Effect of the anticoagulant therapy in the incidence of post-thrombotic syndrome and recurrent thromboembolism: Comparative study of enoxaparin versus coumarin

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Objective: **We evaluated the effect of long-term anticoagulant treatment (enoxaparin vs coumarin) in patients with deep venous thrombosis (DVT) as to incidence of post-thrombotic syndrome (PTS) and recurrent venous thromboembolism. We also analyzed the impact of thrombus regression after the anticoagulant treatment for these two outcomes.**

Methods: **A prospective study was designed in which 165 patients with symptomatic, unilateral, first-episode DVT were randomized to a long-term anticoagulant treatment with coumarin or enoxaparin during at least 3 months. The rate of thrombus regression was defined as the difference in Marder score after 3 months of treatment by venography. Follow-up was performed at 3, 6, and 12 months, and yearly thereafter for 5 years. Venous disease was related to pathologic severity of PTS according to the validated scale of Villalta as rated by a physician blinded to treatment. Recurrence of symptomatic venous thromboembolism was documented objectively.**

Results: **The 5-year follow-up period was completed for 100 patients (enoxaparin, 56; coumarin, 44). A lesser incidence of PTS was observed in the enoxaparin group (39.3% absent, 19.6% severe) than in the coumarin group (29.5% absent, 29.5% severe), although this difference was not statistically significant. The accumulated recurrence rate was 19.3% with enoxaparin compared with 36.6% with coumarin ($P = .02$). Although the mean Marder score was significantly improved in both groups (49.1% for enoxaparin vs 24.0% for coumarin; $P = .016$), a lower reduction in thrombus size was associated with higher clinical events of recurrence (hazard ratio = 1.97; 95% CI, 1.06-3.66; $P = .032$). A significant inverse correlation was also found between the degree of thrombus regression at 3 months and the incidence at 5 years of PTS ($P = .007$).**

Conclusions: **Residual venous thrombosis is an important risk factor for recurrent thromboembolism and PTS. A greater reduction in thrombus size was associated with lesser clinical events of recurrence and consequently a lesser rate of PTS. However, despite a greater recanalization with enoxaparin, the incidence of PTS was similar between both treatment groups, probably because of the small sample size. Further investigations are needed to clarify the implication of the anticoagulant treatment in the severity of PTS. (J Vasc Surg 2008;48:953-9.)**

Post-thrombotic syndrome (PTS) is one the most serious long-term complications of deep venous thrombosis (DVT) in the lower limb. The fundamental pathophysiologic disturbance found in these patients is sustained venous hypertension, which results from valvular incompetence, outflow obstruction, calf muscle dysfunction, or a combination of these. At present, development of PTS is generally unpredictable, with the real incidence unknown because of increases with the passage of the time.[1-4]

Former studies of the natural history of acute DVT have reported that thrombus evolution is a dynamic process, with recanalization and further thrombotic events occurring as competing processes.[5] In fact, the lack of thrombus regression appears to be correlated with clinical recurrence, and recurrent venous thromboembolism (VTE) is one of the most consistent risk factors associated with the severity of post-thrombotic sequelae.[6-9]

Some years ago we published that enoxaparin, a low-molecular-weight heparin, not only could be used safely and effectively to treat DVT long-term, but it also was more effective than coumarin, an oral anticoagulant, in reopening thrombosed veins.[10] This venographic observation has been corroborated in other studies, which concluded that treatment with a low-molecular-weight heparin increased the frequency of thrombus regression.[11]

Today, a thrombus reduction of at least 30% or more is used in several trials as a sign of clinical benefit for the individual patient.[12] Because of this criterion, the purpose of this study was to evaluate the effect of long-term anticoagulant treatment of patients with DVT treated with enoxaparin versus coumarin in the incidence of PTS, with the expectation that a major recanalization might also result in a reduced incidence of PTS after 5 years of follow-up. Second, we determined the accumulated recurrence rate of symptomatic VTE during the observational period, be-

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cause VTE recurrence has been strongly related with development of PTS.

PATIENTS AND METHODS

Study design. A prospective cohort study was designed in which 165 patients with symptomatic, unilateral, and first-episode DVT were previously randomized to a long-term (at least 3 months) anticoagulant treatment with coumarin (international normalized ratio [INR], 2-3) or enoxaparin once daily in fixed doses (4000 anti-Xa units, 40 mg) and then followed up for 5 years.

