Venographic comparison of subcutaneous low–molecular weight heparin with oral anticoagulant therapy in the long-term treatment of deep venous thrombosis

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Purpose: **The primary objective of this study was to evaluate with venography the rate of thrombus regression after a fixed dose of low–molecular weight heparin (LMWH) per day for 3 months compared with oral anticoagulant therapy for deep venous thrombosis (DVT). Secondary endpoints were the comparisons of the efficacy and safety of both treatments.**

Methods: **This study was designed as an open randomized clinical study in a university hospital setting. Of the 165 patients finally enrolled in the study, 85 were assigned LMWH therapy and 80 were assigned oral anticoagulant therapy. In the group randomized to oral anticoagulant therapy, the patients first underwent treatment in the hospital with standard unfractionated heparin and then coumarin for 3 months. Doses were adjusted with laboratory monitoring to maintain the international normalized ratio between 2.0 and 3.0. Patients in the LMWH group were administered subcutaneous injections of fixed doses of 40 mg enoxaparin (4000 anti-Xa units) every 12 hours for 7 days, and after discharge from the hospital, they were administered 40 mg enoxaparin once daily at fixed doses for 3 months without a laboratory control assay. A quantitative venographic score (Marder score) was used to assess the extent of the venous thrombosis, with 0 points indicating no DVT and 40 points indicating total occlusion of all deep veins. The *rate of thrombus reduction* was defined as the difference in quantitative venographic scores after termination of LMWH or coumarin therapy as compared with the scores obtained on the initial venographic results. The *efficacy* was defined as the ability to prevent symptomatic extension or recurrence of venous thromboembolism (documented with venograms or serial lung scans). The *safety* was defined as the occurrence of hemorrhages.**

Results: **After 3 months of treatment, the mean Marder score was significantly decreased in both groups in comparison with the baseline score, although the effect of therapy was significantly better after LMWH therapy (49.4% reduction) than after coumarin therapy (24.5% reduction; $P < .001$). LMWH therapy and male gender were independently associated with an enhanced resolution of the thrombus. A lower frequency of symptomatic recurrent venous thromboembolism was also shown in patients who underwent treatment with LMWH therapy (9.5%) than with oral anticoagulant therapy (23.7%; $P < .05$), although this difference was entirely a result of recurrence of DVT. Bleeding complications were significantly fewer in the LMWH group than in the coumarin group (1.1% vs 10%; $P < .05$). This difference was caused by minor hemorrhages. Coumarin therapy and cancer were independently associated with an enhanced risk of complications. Subcutaneous heparin therapy was well tolerated by all patients.**

Conclusion: **The patients who were allocated to undergo enoxaparin therapy had a significantly greater improvement in their quantitative venographic score, a significantly**

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lower recurrence rate of symptomatic venous thromboembolism, and a significantly lower incidence of bleeding than patients who underwent treatment with coumarin. LMWH can be used on an outpatient basis as a safer and more effective alternative to classical oral anticoagulant therapy for the secondary prophylaxis of selected patients with DVT. (J Vasc Surg 1999;30:283-92.)

Low–molecular weight heparin (LMWH) has been shown to be at least as effective and safe as intravenous adjusted-dose heparin in the initial treatment of proximal deep vein thrombosis (DVT).[1-10] However, common practice is to carry out treatment with oral anticoagulants for at least 3 months as a form of secondary prevention.[11] Oral anticoagulant therapy is associated with a significant risk of bleeding complications, and patients who undergo such therapy require frequent laboratory monitoring. Some of these patients have relative or absolute contraindications to the use of oral anticoagulants.[12] Under such circumstances, an alternative to prevent delayed thromboembolic recurrence is adjusted dose of subcutaneous heparin twice daily.[11-13] Compared with unfractionated heparin, LMWH has a longer half life, significantly fewer hemorrhagic complications, and a greater bioavailability at low doses, which allows once-a-day schedule and therefore may be preferable to standard heparin especially for long-term administration.[14] Some studies have recently evaluated the role of LMWH as an alternative to oral anticoagulation in the prevention of recurrent thromboembolism.[12,15,16] They suggest that fixed doses of LMWH appear to be quite effective and safe, but limited data on the basis of venographic observations are available. Previous investigations that compared LMWH with standard unfractioned heparin in the initial treatment of DVT revealed a phlebographic improvement in the patients who underwent treatment with LMWH when the venograms were performed approximately 1 or 2 weeks later,[14] but no significant differences were seen at the 6 month follow-up examination.[17] From the existing evidence, it is likely that a marked or total reduction of thrombi will reduce the incidence of postthrombotic syndrome.[18] Because a longer duration of the treatment with LMWH may increase the success rate of recanalization of the occluded veins, it seems legitimate to use phlebographic endpoints.[19] For this reason, the primary objective of the present study was to evaluate with venography the rate of thrombus regression after a single subcutaneous injection of LMWH (enoxaparin, 40 mg) per day for 3 months as compared with oral anticoagulant therapy for the treatment of patients with DVT. Secondary endpoints were to compare the efficacy (prevention of symptomatic venous thromboembolism) and safety (occurrence of hemorrhage) of both treatments.

