Superficial Venous Thrombosis and Venous Thromboembolism

A Large, Prospective Epidemiologic Study

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Background: Superficial venous thrombosis (SVT) is perceived to have a benign prognosis.

Objective: To assess the prevalence of venous thromboembolism in patients with SVT and to determine the 3-month incidence of thromboembolic complications.

Design: National cross-sectional and prospective epidemiologic cohort study. (ClinicalTrials.gov registration number: NCT00818688)

Setting: French office- and hospital-based vascular medicine specialists.

Patients: 844 consecutive patients with symptomatic SVT of the lower limbs that was at least 5 cm on compression ultrasonography.

Measurements: Incidence of venous thromboembolism and extension or recurrence of SVT in patients with isolated SVT at presentation.

Results: Among 844 patients with SVT at inclusion (median age, 65 years; 547 women), 210 (24.9%) also had deep venous thrombosis (DVT) or symptomatic pulmonary embolism. Among 600 patients without DVT or pulmonary embolism at inclusion who were eligible for 3-month follow-up, 58 (10.2%) developed thromboembolic complications at 3 months (pulmonary embolism, 3 [0.5%]; DVT, 15 [2.8%]; extension of SVT, 18 [3.3%]; and recurrence of SVT, 10 [1.9%]), despite 540 patients (90.5%) having received anticoagulants. Risk factors for complications at 3 months were male sex, history of DVT or pulmonary embolism, previous cancer, and absence of varicose veins.

Limitation: The findings are from a specialist referral setting, and the study was terminated before the target patient population was reached because of slow recruitment.

Conclusion: A substantial number of patients with SVT exhibit venous thromboembolism at presentation, and some that do not can develop this complication in the subsequent 3 months.

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* For a list of participating committees and investigators, see the **Appendix** (available at www.annals.org).

Superficial venous thrombosis (SVT) is painful and common (1) but thought to have a benign prognosis (2, 3). This perception is now changing, with evidence that SVT can occur with deep venous thrombosis (DVT) or pulmonary embolism (venous thromboembolism). Estimates of the percentage of patients with SVT who also have DVT vary between 6% and 53%, and symptomatic pulmonary embolism has been reported in 0% to 10% of patients with SVT (3). These varying estimates may reflect the limitations of smaller retrospective studies performed in selected patients, and they have fueled controversy over the real risk for venous thromboembolism in patients with SVT (4, 5). The nature and benefit of the therapeutic strategies routinely proposed by physicians and the risk for venous thromboembolic complications in patients with isolated SVT (no DVT or pulmonary embolism at presentation) are similarly unclear (6–8).

We performed a large observational study to ascertain the prevalence of concurrent SVT and venous thromboembolism, to assess how providers are treating SVT, and to determine the 3-month incidence of thromboembolic complications and the risk factors for those complications in patients with isolated SVT at presentation.

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METHODS

The POST (Prospective Observational Superficial Thrombophlebitis) study was a French national, multicenter, prospective, observational study of a cohort of consecutive patients with symptomatic SVT of the lower limbs. We conducted the study in accordance with the Declaration of Helsinki (Hong Kong Amendment), Good Clinical Practice (European Guidelines), and relevant French legal and regulatory requirements. The Ethics Committee of Centre Hospitalier Universitaire de Saint-Étienne, Saint-Étienne, France, approved our protocol. We obtained oral informed consent from all patients.

Setting and Participants

In France, patients with lower-extremity symptoms generally consult their primary care physician, who then refers them to a vascular specialist for compression ultrasonography to confirm the diagnosis of SVT and to exclude concomitant

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DVT. We invited all office- and hospital-based vascular medicine specialists who were registered with 2 specialty societies, the Société Française de Médecine Vasculaire or the Société Française de Phlébologie, to enroll patients into the study. To be eligible, patients had to be 18 years or older and have symptomatic lower-limb SVT, defined as a subcutaneous noncompressible hypoechoic area in the course of an identified superficial vein (appearing circular in cross-sectional view and rectangular in longitudinal view) more than 5 cm in length on compression ultrasonography performed according to a standardized protocol.

We excluded patients who had had surgery in the previous 10 days, those in whom SVT had occurred after sclerotherapy in the previous 30 days, and those for whom follow-up was not considered feasible.

