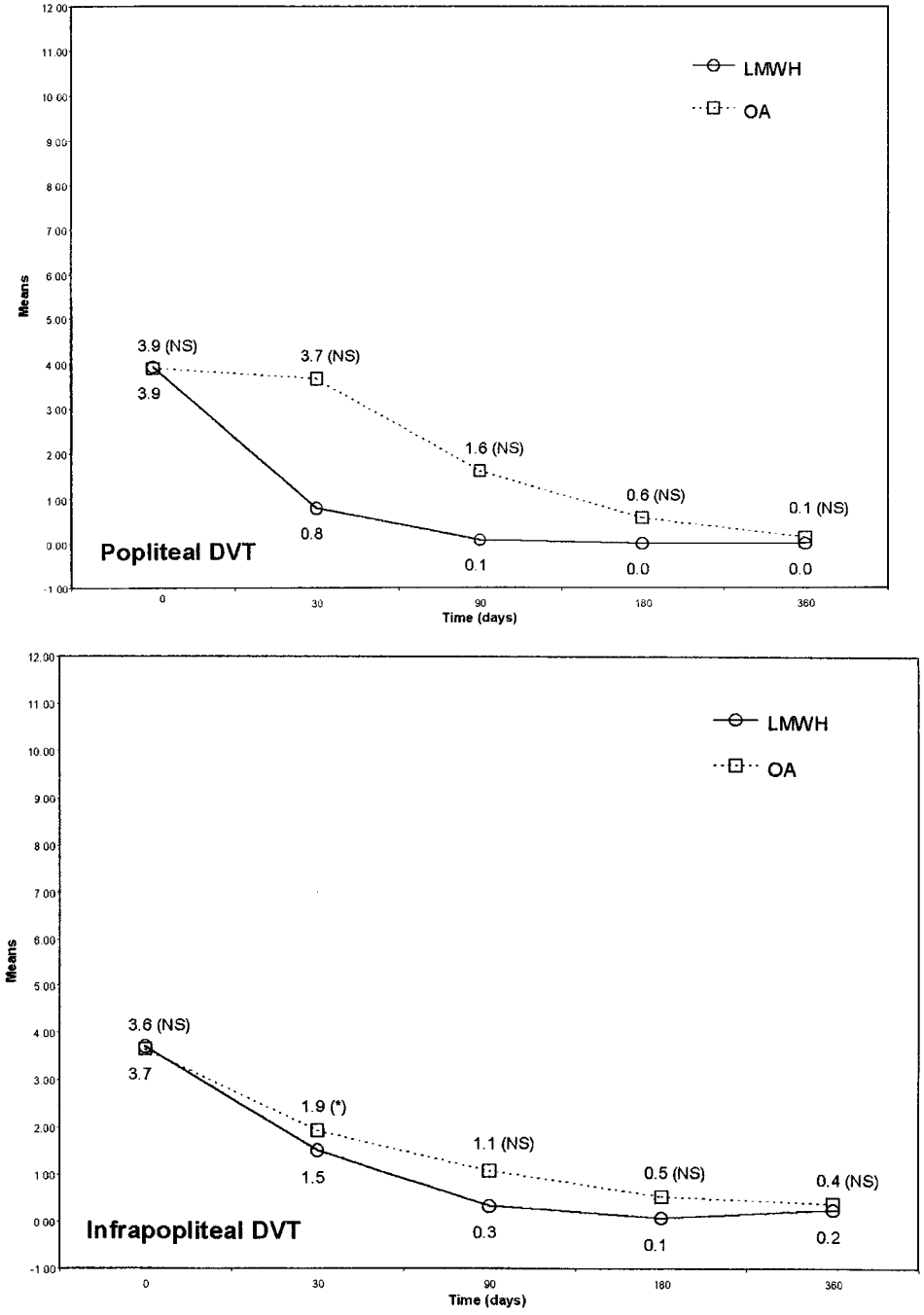

Fig 2 Cont'd.

mental scores were added to obtain the global scores. The initial mean clot size score was similar in both groups and decreased during follow-up in all DVT locations.

We found that the *quantitative* duplex scan score showed statistically significant improvement between nadroparine therapy and acenocoumarol therapy after iliofemoral DVT for every checkpoint interval at the first and third months in femoropopliteal DVT and at the first month in infrapopliteal DVT. Mean thrombus size decreased after nadroparine treatment in popliteal DVT and at the 6th and 12th months in femoropopliteal and infrapopliteal thrombosis, but no statistical significance was found with respect to the OA (Fig 2).

Fig 3 shows the quantitative duplex scan in proximal veins of both groups. A statistically significant decrease in thrombus size was found in the LMWH group versus the

OA group at the 6th and 12th months in the CFV and during all follow-up in the SFV and the PV.