MATERIAL AND METHODS

Study design. This was an open, randomized study comparing conventional coumarin therapy with a 3-month course of enoxaparin (4000 anti-Xa units; 40 mg) subcutaneously once daily in a fixed dose. The primary endpoint was the ability to reopen thromboses veins, defined as the difference in quantitative venographic scores after termination of LMWH or coumarin therapy compared with the scores obtained on the initial venography. The secondary endpoints were the development of symptomatic recurrent pulmonary embolism or symptomatic recurrent venous thrombosis (documented with serial perfusion lung scans or venograms) and bleeding episodes. Randomization was achieved by means of a prescribed schedule. Informed written or verbal consent was obtained from all patients in the study. The study protocol was accepted by the Institutional Review Board.

Patients. Consecutive eligible patients with clinically suspected DVT confirmed with contrast venography were enrolled in the study according to a computer schedule. The reasons for exclusion were: clinically suspected pulmonary embolism, currently active bleeding or coagulation abnormality or disorders contraindicating anticoagulant therapy, pregnancy, two or more previously documented episodes of DVT or pulmonary embolism, ongoing anticoagulant treatment at the time of referral, history of heparin-induced thrombocytopenia, caval filter inserted, allergic reaction to contrast material, a coagulation-inhibitor deficiency, a lupus anticoagulant, or antiphospholipid antibodies. In each patient, anticoagulant therapy was started as soon as possible after DVT had been documented objectively with ascending contrast venography. Whenever possible, the patients were allowed to walk on the third day of treatment, wearing elastic compressive stockings.

Regimens. In the patients randomized to oral anticoagulant therapy, an intravenous bolus of 100 U/kg of unfractioned heparin was administered, followed by a continuous intravenous infusion of heparin. The activated partial thromboplastin time

was measured 4 hours after the beginning of intravenous heparin treatment, and the test was repeated at intervals of 4 to 6 hours until the result was within the prescribed therapeutic range (ratio, 1.5 to 2.0) during the initial 24 hours of therapy. Oral treatment with coumarin (initial dose of 5 mg) was started in patients on day 5 of heparin treatment. The coumarin dose was adjusted daily to maintain the international normalized ratio (INR) between 2.0 and 3.0. Subsequently, heparin treatment was discontinued and the coumarin dose was adjusted with laboratory monitoring for 3 months. Although during this study the classical approach to the treatment of DVT was used, the results of two randomized clinical trials[20,21] have shown that oral anticoagulant therapy starting with heparin at the time of diagnosis is as effective and safe as the conventional regimen. The intensity of anticoagulation therapy in the first 3 months was expressed as the percentage of time during which a patient had a specific INR (<2.0, 2.0 to 3.0, or >3.0), with this period calculated with linear interpolation. No patients underwent oral anticoagulant therapy after 3 months of treatment, unless they had symptomatic recurrent thromboembolism. Patients in the LMWH group were administered subcutaneous injections every 12 hours of fixed doses of 40 mg enoxaparin (corresponding to 4000 international factor Xa inhibitory units) for 7 days. After discharge from the hospital, the patients underwent treatment with 40 mg enoxaparin subcutaneously once daily, which was usually administered by the patients themselves or by relatives and only occasionally by nurses. LMWH was administered at fixed doses, without a laboratory control assay for 3 months.