Design and Outcomes

Our study had a cross-sectional and a prospective component. First, we assessed the prevalence of DVT or symptomatic pulmonary embolism in patients who had received a diagnosis of SVT. Then, we followed patients with isolated SVT (with no DVT or pulmonary embolism at presentation) for 3 months to assess thromboembolic complications and risk factors for those complications. These patients had a second comprehensive ultrasonography of both lower limbs, including the proximal and distal deep veins, 10 days after inclusion (range, 8 to 14 days) and an assessment of symptomatic events at a 3-month (±5 days) follow-up visit. At both visits, we recorded objectively confirmed thromboembolic events and medical and surgical treatments prescribed since inclusion.

Our primary outcome was confirmed thromboembolic complications at 3 months, which we defined as the composite of asymptomatic and symptomatic events at day 10 and symptomatic events at 3 months. The specific events we considered at day 10 were asymptomatic DVT of lower limbs, asymptomatic recurrence of SVT, or asymptomatic downstream (proximal) extension of SVT by more than 5 cm on mandatory compression ultrasonography, and symptomatic pulmonary embolism. The specific events recorded at 3 months were symptomatic thromboembolic events, including DVT of the lower limbs, pulmonary embolism, or extension or recurrence of SVT. Deep venous thrombosis was confirmed by compression ultrasonography or venography. Pulmonary embolism was confirmed by ventilation–perfusion scan or helical computed tomography scan or at autopsy. Extension or recurrence of SVT was confirmed by compression ultrasonography. We defined recurrence of SVT as the occurrence of a thrombotic event in a different superficial vein from that implicated in the initial qualifying event, or such an event in the same vein but clearly differentiated from the initial qualifying event by the presence of an open venous segment between the superficial venous thromboses.

A secondary outcome was overall mortality at 3 months. We considered the cause of death to be pulmonary embolism if established by objective documentation, or if the cause was unexplained and pulmonary embolism could not be confidently ruled out. A critical event validation committee adjudicated all primary and secondary outcome events.

During the study, participants were under the clinical care of their referring physicians, who made all decisions about appropriate medical and surgical procedures.

Context

Superficial venous thrombosis is generally considered benign.

Contribution

In this study of patients with superficial venous thrombosis, about one quarter of patients had deep venous thrombosis at presentation and about 10% developed thromboembolic complications over the next 3 months.

Caution

Study data come from participants who were evaluated by vein specialists in France.

Implication

Superficial venous thrombosis may not be as benign as is commonly believed and may be a marker for more clinically significant thromboembolic risk.

—The Editors

Statistical Analysis

Assuming a 3% incidence of venous thromboembolic events at 3 months (8), we required 1200 patients with isolated SVT to estimate the incidence of venous thromboembolic events at 3 months with a precision of plus or minus 1%. The steering committee prematurely terminated patient enrollment because the slow recruitment rate was incompatible with study continuation.

We report qualitative data as numbers and percentages and quantitative data as median values with interquartile ranges. We estimated cumulative rates of thromboembolic events by using the Kaplan–Meier method.

We built a Cox proportional hazards model to identify variables independently associated with thromboembolism at 3 months. We included well-known predictors for thromboembolism (history of venous thromboembolism, cancer, advanced age [≥75 years], and use of anticoagulant drugs at the time of inclusion [9, 10]) as dependent variables. We also included 3 variables (male sex, no varicose veins, and chronic cardiac or respiratory insufficiency) that were associated with thromboembolism on univariate analysis ($P < 0.150$) and had a prevalence of at least 3%, selected from a pool of variables that we considered important on the basis of previous epidemiologic studies and expert clinical opinion (male sex, obesity [body mass index >30 kg/m^2], cardiac or respiratory insufficiency, history of SVT, short interval [≤7 days] between symptom onset and diagnosis, no varicose veins, and short distance [≤3 cm] between the thrombus and the saphenofemoral junction).

We assessed the proportional hazards assumption and found it to hold for all variables. We used SAS, version 9.1 (SAS Institute, Cary, North Carolina), to analyze and process all data.