Qualitative duplex scan examination showed that at the end of follow-up, the thrombus recanalization rate was higher in the LMWH group versus the OA group in the CFV (63.9% vs 19.3%), the SFV (66.7% vs 14.6%), and the PV (62% vs 27.5%). This difference was found to be statistically significant ($P < .000$; Table III).

In 22 (2.8%) of the 786 venous segments evaluated at 3, 6, and 12 months, a worsening of the degree of thrombosis in a previously affected venous segment that was improved in its immediately previous status was found: 6 in the CFV (2 [LMWH]/4 [OA]), 7 in the SFV (3 [LMWH]/4 [OA]), and 9 in the PV (4 [LMWH]/5 [OA]) (Table III). These events were clinically asymptomatic and were unrelated to specific venous segments, the initial thrombus score, or late development of venous insufficiency. Recanalization after 1 year of follow-up was not affected in these cases in any treatment group.

Venous insufficiency. Reflux patterns at 12 months were similar to those found at the sixth month of follow-up in superficial, deep, and communicating veins. Table IV shows rates of venous insufficiency at the end of follow-up in limb-thrombosed and contralateral veins.

Incompetence of the long saphenous vein was found more frequently after iliofemoral thrombosis in both groups ($P = .0130$). The rate of incompetent perforating veins after DVT in the affected limb was higher in the OA group ($P = .0289$).

DISCUSSION

Drugs. The DVT was usually treated with a short course of intravenous UFH followed by an OA for at least 3 months.[1] Recently, several trials have shown that initial treatment with various LMWHs was more efficacious and safer than treatment with UFH.[2,4] To date, the LMWH long-term efficacy has been evaluated in only a few studies,[6,19-24,37] and it has been compared with standard long-term OA treatment in only two of them.[19,37]

In this randomized study we administered nadroparine calcium, an LMWH produced by nitrous acid depolymerization of UFH with a mean molecular weight around 4.5 d. Several studies have demonstrated that nadroparine was as or more effective than the adjusted dose of UFH in the initial treatment of proximal DVT.[35,38-42] It was adequate for outpatient treament,[26] it had a lower cost,[43] and probably one daily administration of a more concentrated form of the drug was allowed.[36,44]

The complications after the administration of nadroparine in the initial course of DVT and OAs in long-term treatment have been revealed in previous trials, but the exact comparison of reports is not possible because the drugs used, the dosage schedules, the duration of initial and long-term treatment, time of surveillance periods, and methods of evaluation were different. In the review of medical literature, we found only one case for nadroparine long-term administration after DVT.[22]

Our study shows a lower rate of rethrombosis and major bleeding after long-term treatment with nadroparine versus acenocoumarol. However, differences were not significant, perhaps because of the small number of patients (β error).

Although the optimal duration of the anticoagulation therapy is still a subject of debate, we administered treatment during 3 months and extended it to 6 months in several patients with proximal, idiopathic DVT or persistent risk factors for thrombosis. We maintained the INR between 2 and 3 when acenocoumarol was administered.[3] Our regimen of long-term nadroparine dosage (twice daily for 3 months and once daily for the following 3 months) is empirical; there are no data regarding the optimal therapeutic range of LMWH dosage during long-term treatment of thromboembolic disease.

In previous studies, researchers reported one daily subcutaneous injection of another LMWH preparation such as dalteparine[37] and enoxiparine[19] for 3 months after the first episode of DVT, but several observations suggest that the failure to achieve an adequate anticoagulant effect early in the course of anticoagulant treatment can lead to later recurrences.[19,45] We used two daily injections because probably, levels higher than once a day should be preferable at this period.

After this treatment period, we further prolonged the secondary prophylaxis for 3 months in numerous patients; we used nadroparine once a day. The efficacy and safety of this LMWH dosage have been shown during long-term dalteparine administration for up to 70 months.[18] However, the two thrombotic recurrences in the LMWH group occurred 3 months after heparin was stopped, following 6 months of treatment. This may indicate that even this long period of treatment or this dosage was insufficient to prevent new thrombotic events in patients with persistent risk factors for thromboembolic disease.

On the contrary, most recurrences in the OA group occurred during treatment period, with an INR more than 2. This could mean that new thrombotic episodes begin before clinical symptoms appear or routine hematologic laboratory controls are scheduled and could suggest that OA alone is not an eligible treatment in the acute phase of thrombotic disease.[46]

Clinical evaluation showed better results than the improvement shown by duplex scan examinations. No thrombus progression was found in duplex scan follow-up in an unaffected venous segment in absence of symptomatic clinical events,[47] although the increases in pain and edema, etc, did not always indicate rethrombosis.

The bleeding appeared in patients with predisposing disorders.[48,49] The difference in the rate of hemorrhagic complications could mean that the patients' control was better when an LMWH was used.