The primary end point was the incidence of PTS, defined according to the validated scale of Villalta[13] by a physician blinded to treatment. Second, we assessed the development of symptomatic recurrent VTE documented objectively by serial perfusion lung scans or computed tomography angiography (CT-angio) scans for pulmonary embolism, and duplex scans or venograms for venous thrombosis. Finally, we evaluated the impact of thrombus regression, defined as the difference in Marder score after 3 months of treatment by venography, for these two outcomes.

Informed written or verbal consent was obtained from all patients in the study. The study protocol was approved by our hospital's institutional review board and ethical committee.

Patients. All patients enrolled in the present study were consecutive patients with symptomatic, unilateral, and first-episode DVT confirmed by venography; they were randomized by means of a prescribed schedule to long-term treatment with oral anticoagulant therapy (coumarin: INR, 2-3) or low-molecular-weight heparin (twice daily enoxaparin 40 mg for 1 week followed by once-daily enoxaparin 40 mg in fixed doses) for 3 months. The patients' clinical characteristics and the criteria of inclusion and exclusion were previously reported.[10] No patients underwent anticoagulant therapy after 3 months of treatment unless they had a symptomatic recurrent thromboembolism during the follow-up. At this time, all patients were instructed and motivated to wear graduated compression stocking (providing 40 mm Hg in the ankle) daily during diurnal activities for at least 2 years.

Venographic assessment. A quantitative venographic score (Marder score) was used to assess the extent of venous thrombosis, with 0 points indicating no DVT and 40 points indicating total occlusion of all deep veins.[14] Control phlebographies were performed routinely in all patients after 3 months of treatment. The degree of thrombus regression at 3 months was determined venographically by the difference between the baseline and final Marder score after treatment, and expressed as the percentage of reduction in the score. According to this difference, each patient was assigned to one of two groups ($<$30% decrease in score points or $\geq$30% decrease in score points), because this cutoff point has been used in previous studies and thus has been validated.[12,15] The assessment of venograms was scored by two physicians who were blinded to treatment allocation and to the sequence in which the tests were done (before or after treatment).

Recurrent symptomatic VTE. Venograms, perfusion lung scanning, and chest radiography were performed for all patients at baseline. Recurrent DVT was reported if the patients had new clinical signs of DVT and if the signs could be confirmed independently by ultrasound scanning at the vascular laboratory during follow-up as a new thrombus with phlebography (first year) or as no compressibility of a previous normalized venous segment. Patients with clinically suspected pulmonary embolism underwent another perfusion lung scan and chest radiography or angio-CT scan to confirm the diagnosis. The diagnosis of recurrent symptomatic VTE was established by an objective test and confirmed by two independent physicians blinded to the study to exclude bias. The DVT or pulmonary embolism that occurred within the initial anticoagulation period (3 months) was considered in the analysis.

Criteria for PTS. After 5 years of follow-up, the venous disease was related to pathologic severity of PTS according to the Villalta validated scale by a vascular physician who was unaware of previous clinical details of the patient (M.M.P.). The Villalta's scoring system[13] assesses five symptoms (pain, cramps, heaviness, pruritus, and paresthesia), and six signs (pretibial edema, induration of the skin, hyperpigmentation, new venous ectasia, redness, and pain during calf compression). For each item, the investigators assigned a score of 0 (not present or minimal) to 3 (severe). A total score of 15 or more or the presence of a venous ulcer indicated severe PTS; a total score of 5 to 14 indicated mild PTS; and total score less than 5 indicated absent PTS.

Surveillance and follow-up. After discharge, all patients were seen in our vascular clinic every month during the first trimester and then at 6 and 12 months, and yearly during the 5-year observational period. A duplex ultrasound scan of both legs was performed every year in our vascular laboratory by a certificated vascular physician. The patients were instructed to come to the hospital immediately if symptoms or signs of recurrent DVT, pulmonary embolism, or bleeding developed. Adherence to the study was monitored by reviews of the patients' charts. Patients who failed to attend follow-up visits were contacted by telephone, and cause of death for those who died was documented by death certificates obtained from relatives or the Registry of National Bureau of Statistics in Spain.