Main outcome measures. Venography was performed with long-leg films and no ionic contrast material according to the method of Rabinov and Paulin.[22] The criteria for DVT were an intraluminal filling defect confirmed in at least two different projections and no filling of a venous defect despite repeated injections with contrast material. A quantitative venographic score (Marder score[23]) was used to assess the extent of the venous thrombosis, with 0 points indicating no DVT and 40 points indicating total occlusion of all deep veins (Table I). Control phlebographies were performed routinely in all patients after 3 months of treatment. Each patient was assigned to one of the following groups on the basis of differences on the Marder score between initial and post-treatment phlebography: increased thrombosis (an increase in score points), unchanged (unaltered total score or ≤10% decrease in score points), partly cleared (>10% to ≤50% decrease in score points), substantially cleared (>50% to 89% decrease in score points), and completely lysed (≥90% decrease in score points). Perfusion lung scanning and chest radiography were performed for all patients at baseline. To exclude bias, the assessment of venograms and lung scans were scored by two observers who were blind to treatment allocation and to the sequence in which the tests were done (before or after treatment). The *efficacy of treatment* was defined as the ability to prevent symptomatic extension or recurrence of venous thromboembolism. The *safety* was defined as the occurrence of hemorrhages. Bleeding was defined as *major bleeding* if it was intracraneal or retroperitoneal or if it produced a decrease in the hemoglobin level of at least 2.0 g/dL, sufficient to necessitate discontinuation of treatment or the transfusion of 2 or more units of blood. Bleeding was defined as *minor bleeding* if it did not meet the criteria for major bleeding.

Table I. Venographic quantitation of thrombosis (Marder score)

Deep veins	*Score**
Iliac	6
Common femoral	4
Superficial femoral	10
Popliteal	4
Anterior tibial	4 (2 each)
Posterior tibial	6 (3 each)
Peroneal	6 (3 each)

*Total occlusion or nonfilling of a given vein was assigned the maximum score; segmental occlusion or fillings defects were given lesser scores in proportion to the degree of involvement.

Surveillance and follow-up. After discharge, all the patients were seen in our vascular clinic every month during the first trimester and then every 3 months during a total of 1 year of follow-up. They were instructed to come to the hospital immediately if symptoms or signs of recurrent DVT, pulmonary embolism, or bleeding developed. Those patients with suspected recurrent DVT underwent contrast venography. *Recurrent DVT* was defined as a constant intraluminal filling defect not present the first day. Patients with clinically suspected pulmonary embolism underwent another perfusion lung scan and chest radiography. The diagnosis was made on the basis of the presence of at least one segmental defect not seen on the preceding scan and no abnormality on the chest radiograph area. If the results were inconclusive, pulmonary angiography

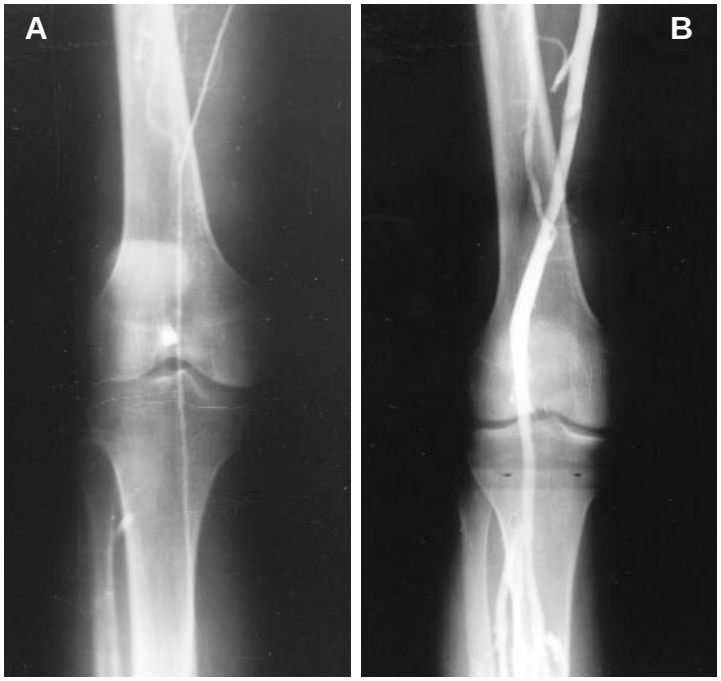

Fig 1. Venographic changes with 40 mg enoxaparin (4000 anti-Xa units). **A,** Total occlusion of popliteal and femoral veins in patient with deep venous thrombosis. **B,** Complete recanalization after fixed dose per day for 3 months of treatment.