Nearly all patients who received nadroparine subcutaneously twice a day had small ecchymoses, subcutaneous nodes, or both in the injection site. They were painless and generally well tolerated by patients. These local hematomas improved when nadroparine was administered once a day[19] and disappeared about 15 days after subcutaneous treatment was stopped.

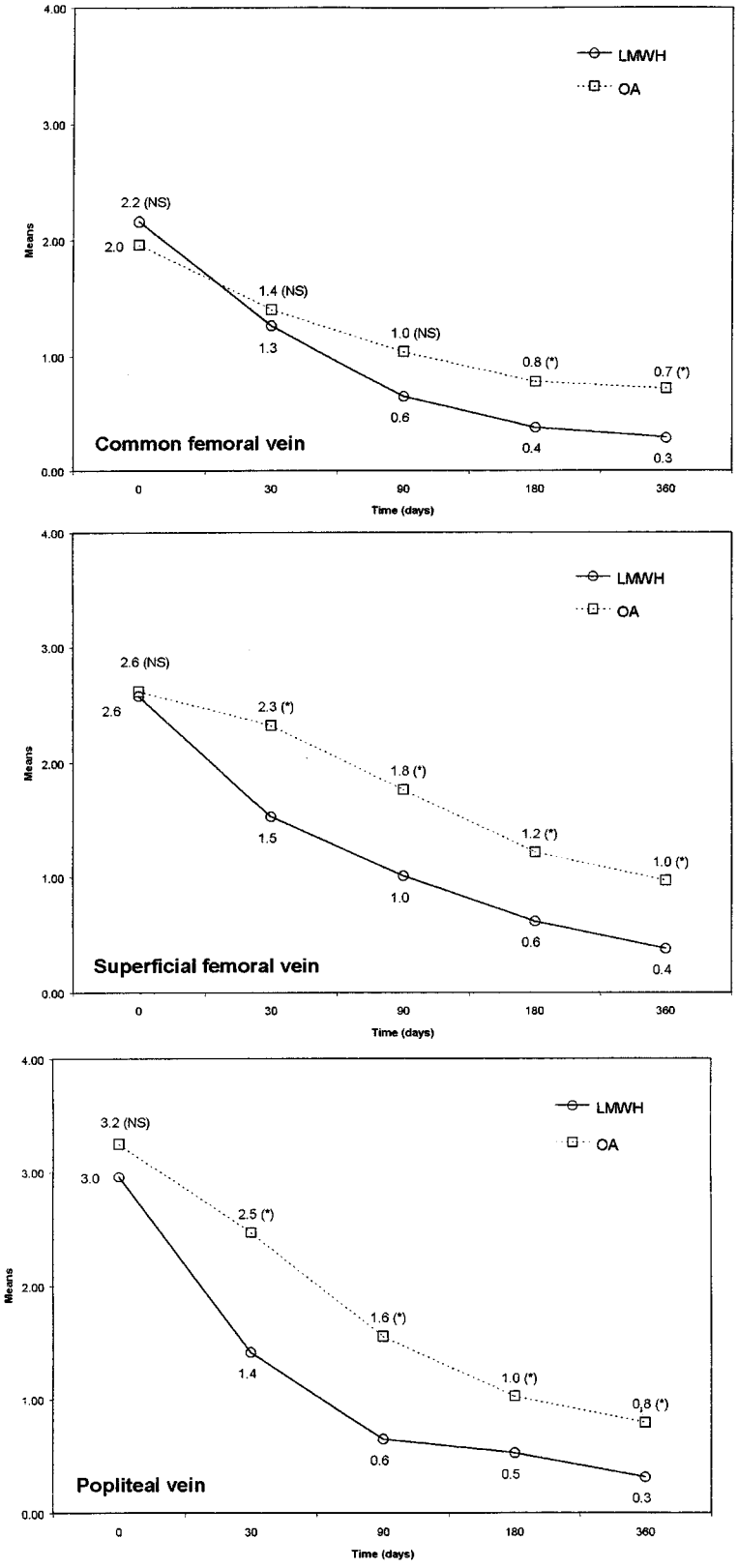

Fig 3. Regression of thrombus size according to duplex scan examination in proximal venous segments. *LMWH,* Low molecular weight heparin; *NS,* Not significant; *OA,* oral anticoagulant; *statistically significant.