Statistical analysis. Descriptive statistics are reported as n (%) or mean $\pm$ SD unless stated otherwise. Univariate analysis was performed to test the potential predictors of PTS and recurrence. Kaplan-Meier estimates and 95% confidence intervals (CIs) were calculated to assess the risk for recurrent VTE in an intention-to-treat analysis. Time-dependent Cox proportional hazards models were used to calculate hazard ratios (HRs) for recurrent VTE in patients with PTS (absent, mild, and severe), for patients with Marder score $<$ 30% versus Marder score $\geq$ 30%, and for patients treated initially with enoxaparin or coumarin. Patients who did not have recurrence were censored at the

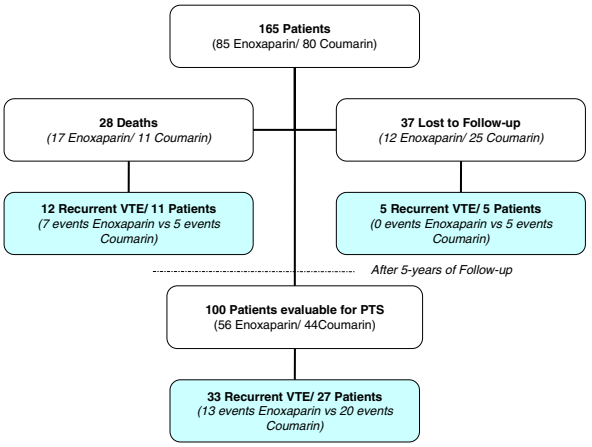

Fig 1. Flowchart of patients in the study for recurrent venous thromboembolism and post-thrombotic syndrome.

end of the available follow-up or at death. To assess the statistical correlation between the Marder score and the risk for PTS, we used the nonparametric Spearman test. All analyses were performed with SPSS statistical software version 14vs (SPSS Inc, Chicago, IL).

RESULTS

Study population. Of the 165 patients initially included in the study, the 100 (60.6%) who completed the 5-year follow-up period constituted our study group: 56 patients treated with enoxaparin and 44 patients treated with coumarin (Fig 1). Baseline clinical characteristics for these 100 patients are shown in Table I.

Twenty-eight (17%) patients died; 17 (20%) were treated with enoxaparin and 11 (13.8%) with coumarin ($P = .28$). One fatal pulmonary embolism was registered in the group with enoxaparin at the beginning of treatment (fifth day), and two pulmonary embolisms occurred during follow-up in the group treated with coumarin. The other causes of death included cancer (17 patients), cardiovascular disease (6 patients), stroke (1 patient), and crash (1 patient).

Thirty-seven (22.4%) patients were lost after the second year of follow-up; 12 (14.1%) were treated with enoxaparin and 25 (31.3%) with coumarin ($P = .008$).

Thrombus regression. A second venogram was performed in all patients. No significant difference in Marder score was observed between the two treatment groups at baseline (Table I). After 3 months of treatment, the mean Marder score was significantly decreased, although the effect of therapy was significantly better after enoxaparin treatment (49.1% ± 51.2% reduction in Marder score) than after coumarin treatment (24.0% ± 51.0% reduction in Marder score, $P = .016$). Indeed, a thrombus regression < 30% was observed in only 15 (26.78%) patients treated with enoxaparin versus 24 (54.55%) patients treated with coumarin ($P = .007$).

Recurrent VTE. During the observational period of 5 years, 50 episodes of symptomatic recurrent VTE were diagnosed in 43 (26.06%) patients. The intensity of oral anticoagulation was 15% with INR < 2.0, 64% with INR from 2.0 to 3.0, and 21% with INR > 3.0. Recurrences were thromboses involving a previously affected extremity in 33 (66%) cases and the contralateral leg in 7 (14%) case; the remaining 10 (20%) cases had pulmonary embolisms. The pulmonary embolisms were fatal in 3 (6%) cases. Seven patients had two or more documented recurrent VTEs. The cumulative incidence of recurrent VTE for the whole series was 21.8% at 12 months, 23.7% at 24 months, 24.6% at 36 months, 24.6% at 48 months, and 27.3% at 5 years.

The cumulative incidence of recurrence at 5 years was 19.3% with enoxaparin and 36.6% with coumarin ($P = .02$; Fig 2). On the basis of the Cox proportional hazards model, the HR for recurrent VTE was 1.97 (95% CI, 1.06-3.66; $P = .032$) in patients treated with coumarin compared with patients treated with enoxaparin.