was performed. During the 3 months of treatment, platelet counts were obtained each month in the patients undergoing LMWH therapy to rule out the possibility of heparin-induced thrombocytopenia. Adherence to the study regimens was monitored by reviews of the patients' charts. At each visit, patients were questioned about the appearance of new symptoms, bleeding, swelling, heaviness of leg, leg tiredness, or pain. The clinical status after 3 months of treatment was graded subjectively by each patient as improved, unchanged, or worse in relation to the pretreatment status.

Statistical analysis. On the basis of results from previous trials,[24] the proportion of patients with an unchanged or improved Marder score after LMWH treatment was assumed to be 90%. By sample size, we determined a 15% absolute difference in the proportions of patients whose conditions were unchanged and improved that were needed to show a statistically significant difference between the two treatments. At an 80% power for showing this difference at the 5% significance level, with a one-sided test, a total of 78 patients would be necessary at least in each treatment group. The number of patients planned for inclusion into each group was therefore 92, to account for an anticipated drop-out rate of 15%. Quantitative data were expressed as mean ± standard error. Confidence intervals (CI) of 95% for the difference between the two treatment groups were calculated with the normal approximation to the binomial distribution. The rates of asymptomatic pulmonary embolism, recurrent thromboembolism, bleeding, death, degree of thrombus regression, and clinical status in the two groups were compared by means of Fisher exact test or χ^2 test as appropriate. The changes in venographic score were analyzed within and between groups with two-sample and matched-pair and unpaired *t* tests. Univariate analysis was performed to identify factors that affected the differences on the Marder score between initial and post-treatment phlebography. A multivariate stepwise regression model was used to identify independent variables that could influence the percentage of change in Marder score and complications of both groups. Two-sided *P* values of less than .05 were considered significant. Software JMP 3.1 from the S.A.S. Institute Inc (Cary, NC) was used.

RESULTS

Patients. From June 1994 to June 1997, 257 consecutive patients with clinically suspected DVT underwent treatment in our hospital. Eligible

Table II. Clinical characteristics of patients with deep venous thrombosis treated with enoxaparin or coumarin

	Enoxaparin (n = 85)	*Coumarin (n = 80)*	*P value*
Mean age (years)	62.7 (r, 19 to 83)	58.3 (r, 20 to 82)	<.05
Sex (male:female)	41:44	46:34	
Days since onset of symptoms	4.9 (r, 1 to 30)	4.1 (r, 1 to 20)	
Asymptomatic pulmonary embolism	21 (24.7%)	45 (56.2%)	<.001
Risk factors to DVT			
Recent trauma, surgery, or immobilization	34 (40%)	23 (28.77%)	
Cancer	10 (11.7%)	8 (10%)	
Unknown	41 (48.2%)	49 (61.2%)	
Location of thrombus			
Calf with popliteal vein	6 (7.05%)	7 (8.7%)	
Popliteal and femoral vein	43 (50.5%)	35 (43.7%)	
Popliteal, femoral, and iliac vein	26 (30.5%)	30 (37.5%)	
Iliac vein	10 (11.7%)	8 (10%)	

DVT, Deep venous thrombosis.

Table III. Venographic evaluation

	*Enoxaparin (n = 84)**	*Coumarin (n = 80)*	*P value*
Marder score			
Before treatment	24.7 ± 1.1	26.06 ± 1.1	
After treatment	12.5 ± 1.05	19.7 ± 1.1	<.001
Difference (Δ)	–12.2 ± 0.9	–6.4 ± 0.8	<.001
Fate of the thrombus			<.001
Increase in size	2 (2.3%)	8 (10%)	
No change	3 (3.5%)	13 (16.2%)	
Partial clearance	39 (46.4%)	45 (56.2%)	
Substantial clearance	24 (28.5%)	13 (16.2%)	
Complete lysis	16 (19.04%)	1 (1.2%)	

*One patient died of massive pulmonary embolism.

