Determinants and Time Course of the Postthrombotic Syndrome after Acute Deep Venous Thrombosis

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Background: The reason some patients with deep venous thrombosis (DVT) develop the postthrombotic syndrome is not well understood.

Objective: To determine the frequency, time course, and predictors of the postthrombotic syndrome after acute DVT.

Design: Prospective, multicenter cohort study.

Setting: 8 Canadian hospital centers.

Patients: 387 outpatients and inpatients who received an objective diagnosis of acute symptomatic DVT were recruited from 2001 to 2004.

Measurements: Standardized assessments for the postthrombotic syndrome using the Villalta scale at 1, 4, 8, 12, and 24 months after enrollment. Mean postthrombotic score and severity category at each interval was calculated. Predictors of postthrombotic score profiles over time since diagnosis of DVT were identified by using linear mixed modeling.

Results: At all study intervals, about 30% of patients had mild (score, 5 to 9), 10% had moderate (score, 10 to 14), and 3% had severe (score >14 or ulcer) postthrombotic syndrome. Greater postthrombotic severity category at the 1-month visit strongly pre-

dicted higher mean postthrombotic scores throughout 24 months of follow-up (1.97, 5.03, and 7.00 increase in Villalta score for mild, moderate, and severe 1-month severity categories, respectively, vs. none; $P < 0.001$). Additional predictors of higher scores over time were venous thrombosis of the common femoral or iliac vein (2.23 increase in score vs. distal [calf] venous thrombosis; $P < 0.001$), higher body mass index (0.14 increase in score per kg/m^2; $P < 0.001$), previous ipsilateral venous thrombosis (1.78 increase in score; $P = 0.001$), older age (0.30 increase in score per 10-year age increase; $P = 0.011$), and female sex (0.79 increase in score; $P = 0.020$).

Limitations: Decisions to prescribe compression stockings were left to treating physicians rather than by protocol. Because international normalized ratio data were unavailable, the relationship between anticoagulation quality and Villalta scores could not be assessed.

Conclusion: The postthrombotic syndrome occurs frequently after DVT. Patients with extensive DVT and those with more severe postthrombotic manifestations 1 month after DVT have poorer long-term outcomes.

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The postthrombotic syndrome is a chronic, burdensome consequence of deep venous thrombosis (DVT) that occurs despite optimal anticoagulant therapy (1). Typical symptoms include pain, heaviness, swelling, and cramping in the leg that are aggravated by standing or walking. In severe cases, venous ulcers, which are resistant to therapy and tend to recur, may develop, causing pain and suffering and incurring high costs to society (2, 3).

Compared with the large number of studies that have addressed the risk for recurrent thromboembolism after DVT, few studies have provided longitudinal data on the risk for the postthrombotic syndrome. Furthermore, why some patients with DVT develop this condition and others do not is poorly understood. To help address these gaps,

we did a prospective, multicenter, cohort study of patients with acute DVT to describe the frequency, time course, and severity of the postthrombotic syndrome and to identify clinical and genetic determinants of this condition. We also aimed to identify predictors of recurrent venous thromboembolism.

Methods

Study Sample

Study personnel approached consecutive patients with acute DVT in the emergency departments, outpatient clinics, and inpatient wards of 8 university-affiliated hospitals in Quebec and Ontario, Canada, from April 2001 to September 2004. Patients were eligible to participate in the study if they had symptomatic DVT of the lower limb that was objectively diagnosed in the preceding 7 days and if they could read and understand English or French. The diagnosis of venous thrombosis required a venous duplex ultrasound that showed lack of compressibility or intraluminal thrombus or a contrast venogram that showed a constant intraluminal filling defect in the calf (peroneal or tibial) or proximal deep veins (4, 5). We excluded patients if they were estimated to live less than 3 months, could not complete a weekly cost diary (required for a separate eco-

Context

Chronic leg symptoms after deep venous thrombosis (DVT) (the postthrombotic syndrome) are common but difficult to predict during the acute episode.

Contribution

By using a standardized scale, the authors periodically evaluated leg symptoms in 387 patients for 2 years after DVT. At each study interval, mild, moderate, and severe postthrombotic syndrome occurred in 30%, 10%, and 3%, respectively, but severity fluctuated over time in individual patients. Age, previous DVT, more extensive DVT, and severity at 1 month were the best predictors of long-term severity.

Caution

Compression stocking use varied, and anticoagulation effectiveness (for example, international normalized ratio) was unavailable.

Implication

The postthrombotic syndrome is common and has a variable course and several known risk factors.

—*The Editors*

nomic analysis), were geographically unable to return for follow-up visits, or could not or declined to provide informed consent. We asked excluded patients for permission to record basic demographic and clinical data to assess their comparability with those of participants.

We obtained ethics approval from the relevant committees in each hospital center and written informed consent from all patients before study entry.

Baseline Assessment

At study entry, trained research nurses recorded demographic and clinical characteristics by using a standardized case report form, including variables considered to be plausible predictors of the postthrombotic syndrome based on a priori hypotheses or previously published reports (6–9) (**Table 1**).

Follow-up Assessments

We evaluated patients at clinic visits scheduled at 1, 4, 8, 12, and 24 months. At each clinic visit, we did a standardized assessment for the postthrombotic syndrome. In addition, we recorded data about ongoing use of warfarin and elastic compression stockings in a standardized form. It was not logistically feasible to collect international normalized ratio results during study follow-up; however, we recorded total duration of warfarin use. We instructed patients to return for an unscheduled evaluation if they developed symptoms that suggested recurrent venous thromboembolism.