Among the evaluated potential risk factors, the presence of residual venous thrombosis increased the risk for recurrent VTE. The cumulative incidence of recurrence at 5 years was 40.5% in patients with a Marder score < 30% compared with 17.8% in patients with a Marder score ≥ 30% after treatment ($P = .001$; Fig 3). Using a time-dependent Cox proportional hazards model, we found that a patient with thrombus regression ≥ 30% had a 62% decrease in the risk for developing a recurrent VTE compared with a patient with a thrombus regression < 30% (HR = 0.38; 95% CI, 0.20-0.70; $P = .002$). In the univariate analysis, patients with cancer had a higher risk for recurrent events ($P = .03$), whereas those with a trauma, surgery, or immobilization as risk factors of DVT had a lower risk for recurrence ($P = .03$). Other factors analyzed were not related with recurrence (Appendix I, online only).

Post-thrombotic syndrome. Despite regular use of compression stockings (75.0%), a total of 65 (65%) patients developed signs and symptoms of PTS. The PTS was considered moderate in 41 patients and severe in 24. Thirty-five patients were asymptomatic after 5 years. A lesser incidence of PTS was observed in the enoxaparin group (39.3% absent, 19.6% severe) than in the coumarin group (29.5% absent, 29.5% severe), although this difference was not statistically significant ($P = .43$). Recurrent VTE and lower thrombus regression after anticoagulant treatment strongly predicted PTS. At 5 years, the cumulative incidence of recurrence was 5.7% among patients without PTS, 31.7% in patients with mild PTS, and 50% in patients with severe PTS ($P = .001$). Patients with mild PTS showed a 6-fold higher risk for recurrence compared with patients without PTS (HR = 6.19; 95% CI, 1.39-27.49; $P = .016$). This risk for recurrence was 11-fold in patients with severe PTS compared with patients without PTS (HR = 11.25; 95% CI, 2.5-50.35; $P = .002$; Fig 4). In contrast, patients without PTS showed a mean Marder reduction of 52.38% ± 44.38% compared with 36.63% ± 50.16% in patients with moderate manifestations, and only 19.62% ± 62.18 % in patients with severe signs and symptoms of PTS ($P = .018$; Fig 5). A significant inverse correlation was found be-

Table I. Patients' demographic and clinical characteristics

	All patients (n = 100)	*Enoxaparin (n = 56)*	*Coumarin (n = 44)*	P
Age (y)	57.4 ± 14.4	59.8 ± 13.3	54.3 ± 15.2	.058
Male gender	50 (50.0%)	25 (44.6%)	25 (56.8%)	.227
Weight (kg)	74.4 ± 11.4	72.7 ± 11.9	76.7 ± 10.5	.082
Elastic stocking	75 (75.0%)	41 (73.2%)	34 (77.3%)	.642
Risk factors for DVT				
Trauma, surgery, or immobilization	26 (26.0%)	19 (33.9%)	7 (15.9%)	.041
Cancer (paraneoplasia)	5 (5.0%)	2 (3.6%)	3 (6.8%)	.652
Thrombophilia	9 (9.0%)	2 (3.6%)	7 (15.9%)	.032
Unknown (idiopathic)	40 (40.0%)	21 (37.5%)	21 (43.2%)	.565
Location of thrombus				
Calf with popliteal vein	9 (9.0%)	5 (8.9%)	4 (9.1%)	.609
Popliteal and femoral vein	57 (57.0%)	35 (61.4%)	22 (50.0%)	
Popliteal, femoral, and iliac vein	24 (24.0%)	11 (19.6%)	13 (29.5%)	
Iliac vein	10 (10.0%)	5 (8.9%)	5 (11.4%)	
Marder score				
Before treatment	21.7 ± 11.2	20.2 ± 11.6	23.6 ± 10.4	.077
After 3-month treatment	13.8 ± 10.9	11.1 ± 10.6	17.3 ± 10.5	.004
% Thrombus reduction	38.1 ± 52.4	49.1 ± 51.2	24.0 ± 51.0	.016
Recurrent thromboembolism				
Recurrence of DVT (events)				
Ipsilateral	23 (23.0%)	9 (16.1%)	14 (31.8%)	.063
Contralateral	6 (6.0%)	3 (5.4%)	3 (6.8%)	1.000
Pulmonary embolism (events)	4 (4.0%)	1 (1.8%)	3 (6.8%)	.317
Total (patients)	27 (27.0%)	10 (17.9%)	17 (38.6%)	.020
Post-thrombotic syndrome				
Absent	35 (35.0%)	22 (39.3%)	13 (29.5%)	.433
Moderate	41 (41.0%)	23 (41.1%)	18 (40.9%)	
Severe	24 (24.0%)	11 (19.6%)	13 (29.5%)	

Values given as n (%) or mean ± SD, as applied.