patients (n = 185) had DVT confirmed with contrast venography, perfusion lung scanning within 48 hours of study entry, and chest radiography. Of these, 93 were assigned to undergo LMWH therapy and 92 to undergo treatment with coumarin. Twenty patients were excluded from the analysis (eight in the LMWH group, and 12 in the coumarin group) because the second venogram was not obtained (n = 12), the regimen of treatment was not performed correctly by the patient (n = 5), or the patients were lost during the follow-up period (n = 3). For the 165 patients finally enrolled into the study, the baseline clinical characteristics are shown in the Table II. The treatment groups were comparable at entry except for age (younger in the coumarin group) and incidence of silent pulmonary embolism (higher in the coumarin group). To assess the possible effect of this potential age and asymptomatic pulmonary embolism imbalance, multiple logistic regression was used. No significant effect was found.

Degree of thrombus regression. The intensity of oral anticoagulant therapy in the coumarin group was 15% with INR less than 2.0, 64% with INR from 2.0 to 3.0, and 21% with INR more than 3.0. A second venogram was performed in all patients. The changes in the extent of venous thrombosis on venography are summarized in Table III. No significant difference in Marder score was observed between the two treatment groups at inclusion. After 3 months of treatment, the mean Marder score was significantly decreased in both groups in comparison with the baseline score, although the effect of therapy was significantly better after LMWH therapy (49.4% reduction of the Marder score) than after coumarin therapy (24.5% reduction of the Marder score; $P < .001$; Fig 1). The results of the stratified analysis of the evolution of the thrombus (Table III), on the basis of the percentage of the differences of score between the initial and post-treatment phlebography, also showed a statistically significant superiority of LMWH therapy over coumarin therapy ($P < .001$).

Table IV. Univariate analysis of risk factors and location of thrombus associated with differences on the Marder score between initial and post-treatment phlebography

	Enoxaparin ΔMarder score	*Coumarin ΔMarder score*	*P value*
Risk factors to DVT			
Recent trauma, surgery, or immobilization	11.4 ± 1.3	6.2 ± 1.04	<.01
Cancer	8.1 ± 2.1	3.5 ± 1.5	
Unknown	13.7 ± 1.5	7 ± 1.2	<.001
Location of thrombus			
Calf with popliteal vein	7 ± 2.3	5.1 ± 2.2	
Popliteal and femoral vein	11.8 ± 1.3	6.1 ± 1.06	<.01
Popliteal, femoral, and iliac vein	15.2 ± 2.07	8.7 ± 1.2	<.05
Iliac vein	8.3 ± 1.8	0.25 ± 4.1	

ΔMarder score, Marder score before treatment – Marder score after treatment; DVT, deep venous thrombosis.

Table V. Independent determinants of the percentage of change in Marder score as selected with multivariate step-wise linear regression model

Significant independent variables	*95% CI*		*F value*	*P value*
	Lower	*Upper*		
Treatment (enoxaparin)	–28.329	–9.889	16.5	.0001
Sex (male)	–20.348	–1.851	5.53	.0199

F, Fisher-Snedecor.
R^2 = 0.11435.

Univariate analysis shows that no significant differences were observed in the distribution of changes in venographic score between both groups when the cause of DVT was cancer or the thrombus was placed only at geniculate or iliac level (Table IV). In contrast, a higher reopening rate of thrombosed veins was shown in the patients assigned to undergo LMWH therapy as compared with the patients assigned to undergo treatment with coumarin when the cause of DVT was recent trauma, surgery, or immobilization (P = .0037), when the DVT was idiopathic (P = .0009), or when the thrombus was placed in popliteal and femoral veins (P = .0011) or affected completely all of the limb (P = .01005). In a step-wise linear regression model, LMWH therapy (P < .0001) and male gender (P = .0199) were independently associated with an enhanced resolution of the thrombus (Table V). The r^2 value was 0.11435.