Table 1. **Baseline Characteristics of Study Participants**

Characteristic	Participants (n = 387)
Demographic characteristics	
Men, n (%)	197 (51)
Age, y	
Mean (SD)	56.3 (14.6)
Range	21–96
Inpatient, n (%)	118 (30)
Outpatient, n (%)	269 (70)
Highest level of education, n (%)	
No schooling	2 (1)
Primary school	34 (8)
High school	134 (35)
College or university	217 (56)
Mean body mass index (SD), kg/m²	27.7 (5.3)
Body mass index category, n (%)	
<25 kg/m²	119 (31)
25–30 kg/m²	170 (44)
≥30 kg/m²	98 (25)
Clinical characteristics, n (%)	
Current smoker	69 (18)
Hypertension	99 (26)
Diabetes	32 (8)
High cholesterol level	80 (21)
Asthma	38 (10)
Chronic obstructive pulmonary disease	16 (4)
Angina or myocardial infarction	39 (10)
Stroke	12 (3)
Congestive heart failure	12 (3)
Known musculoskeletal condition affecting hip or leg, same side as DVT	41 (11)
Characteristics of index DVT	
Median time since index DVT diagnosis (IQR), d	3 (1–7)
Affected leg, n (%)	
Right	189 (49)
Left	198 (51)
Proximal DVT, n (%)	233 (60)
Highest extent	
Popliteal vein	63 (27)
Superficial femoral vein	79 (34)
Common femoral vein	77 (33)
Iliac vein	14 (6)
Distal DVT only, n (%)	154 (40)
Provoking features of DVT, n (%)	
Cancer-related*	48 (12)
Transient risk factors†	163 (42)
Unprovoked‡	176 (46)
Concurrent symptomatic pulmonary embolism, n (%)	56 (15)
Previous DVT, n (%)	73 (19)
Previous ipsilateral DVT, n (%)	40 (55)
Thrombophilia, n (%)	
Factor V Leiden mutation§	48 (16)
Prothrombin gene mutation‖	16 (5)
Either mutation	61 (20)

DVT = deep venous thrombosis; IQR = interquartile range.
* Cancer (metastatic or terminal) diagnosed in the past 6 months or being treated.
† Transient risk factors defined as surgery, trauma, or immobilization for 3 or more days in the past 3 months.
‡ No cancer or transient risk factors.
§ Measured in 307 patients and includes 2 homozygotes.
‖ Measured in 308 patients and all heterozygotes.

Table 2. Ipsilateral Villalta Mean Total Score, Mean Symptoms and Signs Score, and Severity Category at Study Visits*

Score or Category	Study Visit				
	1 Month (n = 347)	4 Months (n = 339)	8 Months (n = 302)	12 Months (n = 295)	24 Months (n = 254)
Mean total score (SD)	5.21 (4.18)	4.36 (4.15)	4.31 (4.37)	4.18 (4.03)	4.56 (4.47)
Range	0–22	0–22	0–26	0–21	0–21
Mean symptoms score (SD)	2.78 (2.66)	2.52 (2.88)	2.46 (2.87)	2.41 (2.80)	2.57 (3.06)
Range	0–12	0–14	0–15	0–12	0–15
Mean signs score (SD)	2.43 (2.61)	1.84 (2.40)	1.84 (2.48)	1.74 (2.11)	1.99 (2.45)
Range	0–13	0–15	0–13	0–11	0–11
Postthrombotic severity category, n (%)†					
None	180 (52)	204 (60)	187 (62)	182 (61)	152 (60)
Mild	118 (34)	99 (29)	77 (26)	82 (28)	66 (26)
Moderate	34 (10)	23 (7)	29 (10)	23 (8)	27 (11)
Severe	15 (4)	13 (4)	9 (3)	8 (3)	9 (3)

* The number of patients at each visit represents the number who attended the follow-up visit and had complete Villalta score data for that visit. Among patients who continued in the study (see **Figure 1**), 94.3% (347/368), 97.8% (339/347), 95.0% (302/318), 97.7% (295/302), and 97.7% (254/260) of patients attended follow-up visits and had complete Villalta score data at 1, 4, 8, 12, and 24 months, respectively.
† Postthrombotic severity category cutoffs are none (score, 0–4), mild (score, 5–9), moderate (score, 10–14), and severe (score >14 or presence of ulcer). The presence of an ulcer indicates a severe category of the postthrombotic syndrome, even if the score is <15. For analyses in which continuous scores were used, if patients had a score <15 but had an ulcer at a given study visit, they were assigned a score of 15 for that visit (4 patients, 1 visit each).

Assessment of the Postthrombotic Syndrome

At clinic visits, trained study personnel assessed each leg by using the Villalta scale, a clinical measure for the postthrombotic syndrome that grades the severity, from 0 (absent) to 3 (severe), of each of 5 patient-rated symptoms (pain, cramps, heaviness, pruritus, and paresthesia) and 6 clinician-rated clinical signs (edema, redness, skin induration, hyperpigmentation, venous ectasia, and pain on calf compression) (10, 11). Study personnel who rated the clinical signs were blinded to patients' responses to the symptoms component of the scale and did not have access to scores obtained on previous visits.

A summative score of 5 or more on the Villalta scale indicates the presence of the postthrombotic syndrome (10). This scale was specifically developed to measure the postthrombotic syndrome (6, 10) and has shown to be valid when measured against quality of life (9, 10, 12) and anatomical and physiologic markers of the postthrombotic syndrome (13, 14), has good-to-excellent interobserver reliability (10, 15), and is responsive to clinical change (16, 17).

Diagnosis of Recurrent Venous Thromboembolism

We evaluated all episodes of suspected recurrent DVT and pulmonary embolism with objective diagnostic testing by using published algorithms and criteria (4, 18). All suspected events and deaths were classified by the study's central adjudication committee, whose members were unaware of the postthrombotic syndrome status of patients.

Thrombophilia Testing

In patients who provided written consent (n = 308), we drew blood samples at the 4-month visit to test for the factor V Leiden G1691A and prothrombin G20210A mutations at a central study laboratory by using well-described techniques (19, 20).

Statistical Analysis

We summarized the raw ipsilateral Villalta postthrombotic scores (total symptoms and signs) and postthrombotic severity scores (total scores: none [0 to 4], mild [5 to 9], moderate [10 to 14], and severe [>14 or presence of a venous ulcer]) (10, 11) as means and SDs and proportions at each of the 5 study visits. We prepared graphical representations of the mean Villalta scores and severity category trajectories over time, showing data for the study sample as well as samples of individual patients.

We modeled the Villalta score profiles over time since diagnosis of DVT using linear mixed modeling with a polynomial function (maximum 4th degree for the 5 visits) and random patient effects to examine the fixed effects of preselected predictor variables (assessed at baseline and during follow-up). Actual visit dates were used. The direct likelihood approach allowed the assumption that missing data were randomly missing. Because of the irregular spacing of visit times, we introduced a spatial power covariance structure to model the positive correlation between the repeated Villalta scores within patients.

Our modeling strategy was to first determine the best-fitting polynomial model and optimal random coefficients or covariance structure, then determine which predictors should remain in the model by using F and likelihood ratio tests and Akaike information criterion, Akaike information criterion with a second order correction for small sample sizes, and Bayesian information criterion. All models included study center. We considered first order interactions with time (months since DVT) after fitting the main effects. Because follow-up predictors could be intermediate variables, we fit a separate model for the baseline predictors alone.