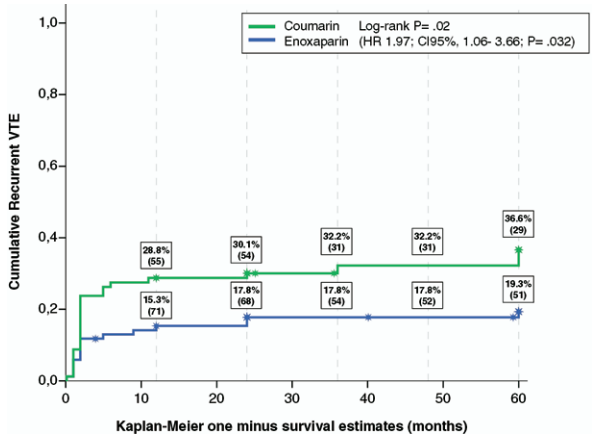

Fig 2. Kaplan-Meier estimates of the risk of recurrent venous thromboembolism according to the treatment with enoxaparin or coumarin (P = .02). The probability of recurrence was greater among patients treated with coumarin than among patients treated with enoxaparin (HR = 1.97; 95% CI, 1.06-3.66; P = .032).

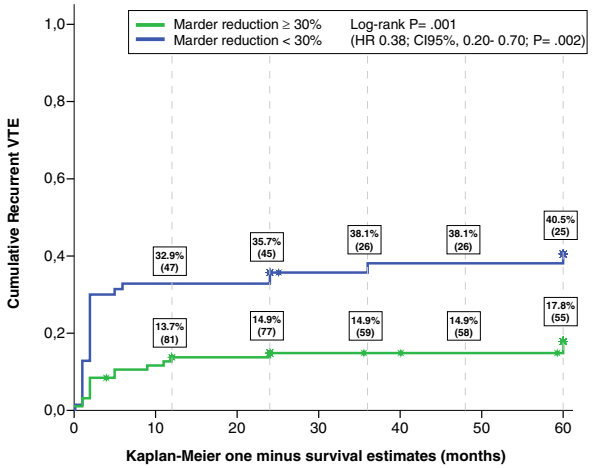

Fig 3. Kaplan-Meier estimates of the risk of recurrent venous thromboembolism according to the degree of thrombus regression (P = .001). The probability of recurrence was greater among patients with Marder score < 30% than among patients with Marder score ≥ 30% (HR = 0.38; 95% CI, 0.20-0.70; P = .002).

tween the degree of thrombus regression at 3 months and the incidence of PTS at 5 years (P = .007). In our patient cohort, an elevated weight was also an important risk factor of PTS. Other factors analyzed in the univariate analysis were not related with the PTS (Appendix II, online only).

DISCUSSION

The short-term outcome of the initial anticoagulant therapy for patients with acute DVT has been studied extensively, and it has been demonstrated that low-molecular-weight heparin treatment is at least as effective and safe for initial treat-

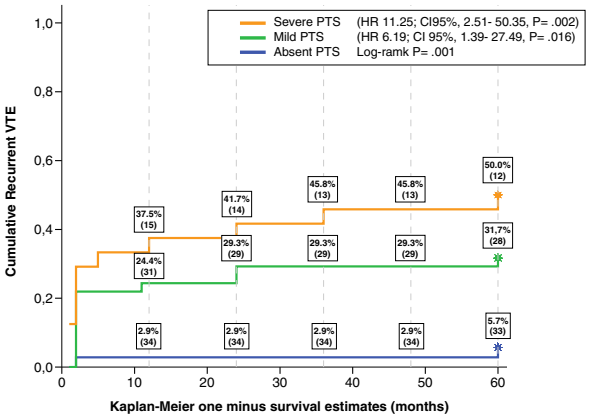

Fig 4. Kaplan-Meier estimates of the risk of recurrent venous thromboembolism according to the presence of post-thrombotic syndrome (PTS) (P = .001). The probability of recurrence was greater among patients with moderate and severe PTS than among patients without PTS (HR = 6.19; 95% CI, 1.39-27.49; P = .016; vs HR = 11.25; 95% CI, 2.51-50.35; P = .002).