Recurrent thromboembolism. Symptomatic extension or recurrent venous thromboembolism confirmed with objective tests developed in eight patients (9.5%) of the LMWH group and in 19 patients (23.7%) assigned to undergo coumarin therapy (P = .0196; Table V). Of the 19 events in the coumarin group, 15 involved recurrent thrombosis (13 recurrences were in the same limb, two were contralateral) and four involved pulmonary embolism (from which all patients required cava filter placement). Of the eight events in the LMWH group, five involved recurrent thrombosis (all in the same limb) and three involved pulmonary embolism (from which one patient died on the fifth day after randomization). The absolute difference in the frequency of pulmonary embolism did not reach statistical significance (P = .7149). However, significant differences were observed in the frequency of recurrent thrombosis (P = .0161). During the 12-month surveillance period, two patients in the coumarin group had a recurrence of symptomatic DVT documented with venography after discontinuation of the anticoagulant treatment (one in the 20th week, and the other in the 24th week). In the LMWH group, three patients had symptomatic recurrent DVT documented with venography (one in the 20th week, another in the 24th week, and another in the 32nd week). Only one patient of the coumarin group was readmitted to the hospital in the 21st week because of symptomatic recurrent pulmonary embolism confirmed with perfusion lung scanning and chest radiography. No symptomatic pulmonary embolisms were observed in the LMWH group. Recurrent thromboembolism was associated with recent surgery or trauma in three patients (three

Table VI. Thromboembolic and bleeding complications during initial treatment and follow-up examination

	Enoxaparin (n = 85)	*Coumarin (n = 80)*	*P value*
Treatment period (3 months)			
Major bleeding	1	2	
Minor bleeding	0	6	.0121
Total events	1	8	.0160
Recurrence of DVT	5	15	.0161
Pulmonary embolism	3*	4	
Total events	8	19	.0196
Surveillance period (9 months)			
Recurrence of DVT	3	2	
Pulmonary embolism	0	1	
Total events	3	3	

DVT, Deep venous thrombosis.
*One fatal pulmonary embolism.

Table VII. Independent determinants of complications (venous thromboembolism and bleeding) as selected with multivariate step-wise logistic regression model

Significant independent variables	*95% CI*		*Odds ratio*	*P value*
	Lower	*Upper*		
Treatment (coumarin)	1.719	4.623	2.82	.0001
Risk factor (cancer)	1.101	4.233	2.15	.0250

CI, Confidence interval.

cases in the LMWH group, and none in the coumarin group), cancer in 10 patients (five cases in the LMWH group, and five in the coumarin group), and idiopathic disease in 20 patients (three cases in the LMWH group, and 17 in the coumarin group).

Bleeding complications. Bleeding complications were significantly fewer in the LMWH group (1.1% vs 10%; $P = .0160$; Table VI). Major bleeding occurred during or immediately after the initial therapy in one patient undergoing LMWH therapy (1.1%) and in 2 patients undergoing treatment with coumarin (2.5%; $P = .6136$). The hemorrhage in the LMWH group consisted of upper gastrointestinal bleeding, and in the coumarin group, there were one upper gastrointestinal bleeding and one retroperitoneal bleeding with hematuria. Minor hemorrhagic complications occurred in none of the patients who underwent LMWH therapy and in six patients who underwent treatment with coumarin (7.5%; $P = .0121$). The minor bleedings in the coumarin group consisted of two hematuriax, three epistaxis, and one hemoptysis. Small hematomas in the abdominal wall were seen in patients assigned to undergo LMWH therapy. In a step-wise logistic regression model (Table VII), coumarin therapy (odds ratio, 2.82; CI, 1.719 to 4.623; $P < .0001$) and cancer (odds ratio, 2.15; CI, 1.101 to 4.233; $P = .025$) were independently associated with an enhanced risk of complications (symptomatic recurrent thromboembolism and bleeding). These conclusions remained unchanged when the few patients with documented DVT who were withdrawn after randomization because of protocol violation were included in an intention-to-treat analysis.

Deaths. One patient from the LMWH group died of massive pulmonary embolism, confirmed with angiography, on the fifth day after the initial treatment. During the 12-month study period, four patients who were assigned to the LMWH group died, as compared with three patients assigned to the coumarin group. The causes of death included cancer (five patients) and cardiovascular disease (two patients).

Compliance. Only one case of thrombocytopenia ($<100.000/mm^3$) was observed immediately after the initial therapy with unfractioned heparin. This disorder dissapeared with oral anticoagulant therapy. Subcutaneous heparin therapy was well tolerated by all patients. No patients showed heparin-induced thrombocytopenia in the 3-month group with LMWH. The clinical status graded subjectively by each patient was significantly better after LMWH

therapy than after coumarin therapy ($P < .001$). There was an improvement after 3 months of treatment in relation to the pretreatment status in 68 of 84 patients (80.9%) in the LMWH group and in 40 of 80 (50%) in the coumarin group. There were no changes in 15 of 84 patients (17.8%) in the LMWH group and in 35 of 80 (43.7%) in the coumarin group. Finally, there was worsening in one of 84 patients (1.1%) and five of 80 (6.2%), respectively.