To assess the appropriateness of the models, we inspected residual and influence statistics graphically. We conducted a sensitivity analysis by using the various missing visit patterns as an additional predictor and assessing their interaction with the other variables in the model.

We calculated the cumulative incidence of recurrent venous thromboembolism by using the Kaplan–Meier survival method and did analyses of predictors of recurrence by using the log-rank test and hazard ratios (HRs) and 95% CIs. We censored losses to follow-up and deaths as of the last date of follow-up.

We did all statistical analyses by using SAS software, version 9.1.3 (SAS Institute, Cary, North Carolina); models were fitted by using PROC MIXED.

Role of the Funding Source

The study was funding by a grant from the Fonds de la recherche en santé du Québec and by an unrestricted grant-in-aid from GlaxoSmithKline. The funding sources had no role in the study design, data collection, analysis, writing of the report, or decision to submit the article for publication.

RESULTS

Patient Characteristics

We screened 1032 potentially eligible patients for inclusion into the study cohort. We enrolled 387 of these patients in the study (**Figure 1**). Compared with enrolled patients, those excluded were older (65 vs. 56 years; $P = 0.001$), more likely to be women (59% vs. 51%; $P = 0.028$, and more likely to have proximal than distal thrombosis (70% vs. 60%; $P = 0.021$).
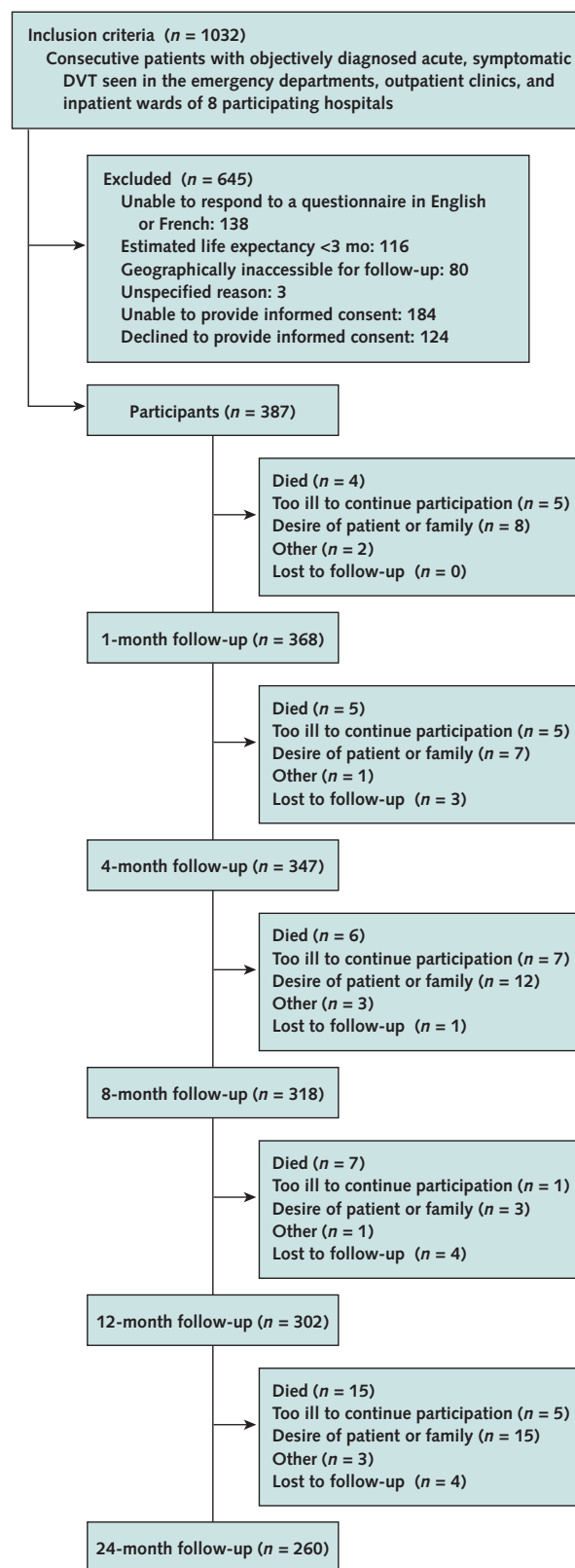
Table 1 shows baseline characteristics of study patients. Deep venous thrombosis was located in proximal venous segments in 60% of patients. Previous DVT for which an objective test was done and an anticoagulant was prescribed was reported by 73 (19%) patients and was ipsilateral to the index (acute) event in 40 patients.

Management of the Index DVT

Initial treatment was low-molecular-weight heparin in 258 (67%) patients, intravenous unfractionated heparin in 101 (26%) patients, and subcutaneous unfractionated heparin in 39 (10%) patients (some received >1 agent); 70% received treatment as outpatients. The mean duration of heparin and warfarin treatment was 7.4 days (95% CI, 6.8 to 8.0 days) and 34.1 weeks (CI, 30.9 to 37.3 weeks), respectively.

Overall, 52% of patients reported the current use of compression stockings during study follow-up: 33% of patients at 1 month (76% of whom reported everyday use), 39% at 4 months (56% everyday use), 37% at 8 months (47% everyday use), 37% at 12 months (47% everyday use), and 35% at 24 months (58% everyday use).

Figure 1. **Study flow diagram.**

Inclusion criteria (*n* = 1032)
  Consecutive patients with objectively diagnosed acute, symptomatic DVT seen in the emergency departments, outpatient clinics, and inpatient wards of 8 participating hospitals

Excluded (*n* = 645)
  Unable to respond to a questionnaire in English or French: 138
  Estimated life expectancy <3 mo: 116
  Geographically inaccessible for follow-up: 80
  Unspecified reason: 3
  Unable to provide informed consent: 184
  Declined to provide informed consent: 124

Participants (*n* = 387)

Died (*n* = 4)
Too ill to continue participation (*n* = 5)
Desire of patient or family (*n* = 8)
Other (*n* = 2)
Lost to follow-up (*n* = 0)

1-month follow-up (*n* = 368)

Died (*n* = 5)
Too ill to continue participation (*n* = 5)
Desire of patient or family (*n* = 7)
Other (*n* = 1)
Lost to follow-up (*n* = 3)

4-month follow-up (*n* = 347)

Died (*n* = 6)
Too ill to continue participation (*n* = 7)
Desire of patient or family (*n* = 12)
Other (*n* = 3)
Lost to follow-up (*n* = 1)

8-month follow-up (*n* = 318)

Died (*n* = 7)
Too ill to continue participation (*n* = 1)
Desire of patient or family (*n* = 3)
Other (*n* = 1)
Lost to follow-up (*n* = 4)

12-month follow-up (*n* = 302)

Died (*n* = 15)
Too ill to continue participation (*n* = 5)
Desire of patient or family (*n* = 15)
Other (*n* = 3)
Lost to follow-up (*n* = 4)

24-month follow-up (*n* = 260)

Numbers in boxes for follow-up intervals represent the number of patients who remained in the study and continued to be followed at a given interval, including patients who may have missed an earlier follow-up visit. DVT = deep venous thrombosis.