Table III. Effect of long-term treatment with nadroparine and acenocoumarol on the evolution of thrombus in proximal vein segments after an initial episode of DVT

	First month					*Third month*		
Venous segment	*N*	*%*	*A*	*%*	P *value**	*N*	*%*	*A*
CFV								
No. duplex scan examinations	45		38			38		34
Recanalization	7	(15.6)	1	(2.6)	.0155	13	(34.2)	1
Substantial regression	6	(13.3)	5	(13.2)		7	(18.4)	9
Moderate regression	8	(17.8)	5	(13.2)		9	(23.7)	11
Slight regression	17	(37.8)	17	(44.7)		8	(21.0)	13
Unchanged	7	(15.6)	10	(26.3)		1	(2.6)	0
Worsening†						0	(0.0)	1
SFV								
No. duplex scan examinations	51		51			45		46
Recanalization	7	(13.7)	1	(2.0)	.0118	13	(28.9)	1
Substantial regression	6	(11.8)	0	(0.0)	.0046	9	(20.0)	5
Moderate regression	10	(19.6)	5	(9.8)		9	(20.0)	12
Slight regression	12	(23.5)	19	(37.2)		7	(15.6)	20
Unchanged	16	(31.3)	26	(51.0)	.0200	7	(15.6)	8
Worsening†						1	(2.2)	2
PV								
No. duplex scan examinations	58		62			53		58
Recanalization	12	(20.7)	3	(4.5)	.0040	20	(37.7)	7
Substantial regression	13	(22.4)	3	(4.45)	.0020	16	(30.2)	14
Moderate regression	9	(15.5)	8	(13.0)		9	(17.0)	17
Slight regression	11	(18.9)	21	(33.9)	.0298	6	(11.3)	14
Unchanged	13	(22.4)	27	(43.5)		2	(3.8)	6
Worsening†						2	(3.8)	3

Figures represent frequency of changes with respect to initial duplex scan score. Values in parentheses are percentages in relation to the number of partial duplex scan venous examinations.
*Contrast of proportions test.
†Worsening with respect to previous duplex scan score.
A, Acenocoumarol group; *CFV,* common femoral vein; *DVT,* deep venous thrombosis; *N,* nadroparine group; *PV,* popliteal vein; *SFV,* superficial femoral vein.

Thrombocytopenia was not observed in the follow-up of this analysis. We found increases in the platelet count on the third and seventh days after initial treatment with nadroparine, as was previously shown with another LMWH.[50] Unfortunately, we have no explanation for this event, and further study of the causal mechanisms is warranted.

In our study, mortality was due to underlying diseases, not to thromboembolic events.[19,22] There were a similar number of deaths due to advanced malignancy in both groups. Those results do not substantiate the previous hypothesis that LMWH administration may exert a favorable influence on cancer progression,[40,51] even if our regimen of treatment was different.

Overall, the mortality rate was higher than that in other studies, perhaps because we included all patients with cancer in the study, independent of their life expectancy. Except for one patient in the OA group, all other patients were free of thromboembolic complications during the last months of their lives. Although neither treatment prolonged their lives, they did improve their quality of life while they lived.

Post-thrombotic syndrome. Persistent abnormalities may occur after acute DVT, which results in PTS[52-54] caused by a combination of abnormal microcirculation and venous hypertension resulting from valvular destruction and persistent obstruction to outflow.[55] The hemodynamic severity of chronic obstruction is complex, differing markedly with the level and extent of affected venous segments,[55,56] the degree of collateralization, and the recanalization that may occur. Some degree of reflux may be present, which also may cause severe symptoms.[57]

We used conventional duplex scanning to document the outcome of thrombus itself[9,56,58-60] and the development of valvular incompetence[9,33,34,61] in the deep and superficial venous system during follow-up because the combination of reflux and venous obstruction probably correlates with ulterior PTS development. In previous studies with duplex scan sequential examinations of patients with DVT treated with UFH and OA, it is confirmed that clearance of a thrombus is a gradual process and that recanalization in previously occluded venous segments occurs over various periods.[9,17,47,59-63] We have not found studies on the long-term evolution of thrombosis after the administration of nadroparine.

The quantitative/qualitative duplex scan score used in this study, which is based in previous histologic,[29] venographic,[32,64] and duplex thrombosis evaluations,[15,65]