DISCUSSION

This study showed that enoxaparin, a LMWH, not only can be used safely and effectively to treat DVT at home for long term but also that its ability to reopen thromboses veins is better than coumarin, an anti–vitamin K oral anticoagulant. Although the mean Marder score was significantly improved in both groups at the 3-month follow-up examination, a higher degree of recanalization was shown with venography in the patients assigned to undergo LMWH therapy (49.4%) as compared with the patients assigned to undergo treatment with coumarin (24.4%). Moreover, in a multivariate analysis, the male patients were independently associated with an enhanced resolution of the thrombus. A thrombus reduction of at least 30% or more is at present used in several trials as a sign of clinical benefit for the individual patient,[19] with the expectancy that a major recanalization may also result in a reduced incidence of post-thrombotic syndrome.[18,19] Because of this, evidence on the basis of venographic findings suggests that a LMWH may reduce the risk of the late sequelae of DVT, although it will open for discussion to what extent the reduction of thrombus size really is accomplished by long-term benefits. The 12-month follow-up period used in this study is too short to reflect the true development of clinical post-thrombotic syndrome. However, LMWH was subjectively associated by each patient with better clinical status than coumarin therapy after 3 months of treatment.

Long-term venographic follow-up data in patients with DVT are limited.[17] Our study is the first to analyse a longer duration of treatment with LMWH and the tendency of thrombus regression in comparison with patients undergoing oral anticoagulant therapy as a form of secondary prevention. The mechanism by which LMWH facilitates thrombus regression is not understood. Probably the inhibition of thrombin formation, the lesser risk of platelet aggregation, and local effects at the endothelial level play a critical role.[25,26] Indeed, endothelial cells are the principal physiologic source of tissue-type plasminogen activator, and the subcutaneous administration of LMWH causes an increase in plasma of tissue-type plasminogen activator with peak at 3 hours after injection.[27,28]

The recanalization of thrombosed veins was quite different in these two patient groups according to the cause of DVT and the localization of the venous occlusion. Particularly, there was a significant trend in favor of LMWH when the cause of DVT was recent trauma, surgery, or immobilization, when the DVT was idiopathic, or when the thrombus was placed in popliteal and femoral veins or affected completely all of the limb. By contrast, if the cause of DVT was cancer or the intraluminal filling defect was exclusively placed at geniculate or iliac level, no significant differences were observed between patients assigned to undergo LMWH therapy and patients assigned to undergo treatment with coumarin. Nevertheless, because of the large standard error and the relatively small number of patients among these subgroups, this study does not have sufficient statistical power to detect significant differences. Further studies are necessary before definitive conclusions can be reached.

LMWH have undergone limited investigations for the secondary prevention of venous thromboembolism.[9] In these studies, patients first underwent treatment in the hospital with standard heparin, and then therapy with LMWH was compared with therapy with warfarin[15,16] or subcutaneous standard heparin[12] for 3 to 6 months. Monreal et al[12] showed, in a consecutive series of patients with contraindication to coumarin therapy, that patients who underwent treatment with LMWH had a lower frequency of either recurrent pulmonary embolism or minor bleeding in comparison with unfractioned heparin, although none of these differences were statistically significant perhaps because of the small number of patients (beta error). Pini et al[15] confirmed these findings in a sufficiently large randomized study of patients with DVT, although the diagnosis of recurrent DVT was often made on the basis of noninvasive testing and diagnosis of pulmonary embolism could be questioned because baseline lung scans were not performed. Despite these facts, they showed essentially no difference in the incidence of recurrent thrombosis between patients who underwent treatment with LMWH (enoxaparin 40 mg) and patients who underwent treatment with warfarin, but patients allocated to undergo LMWH therapy had a significantly lower incidence of bleeding. In the third trial, which has been reported in abstract form, Kakkar[16] corroborated these findings with dalteparin.