Table 3. Model Results: Predictors of Villalta Postthrombotic Syndrome Score during Study Follow-up*

Predictor	Model 1: Baseline Predictors (n = 368)†‡		Model 2: Baseline Predictors Plus Villalta Score at 1 Month (n = 326)‡§		Model 3: Baseline Predictors Plus Villalta Score at 1 Month Plus Follow-up Predictors (n = 318)‡§	
	Mean Change in Villalta Score over 2 Years (95% CI)	P Value	Mean Change in Villalta Score over 2 Years (95% CI)	P Value	Mean Change in Villalta Score over 2 Years (95% CI)	P Value
Continuous type						
Age (per 10 y)	+0.30 (+0.07 to +0.53)	0.011	+0.34 (+0.10 to +0.56)	0.004	+0.31 (+0.08 to +0.54)	0.009
Body mass index (per kg/m²)	+0.14 (+0.08 to +0.21)	<0.001	+0.09 (+0.02 to +0.15)	0.007	+0.07 (+0.02 to +0.14)	0.020
Duration of warfarin use (per mo)	–	–	–	–	+0.09 (+0.04 to +0.13)	<0.001
Categorical type						
Sex						
Female (reference)‖	Reference mean: 5.64 (4.91 to 6.37)‖	–	–	–	–	–
Male	−0.79 (−1.46 to −0.13)	0.020	–	–	–	–
Previous ipsilateral DVT						
No (reference)‖	Reference mean: 4.35 (3.86 to 4.85)‖	–	Reference mean: 5.95 (5.25 to 6.65)‖	–	Reference mean: 6.08 (5.08 to 7.09)‖	–
Yes	+1.78 (+0.69 to +2.87)	0.001	+1.83 (+0.73 to +2.90)	0.001	+1.43 (+0.31 to +2.53)	0.012
Extent of index DVT						
Distal (reference)‖	Reference mean: 4.51 (3.68 to 5.34)‖	–	Reference mean: 6.07 (5.09 to 7.04)‖	–	Reference mean: 6.24 (5.01 to 7.48)‖	–
Popliteal	−0.11 (−1.08 to +0.87)	0.83	+0.72 (−0.24 to +1.69)	0.140	+0.42 (−0.55 to +1.40)	0.39
Superficial femoral	+0.79 (−0.13 to +1.71)	0.091	+0.73 (−0.19 to +1.64)	0.119	+0.44 (−0.49 to +1.37)	0.36
Common femoral or iliac	+2.23 (+1.29 to +3.16)	<0.001	+1.75 (+0.80 to +2.70)	<0.001	+1.35 (+0.36 to +2.34)	0.007
Severity at 1 month (Villalta score)						
None (0–4) (reference)‖	–	–	Reference mean: 3.36 (2.52 to 4.20)‖	–	Reference mean: 3.48 (2.33 to 4.63)‖	–
Mild (5–9)	–	–	+1.97 (+1.28 to +2.77)	<0.001	+1.87 (+1.05 to +2.57)	<0.001
Moderate (10–14)	–	–	+5.03 (+3.05 to +7.01)	<0.001	+4.95 (+2.84 to +7.06)	<0.001
Severe (>14 or ulcer)	–	–	+7.00 (+5.03 to +8.98)	<0.001	+6.69 (+4.59 to +8.80)	<0.001
Compression stockings use						
No (reference)‖	–	–	–	–	Reference mean: 6.63 (5.44 to 7.82)‖	–
Yes	–	–	–	–	+0.33 (−0.40 to +1.07)	0.38
Recurrent ipsilateral DVT						
No (reference)‖	–	–	–	–	Reference mean: 6.67 (5.83 to 7.50)‖	–
Yes	–	–	–	–	+0.26 (−1.40 to +1.91)	0.76

DVT= deep venous thrombosis.
* Values shown are mean changes in Villalta score over 2 years (95% CI), unless noted otherwise. + denotes increase in Villalta score; − denotes decrease in Villalta score.
† After preliminary model fitting to determine the most promising model structures, baseline candidate variables were entered into a random coefficients, mixed model for patient (intercept) and with a second-degree (that is, quadratic) polynomial for time (that is, months and months²): sex; age (continuous); body mass index (continuous); inpatient versus outpatient; side of index DVT (left or right); highest extent of index DVT (common femoral or iliac, superficial femoral, popliteal, or distal); provoking features of DVT (cancer, transient risk factors, or unprovoked); presence of symptomatic, concurrent pulmonary embolism at baseline; previous ipsilateral DVT; thrombophilia (factor V Leiden or prothrombin gene mutation); and comorbid condition (active cancer or cardiac or respiratory disease) (model 1). All models are adjusted by center.
§ Model 2 included baseline variables plus the Villalta score at 1 month categorized as none, mild, moderate, or severe. In addition, model 3 included relevant follow-up variables: duration of warfarin use (months), ipsilateral recurrence of DVT during follow-up, and use of elastic compression stockings during follow-up.
‡ Variables shown were those retained after manual step-down backward elimination approaches (see Methods), except that ipsilateral recurrence of DVT and use of elastic compression stockings during follow-up were forced into model 3. Sex was retained in model 1 but not retained in models 2 and 3.
‖ Reference means are model-predicted adjusted means for each category with all other factors set to their mean values. Because of space constraints, reference means are shown for the 4-month interval only. Because there was no detectable interaction with time for any variables in the models, mean changes were identical for all intervals.

The Postthrombotic Syndrome

Frequency and Variation over Time

Table 2 shows mean ipsilateral Villalta total scores, symptom scores, sign scores, and severity categories at the 5 study visits. At each visit, about 30%, 10%, and 3% of patients had mild, moderate, and severe postthrombotic syndrome, respectively. Among patients with the severe postthrombotic syndrome, 5 had leg ulcers: 2 were noted at 4 months, 1 at 8 months, and 2 at 12 months.