		Sixth month					*12th month*				
%	P *value*	**N*	*%*	*A*	*%*	P *value*	*N*	*%*	*A*	*%*	P *value*
				33			36		31		
(2.9)	.0001	17	(47.2)	5	(15.1)	.0010	23	(63.9)	6	(19.3)	.0000
(26.5)		9	(25.0)	4	(12.1)		4	(11.1)	9	(29.0)	.0322
(32.59)		7	(19.4)	16	(48.4)	.0039	5	(13.9)	12	(38.1)	.0089
(38.2)		3	(8.3)	8	(24.2)	.0348	4	(11.1)	4	(13.0)	
(0.0)		0	(0.0)	0	(0.0)		0	(0.0)	0	(0.0)	
(2.9)		0	(0.0)	1	(3.0)		2	(5.5)	2	(6.4)	
		42		44			42		41		
(2.1)	.0001	21	(50.0)	5	(11.4)	.0000	28	(66.67)	6	(14.6)	.0000
(10.8)		9	(21.4)	15	(34.1)		7	(16.67)	18	(43.9)	.0024
(26.1)		6	(14.3)	11	(25.0)		4	(9.52)	9	(22.0)	
(43.5)	.0011	4	(9.5)	10	(22.7)	.0447	2	(4.76)	5	(12.2)	
(17.4)		2	(4.7)	3	(6.8)		1	(2.38)	3	(7.3)	
(4.3)		2	(4.7)	1	(2.3)		0	(0.0)	1	(2.4)	
		51		55			50		51		
(12.1)	.0006	29	(56.9)	13	(23.6)	.0001	31	(62.0)	14	(27.5)	.0001
(24.1)		14	(27.4)	20	(36.4)		13	(26.0)	23	(45.1)	.0203
(29.3)		4	(7.9)	12	(21.8)	.0188	4	(8.0)	10	(19.6)	.0429
(24.1)	.0357	2	(4.0)	8	(14.5)	.0262	2	(4.0)	2	(3.9)	
(10.3)		2	(4.0)	2	(3.6)		0	(0.0)	2	(3.9)	
(5.2)		2	(4.0)	1			0		1		

shows a higher proportion of venous recanalization (62%-67%) in proximal venous segments after long-term nadroparine administration. Regression of thrombus size also occurred after OA treatment, although to a lesser degree (15%-27%). The reasons for these results could be associated to some LMWH characteristics (bioavailability > 95% after subcutaneous administration, longer half-life, activity not dose dependent, and low binding to plasma proteins and to proteins released from activated platelets and endothelial cells)[66] that make it possible to maintain more stable levels of anticoagulation, which is not always possible to ensure with an OA, in spite of the performance of frequent laboratory controls. The significant major improvement of thrombi in the LMWH group suggests a thrombolytic effect induced by LMWH,[15,17,67] which probably depends on a modulation of the endothelial cell of the vessel wall.[15]

During follow-up we found a worsening of the degree of thrombosis in some affected vein segments that had previously improved. This propagation was found incidentally and did not influence the outcome. It may in part reflect only a progressive occupation of the vein lumen, caused by increased thrombus adherence and retraction.[60] However, symptomatic or asymptomatic extension of thrombi into previously unaffected segments represents true propagation of thromboembolic disease.

With color duplex ultrasound scan, it is possible to evaluate the lack of vein competency after DVT.[8,9,31,55,63,68] This is a result of either destruction of the valve cusp or incorporation of valves in organizing thrombus.[55,60]

The valve closure time is the test most used to determine the degree of reflux within a specific vein segment.[69] The frequency of reflux in the literature depends heavily on the method used for measuring it and its quantification. There is no consensus about threshold value; this may vary between 0.5 seconds and more than 2 seconds.[34,53,69,70] In a previous study with healthy persons, reflux in the femoral vein induced by a pneumatic cuff showed a value of 0.9 seconds.[71] We have chosen a value of 2 seconds to discriminate valve insufficiency avoiding false-positive results, because the aim of this study is not to establish the frequency of reflux after DVT but to compare the rate of venous insufficiency in two regimens of long-term treatment.

Our findings show a similar frequency of reflux at 6 and 12 months. This confirms the irreversibility of the venous insufficiency that arises at this time after DVT.[61]

We found a significantly lower rate of reflux in the communicating veins of patients in the LMWH group, probably because very early recanalization may protect valve function.[1] Furthermore, LMWH has an inhibitory effect on smooth muscle cell proliferation and migra-

Table IV. Total vein reflux measured with duplex scanning 12 months after the initial episode of DVT

	Superficial venous system			*Deep venous system*			*Communicating veins*		
	N n = 67	*A n = 62*	P *value**	*N n = 67*	*A n = 62*	P *value**	*N n = 67*	*A n = 62*	P *value**
DVT level									
Iliofemoral	11	12		7	8		9	9	
Femoropopliteal	0	3		0	3		0	5	
Popliteal	2	4		2	0		1	4	
Infrapopliteal	2	0		0	0		2	2	
Total	15	19		9	11		12	20	
%	22.4	30.6	ns	13.4	17.7	ns	18.0	32.3	.0289
Asymptomatic contralateral leg									
Iliofemoral DVT	2	5		2	2		7	1	
Femoropopliteal	1	1		0	0		1	1	
Popliteal DVT	2	1		0	0		2	1	
Infrapopliteal	0	0		0	0		0	0	
Total	5	7		2	2		10	3	
%	7.5	11.3	ns	3.0	3.2	ns	15.0	4.8	.0248

Percentages of insufficiency are in relation to the number of duplex scan examinations in each venous system.
*Contrast of proportions test.
A, Acenocoumarol group; *DVT,* deep venous thrombosis; *N,* nadroparine group; *ns,* not statistically significant.

tion.[16] We have hypothesized that the reduction of local inflammatory response could contribute to the reduction of the fibrotic reaction and thus also residual valvular lesions and the subsequent appearance of reflux.