In our study, rates of symptomatic recurrent

thromboembolism and bleeding also tended to occur less in the patients undergoing enoxaparin therapy than in those patients undergoing coumarin therapy (odds ratio, 2.82; CI, 1.719 to 4.623). As expected, a low bleeding rate was observed in the LMWH group. The regimen of 40 mg enoxaparin, at a fixed dose once daily subcutaneously, resulted in 1.1% versus 10% of hemorrhagic complications compared with the coumarin treatment ($P < .05$). This difference was a result of minor hemorrhages. Concomittantly, a lower frequency of symptomatic recurrent venous thromboembolism was shown in patients who underwent treatment with LMWH (9.5%) than with oral anticoagulants (23.7%; $P < .05$), although this difference was entirely a result of recurrence of DVT. Thus, we find a statistically significant superiority of LMWH over coumarin regarding both efficay and safety. Although the doses that we used in the present study were actually prophylactic doses rather than treatment doses, especially for the first 7 days of treatment, it is important to consider whether our results were caused by a true property of enoxaparin because adequate dosage finding studies are not available.[29,30] The fact that a patient died in the LMWH group of a recurrent pulmonary embolism on the fifth day of randomization suggests that the dosage used may be insufficient and that higher levels should be preferable in these patients. Particularly, we believe that an adjusted dose per kilogram of body weight would be recommendable for the management of DVT, although further dose-related studies are necessary to define minimal and maximal doses.

Because the two regimens were given by different route and because dose adjustments were necessary in the coumarin group, we could not use a double-blind design. To minimize bias in the assessment of symptomatic recurrent venous thromboembolism, all suspected recurrences were evaluated with objective tests and the data were analyzed by two blinded observers. Given that we did routinely screen all patients with venography at 3 months, silent venous recurrences may not have gone undetected, but silent pulmonary embolism may have occurred, because lung scans were only taken to assist diagnosis of symptomatic pulmonary embolism. Some concern may arise from the finding that there was a higher frequency of silent pulmonary embolism in patients allocated to the coumarin group than in patients allocated to the LMWH group, which could have potentially skewed the results. However, a multiple logistic regression showed that this variable was not independently associated with the recurrence of venous thromboembolism and bleeding. In addition, both groups were comparable according to location of thrombus, predisposing factors, and extension of the venous thrombosis. The higher frequency of silent pulmonary embolism confirms previous studies that show that, by the time the DVT has been diagnosed, many patients have already had a pulmonary embolism.[31]

The number of deaths and, in particular, the proportion of deaths in patients with cancer (three of five in the LMWH group, and two of three in the coumarin group) were comparable in both treatment groups. Our data therefore do not substantiate the hypothesis that LMWH administration could exert a favorable effect on cancer progression.[1,6] However, the patients with cancer were independently associated with more complications (odds ratio, 2.15; CI, 1.101 to 4.233).

Regarding the compliance of the patients with LMWH therapy, this was well tolerated and allowed the patients to be fully ambulant. None of the patients had negative reactions to undergoing treatment at home with a subcutaneous injection daily for 3 months, and no patients showed heparin-induced thrombocytopenia in the 3-month group with LMWH therapy. However, most patients had small hematomas in the injection sites. Although osteoporosis is a well-known side-effect of heparin therapy, particularly in long-term therapy, we have not performed any bone density measurements, x-rays, or other studies to look for this potential complication. According to the only study that has analyzed this fact, LMWH therapy was associated with a lesser risk of bone fracture than unfractionated heparin therapy.[12] This means that LMWH seems to be a good alternative to standard heparin for patients in whom oral anticoagulant therapy is contraindicated, especially elderly patients, in whom spine fractures are quite common.

In conclusion, the patients allocated to undergo treatment with enoxaparin had a significantly greater improvement in their clinical status and quantitative venographic score, a significantly lower recurrence rate of symptomatic venous thromboembolism, and a significantly lower incidence of bleeding than patients who underwent treatment with coumarin. These promising results obtained with LMWH therapy administered by subcutaneous injection, without laboratory monitoring, raise the possibillity that these agents can be used on an outpatient basis as a safer and more effective alternative to classic oral anticoagulant therapy for the secondary prophylaxis of selected patients with established DVT. Particularly good candidates would be pregnant women, patients with a

high risk of bleeding, elderly people, patients with life-threatening diseases, and those patients in whom the periodic monitoring is impossible because they live in remote areas or are unable to cooperate (dementia, chronic alcoholism, etc).

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