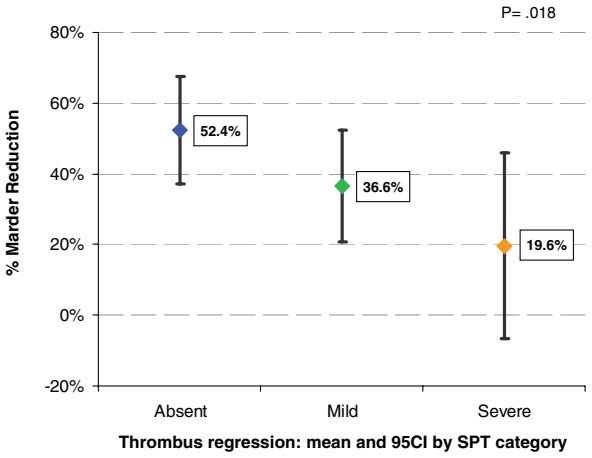

Fig 5. Percentage of Marder reduction according to post-thrombotic syndrome (PTS) category (P = .018).

ment as unfractionated heparin.[11,12,16] However, the long-term clinical courses of the anticoagulant treatment and its impact on PTS have been less well investigated. This series is a prospective cohort study that offers the opportunity to analyze PTS in a large number of well-defined patients with a first episode of DVT. Predefined criteria were strictly applied to the diagnosis of recurrent VTE, and a validated scale was used to assess PTS. In addition, the venographic assessment of the change in thrombus size over time permitted objective evaluation of treatment effects in every patient with two venograms.

This study demonstrated a significant inverse correlation between the venographic effects of thrombus regression and the risk for PTS. Indeed, patients without PTS showed a mean Marder reduction of 52.38% compared with a 36.63% thrombus reduction in patients with moderate manifestations, and only a 19.6% reduction in patients with severe signs and symptoms of PTS (P = .018). This finding means that patients with lower thrombus reduction after anticoagulant treatment have a greater risk for PTS sequelae during ensuing years. The clinical end point of symptomatic recurrent VTE was also significantly correlated with the venographics results. A residual venous thrombosis conferred an increased likelihood of recurrence. The cumulative incidence of recurrence at 5 years was 40.5% in patients with a Marder score $<$ 30% and 17.8% in patients with a Marder score $\geq$ 30% after treatment (P = .001). Our results, therefore, support the hypothesis that residual venous thrombosis in patients with previous DVT is a predictive risk factor for recurrent VTE[6,17,18] and PTS.

With regard to treatment, long-term therapy with enoxaparin was significantly more effective than coumarin in reducing the size of the thrombus (49.1% reduction vs 24.0% reduction; P = .016), as well as the cumulative recurrence rate of VTE (19.3% vs 36.6%; P = .024). In fact, patients treated with coumarin had a two-fold increase in the risk for developing recurrent VTE compared with patients treated with enoxaparin (HR = 1.97; 95% CI, 1.06-3.66; P = .032). However, these findings were not associated with a significant lesser rate of PTS.

The incidence of PTS at 5 years was similar in both groups of patients, although the most favorable tendency was seen in those treated with enoxaparin (39.3% absent and 19.6% severe) than in those treated with coumarin (29.5% absent and 29.5% severe). The small sample size of patients followed in each group, however, probably indicates that this study did not have the statistical power to show this difference. Thus, further investigations are needed to clarify the implication of the anticoagulant treatment in the incidence of PTS.

Post-thrombotic syndrome occurred in 65% of the patients of our series. Data concerning risk factors for developing PTS are contradictory.[1,2,4,7,9,17] Although we had expected that the extent of the initial DVT and its location would be related to the risk for developing PTS, we could not show such a relation, probably because all the patients with distal DVT in our study had popliteal vein involvement. In our patient cohort, only weight was linked with an increased risk for PTS. Other factors analyzed were not significant with regard to risk for PTS. Comparison of data about PTS is hampered by a lack of standardized diagnostic criteria and different observation times. We did not use the CEAP classification system, because the clinical stage assigned using this method is arbitrary and subjective (Table II). Moreover, the discriminatory power is limited compared with Villalta's scoring system because of the difficulty in establishing exactly what constitutes moderate or severe PTS. In fact, this consideration varies in the literature, that is, C4 sometimes is referred as mild PTS and other times as severe PTS.[4,6,19] In contrast, Villalta's scoring system combines good discriminatory power with a reasonable relation to the ambulatory venous pressure.[19] This score, based on subjective complaints and objective clinical signs, has been shown to have good reproducibility