Figure 2 shows the patterns of movement of patients across postthrombotic severity categories over time. Most patients categorized as none or mild at the 1-month visit were also in none or mild categories at the end of follow-

up, whereas about half of patients categorized as moderate or severe at 1 month improved to none or mild at the end of follow-up. **Figure 3** shows that patients who had worse 1-month postthrombotic severity category had higher average Villalta scores over time. **Figure 4** shows plots of Villalta score trajectories for individual patients over time, stratified by 1-month postthrombotic severity category. There was considerable within-patient and between-patient

Figure 2. **Movement of patients among postthrombotic severity categories during study follow-up.**
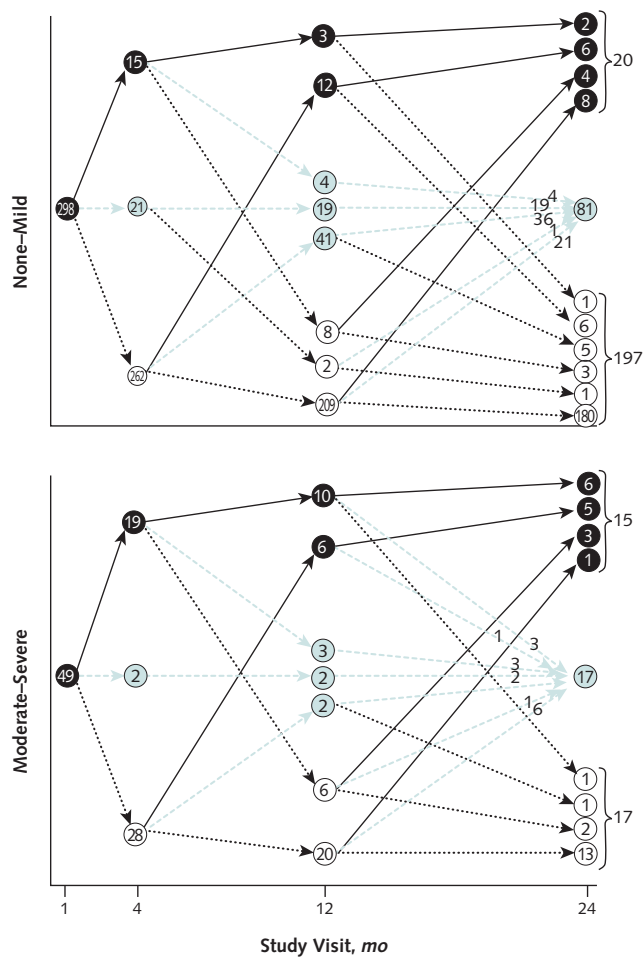
The top panel represents study patients whose postthrombotic severity category was none (Villalta score, 0 to 4) or mild (Villalta score, 5 to 9) at the 1-month visit ($n = 298$); the bottom panel represents study patients whose postthrombotic severity category was moderate (Villalta score, 10 to 14) or severe (Villalta score >14 or ulcer present) at the 1-month visit ($n = 49$). Open circles represent patients with scores in the none or mild range and solid circles indicate patients with scores in the moderate or severe range for a given visit (indicated on x-axis). Green circles represent patients with missing data for that visit. Numbers in circles indicate the number of patients. Solid arrows signify movement from none–mild to moderate–severe postthrombotic severity category for the subsequent visit. Dotted arrows indicate movement from moderate–severe to none–mild category for the subsequent visit. Dashed green arrows represent movement from any category to missing for the subsequent visit. Data are shown for all study patients who had nonmissing 1-month Villalta scores ($n = 347$). Data for the 8-month visit are not shown.

Figure 3. **Mean Villalta scores during study follow-up, stratified by 1-month postthrombotic severity category.**
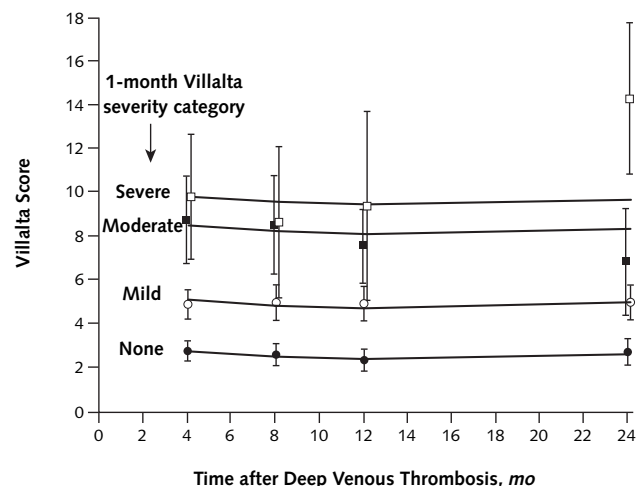
Data shown are actual means (*squares* and *circles*) at study follow-up visits (4, 8, 12, and 24 months) and model-predicted means (*solid line*) over continuous time, stratified by actual 1-month postthrombotic severity category (none: Villalta score, 0 to 4; mild: score, 5 to 9; moderate: score, 10 to 14; and severe: score >14 or ulcer present). Vertical bars around actual means represent 95% CIs. Open squares represent patients with mean Villalta score values categorized as severe at the 1-month visit. Solid squares represent patients with mean Villalta score values categorized as moderate at the 1-month visit. Open circles represent patients with mean Villalta score values categorized as mild at the 1-month visit. Solid circles represent patients with mean Villalta score values categorized as none at the 1-month visit. Model 2 (see **Table 3**) was used to generate model-predicted data.

variation in Villalta scores over time, particularly for patients in the mild, moderate, and severe 1-month severity strata.

Predictors of Villalta Score Profiles over Time

We treated the Villalta total scores for each patient as our continuous dependent variable and described the pattern of responses by using a linear mixed model consisting of a polynomial function of months since diagnosis of DVT and linear terms of candidate categorical and continuous predictors (**Table 3**), with both random effects and various covariance structures. A quadratic model over time (that is, months and months^2) with random intercepts and slopes provided the most consistent and best fit. Adding a covariance structure for the fixed effects resulted in overfitting and poor convergence. None of the predictor-by-time interactions were statistically significant. **Table 3** shows the best models that used only baseline predictors (model 1; $n = 368$), baseline plus the 1-month Villalta scores (model 2; $n = 326$), and both baseline and relevant follow-up predictors (model 3; $n = 318$). Baseline characteristics that were independently associated with higher Villalta scores during study follow-up included age (0.30 increase in score per 10-year age increase [CI, 0.07 to 0.53]; $P = 0.011$), body mass index (BMI) (0.14 increase in score per 1-kg/m^2