Role of the Funding Source

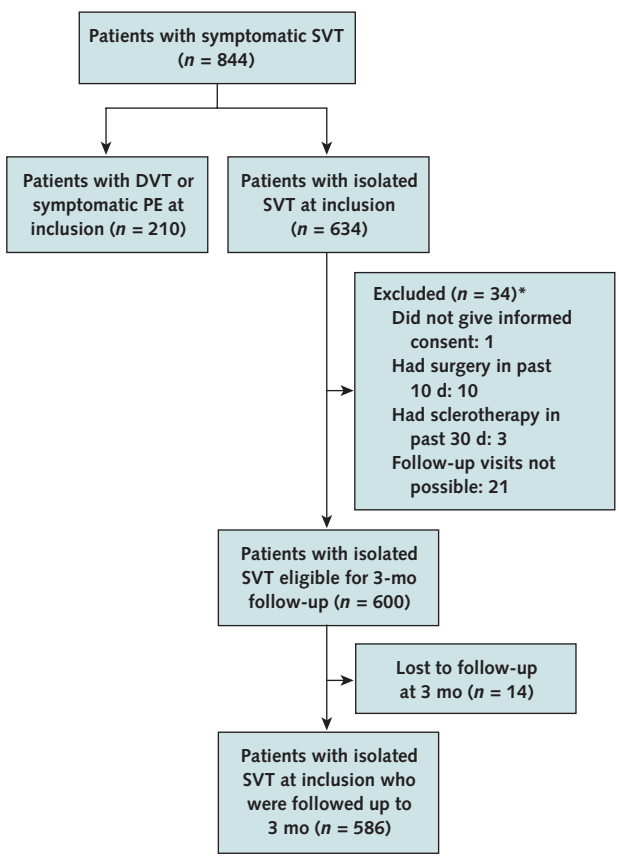
GlaxoSmithKline, sanofi-aventis, the Ministère Français de la Santé et des Sports (Programme Hospitalier de Recherche Clinique), the Société Française de Médecine Vasculaire, and the Société Française de Phlébologie provided funding for the study. The funding sources had no involvement in the design of the study; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

RESULTS

Total Population

Of the 211 medical centers with vascular specialists distributed throughout metropolitan France whom we invited to participate in the study, 96 (79 private centers and 17 public hospitals) enrolled 844 patients between March 2005 and October 2006 (**Figure**). The median patient age was 65 years (interquartile range [IQR], 50 to 74 years), 24.5% were at least 75 years of age, 28.8% were obese, and more women (64.9%) were enrolled than men (**Table 1**). The median time between first symptoms and consultation with a vascular medicine specialist was 6 days (IQR, 3 to 11 days); 38.3% of patients consulted a specialist more than 7 days after their first symptoms, and 29.3% had received anticoagulant treatment before consulting a vascular medicine specialist (day 1). Most SVTs (65.8%) involved the long saphenous vein. Extension to perforating veins was observed in 13.8% of patients. **Table 1** details the characteristics of patients with and without concomitant DVT or pulmonary embolism at inclusion.

Figure. **Study flow diagram.**



DVT = deep venous thrombosis; PE = pulmonary embolism; SVT = superficial venous thrombosis.
* Reasons are not mutually exclusive.

Patients With DVT or Pulmonary Embolism at Inclusion

Physicians confirmed DVT or symptomatic pulmonary embolism in 210 (24.9%) patients with SVT at inclusion (**Table 1**). They diagnosed proximal DVT in 82 (9.7%) patients and symptomatic pulmonary embolism in 33 (3.9%) patients. Deep venous thrombosis was not contiguous to SVT in 83 of the 198 patients (41.9%) with DVT.

Patients With Isolated SVT at Inclusion

A total of 634 patients had isolated SVT at inclusion (**Table 1**). We had information about the treatment that 597 of them received during the 3-month observation period. Of these, 540 (90.5%) received 1 or more anticoagulant drugs, mostly low-molecular-weight heparins administered at therapeutic doses to 374 (62.9%) patients for a median of 11 days (IQR, 9 to 13 days), or at prophylactic doses to 216 patients (36.7%) for a median of 11 days (IQR, 10 to 17 days). Ninety-nine (16.8%) patients received vitamin K antagonists for a median of 81 days (IQR, 57 to 92 days), 584 (97.7%) received elastic compression stockings, 278 (47.2%) received topical nonsteroidal anti-inflammatory drugs, and 48 (8.2%) received oral nonsteroidal anti-inflammatory drugs. Sixty (10.2%) patients had venous surgery (for example, stripping or ligation).

Fourteen patients with isolated SVT at inclusion were lost to follow-up at 3 months (**Figure**). Of the remaining 586 patients, 58 had thromboembolic complications (Kaplan–Meier estimate, 10.2%) (**Table 2**), which were asymptomatic (diagnosed by ultrasonography at day 10) in 12 (2.1%) patients and symptomatic in 46 (8.3%). Among the 46 symptomatic events, 7 (15.2%) were proximal DVT, 3 (6.5%) were pulmonary embolism, and 5 (comprising 2 deep venous thromboses and 3 extensions of SVT) were observed at day 10.