Table II. CEAP classification

CEAP	*Enoxaparin (n = 56)*	*Coumarin (n = 44)*	P < .05
Class 0	5 (8.9%)	2 (4.5%)	NS
Class 1	1 (1.8%)	1 (2.3%)	NS
Class 2	7 (12.5%)	7 (15.9%)	NS
Class 3	10 (17.9%)	9 (20.5%)	NS
Class 4	24 (42.9%)	18 (40.9%)	NS
Class 5	7 (12.5%)	6 (13.6%)	NS
Class 6	2 (3.6%)	1 (2.3%)	NS

NS, Not significant.
Values given as n (%).

and to correlate well with the patient's perception of interference with daily life.[6,20]

On the other hand, we found that a high risk for recurrent VTE persists after anticoagulant treatment; this risk resulted in a cumulative 27.3% incidence of this complication after 5 years of follow-up, which is consistent with other studies.[7,9,16,21] However, the recurrent rate in the coumarin group was quite high, mainly during the first year. The effect of duration (only 3 months) and the quality of the anticoagulation could influence the overall rate of recurrence, particularly in patients with continued risk for recurrence. In accordance with previous studies,[7,9,16,21] patients with cancer had a higher risk for recurrent events, and patients with transient risk factors for DVT (trauma, surgery, or immobilization) had a lower risk for recurrent events. Other factors analyzed were not related with recurrence.

Residual thrombosis probably reflects an underlying hypercoagulable state or a reduced thrombolytic capacity that puts patients at higher risk for recurrent events. The impaired venous flow, resulting in blood stasis and clot formation, could increase venous hypertension and the risk for valve incompetence.[6] These pathophysiologic mechanisms could justify the interrelation between PTS and venous recurrence. Indeed, at 5 years the cumulative incidence of recurrence was 5.7% among patients without PTS, 31.7% in patients with mild PTS, and 50% in patients with severe PTS ($P = .001$). The presence of moderate PTS conferred a 6-fold increased risk for recurrence, and this rate was 11-fold when the patient showed severe PTS. Because recurrent VTE strongly predicted development of PTS, prevention of recurrence might be the key to decreasing the incidence of this condition. Our findings correlate with recent data suggesting that an elevated D-dimer at the end of treatment is predictive of recurrence, and this outcome could reflect insufficient anticoagulation despite apparently adequate antithrombotic treatment.[22,23] It seems logical that the intensity and prolongation of anticoagulation could be considered in selected patients, depending on the presence of thrombus. Several studies have recently investigated this fact.[6,17,24,25] They showed that the absence of normalization in a Doppler ultrasound scan after the first episode of DVT appears to be a factor that promotes recurrence. A higher recurrence rate among patients with limited thrombus regression, therefore, could justify a prolonged prophylactic therapy.[6,8,17,22,24]

This study has several limitations. The small sample size probably did not have sufficient statistical power with regard to the incidence of PTS between both groups of treatment. Indeed, at least 286 patients would be needed to show a statistical difference for the incidence of absent PTS. There was a significant loss to follow-up, despite our contacting by telephone patients who did not attend follow-up visits and documenting the cause of death (from death certificates) for patients who died during the study. Finally, the doses of enoxaparin used may have been insufficient; an adjusted dose per kilogram of body weight would have been more appropriate.

From a clinical practice standpoint, it would be of great clinical importance if we could more effectively identify patients with the highest risk for PTS. According to our results, thrombus size evolution is an important predictor of morbidity, in particular patients with poor recanalization after long-term anticoagulant treatment show a greater risk for recurrent VTE and PTS during ensuing years. It does appear that, compared with coumarin, the rapid recanalization with enoxaparin after DVT is associated with less incidence of recurrence and minimizes PTS morbidity, although additional research is needed to recommend enoxaparin for long-term therapy. Otherwise, the use of venographic score ensures an objective evaluation about evolution of the thrombus and the efficacy of a treatment in patients with DVT; however, venography is an invasive technique that is used infrequently today. For this reason, repeated noninvasive Doppler ultrasound scanning, despite its limitations, could be an alternative method that might help to stratify the risk for recurrence and development of PTS during follow-up.