Figure 4. **Plots of individual patient Villalta score trajectories, stratified by 1-month postthrombotic severity category.**
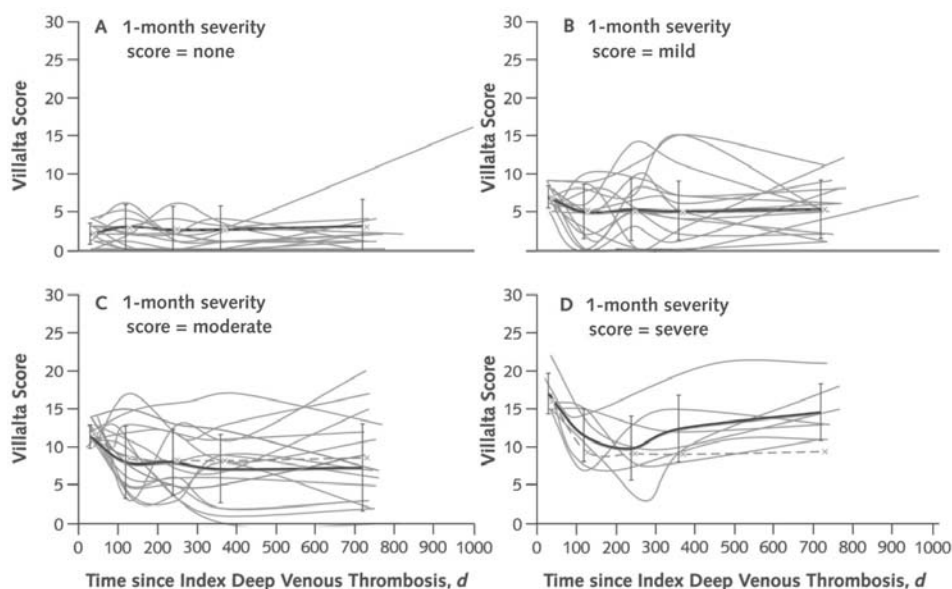
For each panel, the solid black line with bars represents the overall actual means of participants with complete data, and the error bars represent the SDs. The shaded line with "X" symbols on each panel represents the mean of the model-predicted values based on all 347 participants with 1-month score data, stratified by actual 1-month postthrombotic severity category. For clarity, the "X" symbol is slightly offset from the SD bars on the solid black line in each panel. **A.** Data shown represent a stratified random sample (*n* = 15) of participants with a postthrombotic severity category of none (score, 0 to 4) at 1-month follow-up (*n* = 3 for each score) who had complete data throughout follow-up (*n* = 124). **B.** Data shown represent a stratified random sample (*n* = 15) of participants with scores in the mild category (score, 5 to 9) at 1-month follow-up (*n* = 3 for each score) who had complete data throughout follow-up (*n* = 88). **C.** Data shown represent a random sample (*n* = 16) of participants with scores in the moderate category (score, 10 to 14) at 1-month follow-up who had complete data throughout follow-up (*n* = 22). **D.** Data shown represent all participants with scores in the severe category (score >14 or ulcer) at 1-month follow-up who had complete data throughout follow-up (*n* = 7).

increase in BMI [CI, 0.08 to 0.21]; *P* < 0.001), female sex (0.79 increase in score for women compared with men [CI, 0.13 to 1.46]; *P* = 0.020), common femoral or iliac venous thrombosis (2.23 increase in score for common femoral or iliac venous thrombosis vs. distal [calf venous] thrombosis [CI, 1.29 to 3.16]; *P* < 0.001), and previous ipsilateral DVT (1.78 increase in score compared with no previous ipsilateral DVT [CI, 0.69 to 2.87]; *P* = 0.001) (model 1). In model 2, 1-month postthrombotic severity category was strongly predictive of Villalta score during follow-up (1.97 [CI, 1.28 to 2.77], 5.03 [CI, 3.05 to 7.01], and 7.02 [CI, 5.03 to 8.98] increase in score for mild, moderate, and severe 1-month categories, respectively; *P* < 0.001). We found similar results when we examined the 1-month postthrombotic score as a continuous predictor variable (data not shown). In model 3, neither use of compression stockings (0.33 [CI, −0.40 to 1.07]; *P* = 0.38) nor recurrent ipsilateral DVT (0.26 [CI, −1.40 to 1.91]; *P* = 0.76) during follow-up predicted Villalta scores over time, whereas longer duration of warfarin use was associated with modestly higher Villalta scores over time (0.09 increase in score per additional month of warfarin use [CI, 0.04 to 0.13]; *P* < 0.001). The **Appendix Figure** (available at www.annals.org) shows plots of model-predicted Villalta score over time, by categorical predictor variables.

Of 1840 potential Villalta scores during follow-up in the 368 patients who remained in the study at 1-month follow-up, 303 (16.5%) scores were missing (although 5% were missing because of death). Overall, we identified 6 missing visit patterns: no first visit (8 unique patterns, 21 occurrences); first visit only (1 pattern, 21 occurrences); first 2 visits only (1 pattern, 28 occurrences); first 3 visits only (1 pattern, 15 occurrences); first 4 visits and no final visit (3 patterns, 34 occurrences); and attended all visits (5 patterns, 249 occurrences). Sensitivity analysis using the visit patterns as predictors in the final models yielded no statistically significant additional effects or interactions.

Finally, to assess whether explanatory variables differed for patient-rated and clinician-rated subscales, we fit similar models for total Villalta score to the symptoms and signs subscale scores. We found substantially similar results for signs scores as for total Villalta score, whereas the sole independent predictor of symptoms scores over time was 1-month symptoms score (**Appendix Table**, available at www.annals.org).

Recurrent Venous Thromboembolism during Study Follow-up

Thirty patients had 31 confirmed, recurrent venous thromboembolic events during follow-up; 14 were ipsilat-

eral to the index thrombosis. The cumulative incidence was 6.3% (CI, 3.7% to 9.0%) at 1 year and 9.9% (CI, 6.5% to 13.3%) at the end of 2 years. The risk for recurrence was increased in patients with cancer-associated venous thrombosis (univariate HR, 10.7 [CI, 3.5 to 32.8]; $P < 0.001$) and unprovoked venous thrombosis (absence of recent surgery, fracture, or plaster casting of a leg; immobilization; or known cancer) (univariate HR, 3.4 [CI, 1.3 to 9.1]; $P < 0.001$), compared with DVT due to transient risk factors. The risk for recurrence was also higher in patients with proximal (vs. distal) thrombosis (univariate HR, 2.4 [CI, 1.1 to 5.6]; $P = 0.036$) and symptomatic pulmonary embolism at study enrollment (univariate HR, 2.3 [CI, 1.0 to 5.1]; $P = 0.048$). Men tended to have a higher risk for recurrence than women (univariate HR, 1.9 [CI, 0.9 to 4.0]; $P = 0.078$). The factor V Leiden or prothrombin gene mutation did not influence the risk for recurrence (univariate HR, 0.7 [CI, 0.3 to 2.1]; $P = 0.64$).