Reflux in deep, superficial, and communicating veins was significantly greater after iliofemoral DVT in both groups. However, the location and extent of reflux were not always associated with thrombosis involvement in the venous segment and are not entirely limited to thrombosed vein segments.[9,55]

The rate of incompetent communicating veins was greater in the OA group. The fact that this proportion is reversed in the involved opposite limb suggests that these findings are associated with the treatment used, rather than with the existence of previous venous insufficiency at that level or systemic factors that cause valvular incompetence.[67]

We thank Rafael Cuena for the randomization, Miguel Angel Adrados for the oral anticoagulant therapy control, Raquel López for her statistical support, and Rosa Bernardo for her assistance in the follow-up of patients.

REFERENCES

1. Hirsh HJ. Heparin. N Engl J Med 1991;324:1565-74.
2. Volteas SK, Kalodiki E, Nicolaides AN. Low molecular weight heparins in the initial treatment of deep venous thrombosis. Int Angiol 1996;15:67-74.
3. ten Cate JW, Koopman MM, Prins MH, Buller HR. Treatment of venous thromboembolism. Thromb Haemost 1995;74:197-203.
4. Leizorovicz A. Comparison of the efficacy and safety of low molecular weight heparins and unfractionated heparin in the initial treatment of deep venous thrombosis: an updated meta-analysis. Drugs 1996;52 Suppl 7:30-7.
5. Turkstra F, Koopman MM, Buller HR. The treatment of deep vein thrombosis and pulmonary embolism. Thromb Haemost 1997;78: 489-96.
6. Harenberg J, Schmitz-Huebner U, Breddin KH, et al. Treatment of deep vein thrombosis with low molecular-weight heparins: a consensus stament of the Gesellschaft fur Thrombose und Hamostaseforschung (GTH). Semin Thromb Hemost 1997;23:91-6.
7. Pineo GF, Hull RD. Unfractionated and low-molecular-with heparin: comparisons and current recommendations. Med Clin N Am 1998;82:587-99.
8. Meissner MH, Manzo RA, Bergelin RO, Strandness DE Jr. Deep venous insufficiency: the relationship between lysis and subsequent reflux. J Vasc Surg 1993;18:596-605.
9. Killewich LA, Bedford GR, Beach KW, Stradness DE Jr. Spontaneous lysis of deep venous thrombi: rate and outcome. J Vasc Surg 1989;9: 89-97.
10. Vairel EG, Bouty Boye M, Toulemonde F, et al. Heparin and low molecular weight fraction enhances thrombolysis and by this pathway exercises a protective effect against thromboses. Thromb Res 1983;30: 219-24.
11. Barbanti M, Fantuz M, Mastacchi R. Fibrinolytic activity of OP/LMWH in experimental venous thrombosis [abstract]. Thromb Res 1986;44 Suppl 6:87.
12. Juhan-Vague I, Stassen JM, Alessi MC et al. L'hèparine de bas poids moléculare CY 222 (Choay) potentialise l'effect thrombolytique du t-PA chez le lapin avec thrombose expérimentale yugulaire. J Mal Vasc 1987;12:64-5.
13. Bacher P, Welzel D, Iqbal O, et al. The thrombolytic potency of LMW-heparin compared to urokinase in a rabbit jugular vein clot lysis model. Thromb Res 1992;66:151-8.
14. Stassen JM, Juhan-Vague I, Alessi MC, et al. Potentiation by heparin fragments oh thrombolysis induced with human tissue-type plasminogen activator on human single-chain urokinase type plasminogen activator. Thromb Haemost 1987;58:947-50.
15. Kirchmaier CM, Lindhoff-Last E, Rübesam D, et al. Regression of deep vein thrombosis by i.v.—administration of a low molecular weight heparin. Results of a pilot study. Thromb Res 1994;73:337-48.
16. Lojewski B, Bacher P, Iqbal O, et al. Evaluation of hemostatic and fibrinolytic alterations associated with daily administration of low-molecular-weight heparins for a 12 week period. Semin Thromb Hemost 1995;21: 228-39.
17. Killewich LA, Macko RF, Cox K, et al. Regression of proximal deep venous thrombosis is associated with fibrinolytic enhancement. J Vasc Surg 1997;26:861-8.
18. Harenberg J, Leber G, Dempfle CE, et al. Long term anticoagulation with low molecular weight heparin in outpatients with side effects on oral anticoagulants. Nouv Rev Fr Hematol 1989;31:363-9.
19. Pini M, Aiello S, Manotti C. Low molecular weight heparin versus