In multivariate analyses, male sex, a history of DVT or pulmonary embolism, previous cancer, and no varicose veins were independent risk factors for symptomatic thromboembolic events at 3 months, including recurrence or extension of SVT (**Table 3**). Two patients died, one of metastatic cancer and the other of possible pulmonary embolism, before the end of the 3-month follow-up (Kaplan–Meier estimate, 0.4%).

Table 1. **Patient Characteristics at Inclusion**

Variable	SVT With DVT or PE (*n* = 210)	Isolated SVT (*n* = 634)	Total (*n* = 844)
Median age (IQR), *y*	70 (61–78)	61 (48–73)	65 (50–74)
Aged ≥75 years, *n (%)*	76 (36.2)	131 (20.7)	207 (24.5)
Women, *n (%)*	136 (64.8)	412 (64.9)	548 (64.9)
Median body mass index (IQR), *kg/m²*	26.6 (23.6–30.3)	27.2 (23.8–30.5)	27.0 (23.8–30.4)
Body mass index >30 kg/m², *n (%)*	59 (28.2)	183 (29.0)	242 (28.8)
Risk factors, *n (%)*			
Varicose veins	143 (68.4)	547 (86.3)	690 (81.8)
History of thrombosis			
SVT	57 (27.4)	228 (36.5)	285 (34.2)
DVT or PE	60 (29.4)	120 (19.4)	180 (21.9)
Family history	51 (25.4)	206 (32.7)	257 (31.0)
The postthrombotic syndrome	20 (9.6)	35 (5.5)	55 (6.5)
Cancer			
Active	26 (12.7)	24 (3.8)	50 (6.0)
Previous	14 (6.7)	29 (4.6)	43 (5.1)
Immobility			
Permanent	30 (14.5)	34 (5.4)	64 (7.7)
Recent			
Past 20 d			
Bedridden (>3 d)	29 (13.8)	32 (5.1)	61 (7.2)
Hospitalization	49 (23.3)	30 (4.7)	79 (9.4)
Travel	8 (3.8)	59 (9.3)	67 (7.9)
Trauma	5 (2.4)	41 (6.5)	46 (5.4)
Past 60 d			
Surgery	11 (5.2)	25 (3.9)	36 (4.3)
Endocrine			
Oral contraceptive use	9 (4.3)	32 (5.1)	41 (4.9)
Hormone replacement therapy*	6 (2.9)	18 (2.9)	24 (2.9)
Pregnancy or postpartum	2 (1.0)	36 (5.7)	38 (4.5)
Chronic cardiac or respiratory insufficiency	18 (8.6)	33 (5.3)	51 (6.1)
Known biological thrombophilia	14 (6.8)	34 (5.4)	48 (5.7)
Autoimmune disease	11 (5.3)	8 (1.3)	19 (2.3)
Infection	12 (5.7)	18 (2.8)	30 (3.6)
Receiving anticoagulant drugs, *n (%)*	72 (34.4)	173 (27.6)	245 (29.3)
Interval between symptom onset and diagnosis			
Median interval (IQR), *d*	7 (4–12)	5 (3–10)	6 (3–11)
>7 d, *n (%)*	69 (42.6)	232 (37.2)	301 (38.3)
Characteristics of venous thromboembolic events			
SVT			
Long saphenous vein, *n (%)*†	153 (72.9)	401 (63.4)	554 (65.8)
Median distance between thrombus and saphenofemoral junction (IQR), *cm*	16 (0–40)	25 (12–42)	23 (7–42)
Distance between thrombus and saphenofemoral junction ≤3 cm, *n (%)*	53 (36.8)	53 (13.7)	106 (20.0)
Distance between thrombus and saphenofemoral junction ≤10 cm, *n (%)*	64 (44.4)	92 (23.8)	156 (29.4)
Short saphenous vein, *n (%)*	54 (25.7)	90 (14.2)	144 (17.1)
Other superficial veins, *n (%)*‡	64 (30.5)	231 (36.5)	295 (35.0)
At least 2 superficial veins, *n (%)*	53 (25.2)	84 (13.3)	137 (16.3)
Bilateral SVT, *n (%)*	22 (10.5)	48 (7.6)	70 (8.3)
Extension to perforating veins, *n (%)*	76 (36.2)	40 (6.3)	116 (13.8)
SVT in varicose veins, *n (%)*	123 (59.1)	514 (81.5)	637 (75.9)
DVT, *n (%)*§	198 (94.3)	–	198 (23.5)
Proximal	82 (39.0)	–	82 (9.7)
Distal	114 (54.3)	–	114 (13.5)
Symptomatic PE, *n (%)*§	33 (15.7)	–	33 (3.9)