Deaths during Study Follow-up

Thirty-seven (9.6%) patients died during follow-up. Pulmonary embolism was a contributing cause of death in 6 patients: 5 died of metastatic cancer and 1 of pulmonary fibrosis.

DISCUSSION

We found that the postthrombotic syndrome occurs in almost half of patients within 2 years after DVT, and about 3% of patients develop severe postthrombotic syndrome, including venous ulcers. We also found that postthrombotic symptoms and signs are not static but tend to fluctuate over time for many patients. Variables that predicted higher (worse) postthrombotic scores over time included greater severity of residual venous symptoms and signs 1 month after the diagnosis of DVT, thrombosis of the common femoral or iliac vein, previous ipsilateral venous thrombosis, higher BMI, older age, and female sex.

To our knowledge, this is the first prospective, multicenter study in North America that addresses the frequency, time course, and predictors of the postthrombotic syndrome after DVT. Strengths of our study include a well-defined source sample; examination of several demographic, clinical, and biological predictors identified a priori; use of trained evaluators to assess the clinical sign components of the Villalta scale who were blinded to patient-reported symptoms and scores on previous visits; and central adjudication of suspected cases of recurrent venous thromboembolism. To identify prognostic variables, we did longitudinal analysis of continuous Villalta scores over time, which enabled us to exploit the richness of available score data more fully than by using an algorithmic approach that categorizes patients as having or not having the postthrombotic syndrome based on scores at 2 consecutive visits (6, 7). Our findings are likely to be generalizable because we enrolled patients at 8 hospital centers, inclusion

criteria were broad, management of the index thrombosis was similar across centers and guided by contemporary consensus recommendations (21), and underlying thrombosis risk factors and predictors for recurrent venous thromboembolism were similar to those in other samples with venous thrombosis (6, 22, 23).

Important new findings of our study are that more severe postthrombotic manifestations 1 month after diagnosis of DVT and more extensive (that is, common femoral or iliac vein) thrombosis are strong predictors of worse outcome over 2 years. The persistence of venous symptoms and signs at 1 month may reflect residual venous thrombosis, which is important in the pathophysiology of the postthrombotic syndrome (13). Similarly, more extensive thrombosis may be associated with worse outcome by way of a greater propensity to result in residual thrombosis (24). Given these findings, we advocate trials to evaluate the role of therapeutic strategies that enhance early clot lysis (such as catheter-directed thrombolysis) as a potential means to prevent the postthrombotic syndrome.

The association between previous ipsilateral thrombosis and higher postthrombotic scores is probably due to exacerbation of venous outflow obstruction or damage to already compromised venous valves. Recurrent ipsilateral thrombosis during study follow-up did not further increase postthrombotic scores, which contrasts with previous reports (6, 7, 11) but could be explained by the relatively low number of recurrences, probably because we included patients with isolated calf venous thrombosis. Why older age and higher BMI are associated with higher postthrombotic scores is uncertain but may relate to age- or weight-related impaired fibrinolysis or vein wall changes (25, 26). We found that women had higher scores than men, which contrasts with a recent report that male sex was a weak risk factor for the postthrombotic syndrome (8). In a previous study, we reported the unexpected finding that factor V Leiden and prothrombin mutations seemed to protect against the postthrombotic syndrome (9); neither this nor other studies have confirmed this finding (7, 8, 11).

The frequency of the postthrombotic syndrome at each study visit was similar to the overall cumulative frequency of the syndrome in 2 contemporary prospective studies (7, 11) but was almost twice as high as that reported by Prandoni and colleagues a decade ago in a single-center prospective cohort study (6). This may be partly explained by the universal prescription of compression stockings in that study.

Our study has some limitations. We systematically collected data on compression stocking use during follow-up, but we allowed treating physicians to make decisions about prescribing stockings; thus, we could not directly evaluate whether use of stockings influenced the postthrombotic syndrome (11, 27). However, when we included compression stocking use as a variable in longitudinal modeling, it was not associated with Villalta scores over time. Because we did not have access to international normalized ratio

test results, we could not evaluate if anticoagulation intensity influenced the risk for the postthrombotic syndrome (7). Longer duration of warfarin use was associated with modestly higher Villalta scores during follow-up, a finding that we believe is due to confounding by indication, whereby patients with postthrombotic manifestations continue to receive warfarin for a longer period, or patients with previous or more extensive DVT receive a prescription for a longer course of warfarin. We excluded about half of the patients from the study because of inability or unwillingness to provide consent, which we believe is probably due to older age and reluctance to attend frequent study visits. Because recurrent ipsilateral venous thrombosis events during follow-up were uncommon, we could not estimate precisely the association between ipsilateral recurrence and postthrombotic scores during follow-up. About 1 in 6 Villalta scores were missing, predominantly due to missed study visits. Finally, while there was statistical variation in the modeling due to individual patient random effects, we nevertheless were able to detect statistically significant fixed effects of many predictor variables.

In conclusion, the postthrombotic syndrome occurs frequently after DVT. Patients with more severe postthrombotic manifestations 1 month after venous thrombosis and those with common femoral venous or iliac venous thrombosis have substantially poorer outcomes. They may be clinically identifiable as a group to be targeted for measures to prevent the postthrombotic syndrome, such as long-term use of compression stockings or extended courses of anticoagulation to prevent recurrent venous thrombosis. Our study provides clinically relevant longitudinal data on prognosis after venous thrombosis and emphasizes the need for better preventive and treatment strategies for the postthrombotic syndrome.