warfarin in the prevention of recurrences after deep vein thrombosis. Thromb Haemost 1994;72:191-7.
20. Monreal M, Lafoz E, Olive A, et al. Comparison of subcutaneous unfractionated heparin with a low molecular with heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994;71:7-11.
21. Schulman S. Anticoagulation in venous thrombosis. J R Soc Med 1996;89:624-30.
22. Zuger M, Demarmels BF, Wuillemin WA, et al. Subcutaneous low-molecular-weight heparin for treatment of Trousseau's syndrome. Ann Hematal 1997;75:165-7.
23. Walsh-McMonagle D, Green D. Low-molecular-weight heparin in the management of Trousseau's syndrome. Cancer 1997;80:649-55.
24. Suarez C, Gómez N, Casado LF, Nuche JM. Comparación de la heparina subcutánea con la de bajo peso molecular en el tratamiento a largo plazo de la TVP en pacientes mayores de 60 años. III Cong Nac Cap Flebol de la SEAC 1995; num 15. Costa de Almería.
25. Muir JM, Hirsh J, Weitz JI, Andrew M, Young E, Shaughnessy SG. A histomorphometric comparison of the effects of heparin and low molecular weight heparin on cancellous bone in rats. Blood 1997;89: 3236-42.
26. Koopman MMW, Prandoni P, Piovella F, et al. The Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. N Engl J Med 1996;334:682-7.
27. Schulman S, Rhedin AS, Lindmarker P, et al. Duration of anticoagulation trial study group: a comparison of six weeks with six month of oral anticoagulant therapy after a first episode of venous thromboembolism. N Engl J Med 1995;332:1661-5.
28. Moneta GL, Porter JM. Peripheral vascular ultrasongraphy. In: Lanzer P, Rösch J, editors. Vascular diagnostics. Springer; 1994. p. 163-76.
29. López-Beret P. Profilaxis de la trombosis en microcirugía vascular. Estudio experimental en ratas. Archivos de la Facultad de Medicina. Universidad Complutense de Madrid. Junio 1990: 93-108.
30. Merrit CR. Evaluation of peripheral venous disease. Clin Diagn Ultrasound 1992;27:113-40.
31. Florensa VJ. Trombosis de miembros inferiores. Estudio comparativo entre ecografía duplex—doppler color y flebografía. Tesis Doctoral, 1993. Universidad Autónoma de Madrid. Facultad de Medicina.
32. Arnesen H, Helio A, Jacobsen L. A prospective study of streptokinase and heparin in the treatment of deep venous thrombosis. Acta Med Scand 1978;203:457-63.
33. Vasdekis SN, Clarke GH, Nicolaides AN. Quantification of venous reflux by means of duplex scanning. J Vasc Surg 1989;10:670-7.
34. Evers EJ, Wuppermann T. Die charakterisierung des poetthrombotischen refluxes mittels farbcodierter duplexsonographie. Vasa 1997;26: 190-3.
35. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep venous thrombosis. A collaborative European multicentre study. Thromb Haemost 1991;65:251-6.
36. Charbonier BA, Fiessinger JN, Banga JD, et al, on behalf of the FRADOXI group. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. Thromb Haemost 1998;79:897-901.
37. Kakkar VV. Dalteparin prevention of recurrent DVT: a study versus warfarin [abstract]. Haemostasis 1994;24 Suppl 1:45.
38. Fontcuberta J, Martinez Jubitero JM, Cairols M, et al. Tratamiento de las trombosis venosas profundas con fracciones de heparina de bajo peso molecular. Resultados preliminares. Sangre 1986;31:124.
39. Faivre R, Neuhart Y, Kieffer Y, Toulemonde F, et al. Subcutaneous administration of a low molecular weight heparin CY 222 compared with subcutaneous administration of standard heparin in patients with acute deep vein thrombosis. Thromb Haemost 1987;58 Suppl 120;430.
40. Prandoni P, Lensing AWA, Büller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet 1992;339:441-5.
41. Lopaciuk S, Meissner AJ, Filipecki S, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. Thromb Haemost 1992;68:14-8.
42. Grau E, Real E, Pastor E, et al. Home treatment of deep vein thrombosis: a two years experience of a single institution. Haematologica 1998; 83:438-41.
43. Lloyd AC, Aitken JA, Hoffmeyer UK, et al. Economic evaluation of the use of Nadroparin in the treatment of deep vein thrombosis in Switzerland. Ann Pharmacother 1997;31:842-6.
44. Boneu B, Navarro C, Cambus JO, et al. Pharmaco-dynamics and tolerance of two Nadroparin formulations (10,250 and 20,500 anti Xa IU ml) delivered for 10 days at therapeutic dose. Thromb Haemost 1998;79:338-41.
45. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low molecular weight heparin compared with continuous intravenous heparin in the treatment of proximal vein thrombosis. N Engl J Med 1992;326: 975-82.
46. Brandjes DPM, Heijboer H, Büller HR, et al. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal vein thrombosis. N Engl J Med 1992;327:1485-9.
47. Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thromboses. Circulation 1993;88:1731-5.
48. Fihn S, McDonnel M, Martin D, et al. Risk factors for complications of chronic anticoagulation. Ann Intern Med 1993;118:511-20.
49. van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briét E. Bleeding complications in oral anticoagulant therapy: an analysis of risk factors. Arch Intern Med 1993;153:1557-62.
50. Rizzieri DA, Wong WM, Gockerman JP. Thrombocytosis associated with low-molecular-weight heparin [letter]. Ann Intern Med 1996;126:742-3.
51. Valentine KA, Hull RD, Pineo GF. Low-molecular-weight heparin therapy and mortality. Semin Thromb Hemost 1997;23:173-8.
52. Strandness DE Jr, Langlois Y, Cramer M, et al. Long-term sequelae of acute venous thrombosis. JAMA 1983;250:1289-92.
53. Franzeck UK, Schalch I, Jäger KA, et al. Prospective 12-year follow-up study of clinical and hemodynamic sequelae after vein thrombosis in low-risk patients (Zurich study). Circulation 1996;93:74-9.
54. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
55. Haenen JH, Janssen MC, van Langen H, et al. Duplex ultrasound in the hemodynamic evaluation of the late sequelae of deep vein thrombosis. J Vasc Surg 1998;27:472-8.
56. Labropoulos N, Giannoukas AD, Delis K, et al. Where does venous reflux start? J Vasc Surg 1997;26:736-42.
57. Labropoulos, N, Giannoukas AD, Nicolaides AN, et al. New insights into the pathophysiology of venous ulceration using colour flow duplex imaging: implications for treatment. J Vasc Surg 1995;22: 45-50.
58. Franzeck UK, Schalch I, Bollinger A. On the relationship between changes in the deep veins evaluated by duplex sonography and the post-thrombotic syndrome 12 years after deep vein thrombosis. Thromb Haemost 1997;77:1109-12.
59. Baud JM, Stephas L, Ribadeau-Dumas C, et al. Short and medium-term duplex sonography follow-up of deep venous thrombosis of the lower limbs. J Clin Ultrasound 1998;26:7-13.
60. Van Ramshorst B, van Bemmelen P, Hoeneveld H, et al. Thrombus regression in deep venous thrombosis: quantification of spontaneous thrombolysis with duplex scanning. Circulation 1992;86:414–9.
61. Van Bemmelen SP, van Papendrecht AA, Hodde K, Klopper PJ. A study of valve incompetence that developed in a experimental model of venous hypertension. Arch Surg 1986;121:1048-52.
62. Murphy TP, Cronan JJ. Evolution of deep venous thrombosis: a prospective evaluation with US. Radiology 1990;177:543-8.
63. Caprini JA, Arcelus JI, Hoffman KN, Size G, Lauback M, Traverso CI. Venous duplex imaging follow-up of acute symptomatic deep venous thrombosis of the leg. J Vasc Surg 1995;21:472-6.
64. Marder VJ, Soulen RL, Atichartakarn V, et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977,89:1018-29.
65. Porter JM, Rutherford RB, Clagget P, et al. Reporting standards in venous diseases. Thromb Haemost 1982;48:1-5.

66. Barrowcliffe TW. Low molecular weight heparin (s). Br J Haematol 1955;9:1-7.
67. Bacher P, Lojewski B, Iqubal O, et al. Does anticoagulation with heparin followed by daily long-term LMW heparin activate the fibrinolytic system? Thromb Haemost 1993;69:538-42.
68. Van Haarst EP, Liasis N, van Ramshorst B, Moll FL. The development of valvular incompetence after deep vein thrombosis: a 7 year follow-up study with duplex scanning. Eur J Vasc Endovasc Surg 1996;12:295-9.
69. Van Bemmelen PS, Bedford G, Beach K, Stradness DE Jr. Quantitative segmental evaluation of venous valvular reflux with duplex ultrasound scanning. J Vasc Surg 1989;10:425-31.
70. Johnson BF, Manzo RA, Bergelin RO, Stradness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. J Vasc Surg 1995;21:307-13.
71. Van Ramshorst B, van Bemmelen PS, Hoeneveld H, et al. The development of valvular incompetence after deep vein thrombosis: a follow-up study with duplex scanning. J Vasc Surg 1994;19:1059-66.

Submitted Jul 14, 1999; accepted Apr 17, 2000.