AUTHOR CONTRIBUTIONS

Conception and design: JAGF
Analysis and interpretation: JAGF, JC, ST, CVP
Data collection: MMP
Writing the article: JAGF
Critical revision of the article: MMP, CVP
Final approval of the article: JAGF, MMP, JC, ST, CVP
Statistical analysis: JC, ST
Overall responsibility: JAGF

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Appendix I (online only). Univariate analysis of risk factors for recurrent venous thromboembolism

	No recurrence	*Recurrence*	P
Age (y)	59.6 ± 13.2	59.8 ± 14.7	.93
Gender			.59
Male	66 (54.1%)	21 (48.8%)	
Female	56 (45.9%)	22 (51.2%)	
Weight (kg)	73.7 ± 10.9	76.0 ± 11.7	.35
Elastic stocking	59 (72.8%)	22 (81.5%)	.37
Etiology			
Trauma, surgery, immobilization	54 (44.3%)	11 (25.6%)	.03
Cancer	12 (9.8%)	10 (23.3%)	.03
Thrombophilia	7 (5.7%)	4 (9.3%)	.42
Unknown (idiopathic)	50 (41%)	18 (41.9%)	.92
Location of thrombus			.18
Calf with popliteal vein	14 (11.5%	6 (14.0%)	
Popliteal and femoral vein	63 (51.6%)	14 (32.6%)	
Popliteal, femoral, and iliac vein	33 (27.0%)	16 (37.2%)	
Iliac vein	12 (9.8%)	7 (16.3%)	
% Marder score	46.1 ± 29.9	11.1 ± 63.8	.001
PTS			.001
PTS Absent	33 (45.2%)	2 (7.4%)	
PTS Moderate	28 (38.4%)	13 (48.1%)	
PTS Severe	12 (16.4%)	12 (44.4%)	
Treatment			.029
Enoxaparin	69 (56.6%)	16 (37.2%)	
Coumarin	53 (43.4%)	27 (62.8%)	

PTS, Post-thrombotic syndrome.
Values given as n (%) or mean ± SD, as applied.

Appendix II (online only). Univariate analysis of risk factors for post-thrombotic syndrome (PTS)

	Absent PTS	*Moderate PTS*	*Severe PTS*	P
Age (y)	55.7 ± 15.9	57.6 ± 13.5	59.4 ± 13.4	.26
Gender				.56
Male	19 (54.3%)	18 (43.9%)	13 (54.2%)	
Female	16 (45.7%)	23 (56.1%)	11 (45.8%)	
Weight (kg)	66.4 ± 9.6	76.4 ± 9.2	82.6 ± 10.0	.000
Elastic stocking	25 (71.4%)	33 (80.5%)	17 (70.8%)	.57
Etiology				
Trauma, surgery, immobilization	16 (45.7%)	20 (48.8%)	10 (41.7%)	.86
Cancer	1 (2.9%)	3 (7.3%)	1 (4.2%)	.66
Thrombophilia	4 (11.4%)	1 (2.4%)	4 (16.7%)	.13
Unknown (idiopathic)	15 (42.9%)	17 (41.5%)	8 (33.3%)	.74
Location of thrombus				.282
Calf with popliteal vein	1 (2.9%)	5 (12.2%)	3 (12.5%)	
Popliteal and femoral vein	19 (54.3%)	26 (63.4%)	12 (50.0%)	
Popliteal, femoral, and iliac vein	9 (25.7%)	7 (17.1%)	8 (33.3%)	
Iliac vein	6 (17.1%)	3 (7.3%)	1 (4.2%)	
% Marder score	52.37 ± 44.37	36.63 ± 50.16	19.61 ± 62.17	.018
Recurrent VTE				
DVT ipsilateral	1 (2.9%)	12 (29.3%)	10 (41.7%)	.001
DVT contralateral	1 (2.9%)	1 (2.4%)	4 (16.7%)	.041
PE	0 (0%)	3 (7.3%)	1 (4.2%)	.268
Treatment				.433
Enoxaparin	22 (62.9%)	23 (56.1%)	11 (45.8%)	
Coumarin	13 (37.1%)	18 (43.9%)	13 (54.2%)	

VTE, Venous thromboembolism; *DVT,* deep venous thrombosis; *PE,* pulmonary embolism.
Values given as n (%) or mean ± SD, as applied.