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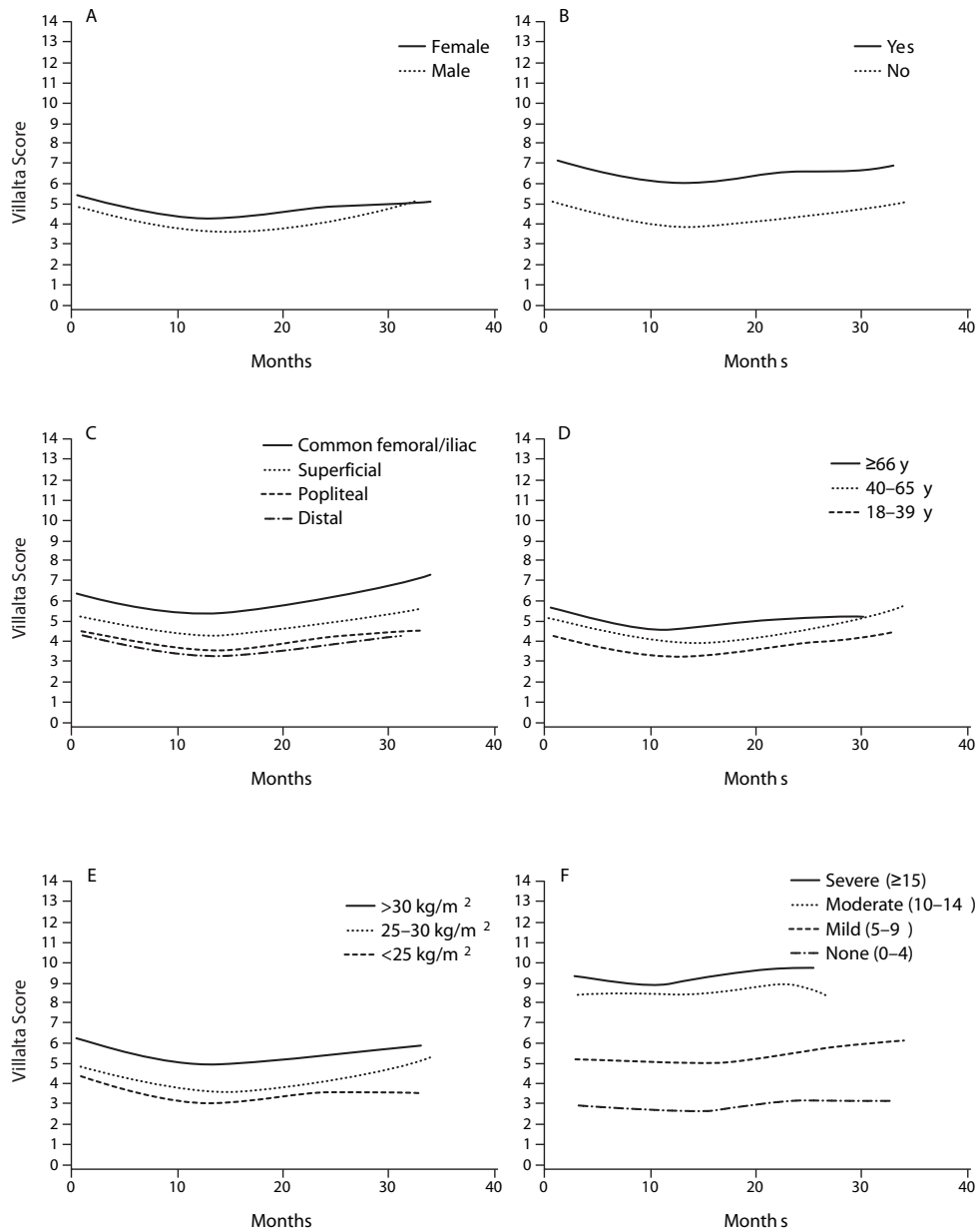
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Plots show smoothed model-predicted Villalta scores over time for individual predictor variables (sex, previous ipsilateral deep venous thrombosis, extent of index deep venous thrombosis, age, body mass index, and Villalta severity category at 1 month). Model 2 (see **Table 3**) was used to generate model-predicted data. For all plots, the x-axis is follow-up time, and the y-axis is Villalta score (continuous). **A.** Model 2, smoothed predicted Villalta total score over time, by sex. **B.** Model 2, smoothed predicted Villalta total score over time, by previous ipsilateral deep venous thrombosis. **C.** Model 2, smoothed predicted Villalta total score over time, by extent of index deep venous thrombosis. **D.** Model 2, smoothed predicted Villalta total score over time, by age group. **E.** Model 2, smoothed predicted Villalta total score over time, by body mass index group. **F.** Model 2, smoothed predicted Villalta total score over time, by Villalta severity category at 1 month.

Appendix Table. **Model Results: Predictors of Villalta Postthrombotic Syndrome Signs and Symptoms Scores during Study Follow-up**

Predictor	Mean Change in Villalta Score over 2 Years (95% CI)	P Value
Signs score		
Continuous variables		
Age (per 10 y)	+0.28 (+0.16 to +0.41)	<0.001
Body mass index (per kg/m^2)	+0.04 (+0.005 to +0.73)	0.027
Villalta sign score at 1 month (per 1-unit increase in score)	+0.32 (+0.24 to +0.39)	<0.001
Categorical variables		
Previous ipsilateral DVT		
No (reference)*	Reference mean: 1.52 (1.23 to 1.80)*	–
Yes	+1.00 (+0.35 to +1.65)	0.001
Extent of index DVT		
Common femoral or iliac vein (reference)*	Reference mean: 2.60 (2.07 to 3.13)*	–
Superficial femoral vein	−0.73 (−1.30 to −0.16)	0.012
Popliteal vein	−0.88 (−1.45 to −0.31)	0.003
Distal	−0.76 (−1.28 to −0.24)	0.005
Symptoms score		
Continuous variable: Villalta symptom score at 1 month (per 1-unit increase in score)	+0.52 (+0.43 to +0.61)	<0.001

DVT = deep venous thrombosis. + denotes increase in Villalta score; − denotes decrease in Villalta score.
* After preliminary model fitting to determine the most promising model structures, baseline candidate variables were entered into a random coefficients, mixed model for patient (intercept) and time with a second-degree (that is, quadratic) polynomial for time (that is, months and months^2: sex; age (continuous); body mass index (continuous); inpatient versus outpatient; side of index DVT (left or right); highest extent of index DVT (common femoral or iliac, superficial femoral, popliteal, or distal); provoking features of DVT (cancer, transient risk factors, or unprovoked); presence of symptomatic, concurrent pulmonary embolism at baseline; previous ipsilateral DVT; thrombophilia (factor V Leiden or prothrombin gene mutation); comorbid condition (active cancer or cardiac or respiratory disease); and Villalta 1-month signs score or 1-month symptom score, as appropriate. All models are adjusted by center. Variables shown were those retained after manual step-down backward elimination approaches (see Methods). There was no interaction with time for any variables in the models. Reference means are provided for 4-month visit only; means for other visits were similar.