DVT = deep venous thrombosis; IQR = interquartile range; PE = pulmonary embolism; SVT = superficial venous thrombosis.
* Estrogens or progestogens.
† The saphenofemoral junction connects the superficial (long or great saphenous vein) to the deep venous (common femoral vein) systems; vascular specialists in France usually treat an SVT within 3–10 cm of the saphenofemoral junction as if it were a DVT because of the risk for extension to the deep venous system.
‡ Including tributaries of long and short saphenous veins.
§ Patient could experience more than 1 venous thromboembolic event (210 patients experienced at least 1 event).

Discussion

In our large observational study, we found that venous thromboembolism accompanied symptomatic SVT in nearly 25% of patients. Most of these patients had DVT, but 3.9% had symptomatic pulmonary embolism. Our findings are consistent with previous studies (identified by a MEDLINE search up to August 2009), which reported a 6% to 53% prevalence of venous thromboembolism (3, 11) and a 0% to 10% prevalence of pulmonary embolism (3) in this population. They are also similar to the rates

Table 2. **Three-Month Incidence of Venous Thromboembolic Events in Patients With Isolated SVT at Inclusion**

Thromboembolic Event (n = 586)	Incidence [95% CI], n (%)*
Any	58 (10.2 [7.7–12.7])
Symptomatic†	46 (8.3 [6.0–10.6])
PE or DVT	18 (3.3 [1.8–4.8])
DVT	15 (2.8 [1.4–4.2])
Proximal	7
Distal	8
PE	3 (0.5 [0–1.2])
SVT	
Recurrence	10 (1.9 [0.7–3.0])
Extension	18 (3.3 [1.8–4.8])
Asymptomatic‡	12 (2.1 [0.9–3.2])

DVT = deep venous thrombosis; PE = pulmonary embolism; SVT = superficial venous thrombosis.
* Percentages are probabilities computed by using survival curve analysis.
† Determined by medical record review at 90-day visit. Three patients experienced 2 events but are counted once. PE was a possible cause of death in 1 patient.
‡ Assessed by compression ultrasonography 8–14 days after presentation.

observed in surgical patients not receiving thromboprophylaxis who were classified in the high to highest risk categories for venous thromboembolism (9).

We also found that among patients with isolated SVT at inclusion, 8.3% developed at least 1 symptomatic thromboembolic event at 3 months (symptomatic DVT, 2.8%; symptomatic pulmonary embolism, 0.5%; symptomatic extension of SVT, 3.3%; and symptomatic recurrence of SVT, 1.9%), despite more than 60% having received anticoagulant drugs at therapeutic doses and nearly all having received elastic stockings. In a recent study of patients with SVT (5), the 6-month rate of symptomatic DVT was 2.7%. In 2 recent randomized clinical trials (12, 13), approximately 3% of patients with isolated SVT experienced symptomatic DVT or pulmonary embolism during the 3-month follow-up, despite having received an active drug. By comparison, the 3-month rate of recurrent venous thromboembolism was 4% to 5% in recent trials in which patients with DVT or pulmonary embolism received state-of-the-art anticoagulant therapy (14, 15).

Risk factors for subsequent development of symptomatic thromboembolic events in patients with isolated symptomatic SVT at presentation included a history of DVT or pulmonary embolism and cancer (consistent with well-established risk factors for venous thromboembolism [10]), male sex, and the absence of varicose veins. Male sex has previously been identified as a risk factor for thromboembolic complications in patients with isolated SVT (6) and for recurrent venous thromboembolism in patients with venous thromboembolism in whom anticoagulant treatment had been stopped (16); it is unclear why male sex confers excess risk. The association between SVT and DVT in patients without varicose veins, the reasons for which are also unclear, has already been reported (17, 18). Stasis is the primary mechanism of SVT in patients with varicose veins, and inflammation may play a larger role in thrombus formation in patients without varicose veins and thereby confer a higher risk for more clinically serious thromboembolism. Of note, these variables are risk factors for the combination of future thromboembolic events involving the superficial and deep venous systems; too few events had occurred at 3 months to meaningfully assess risk factors for DVT or pulmonary embolism alone (excluding SVT extension or recurrence).

The mortality rate of 0.4% that we observed in patients with isolated SVT at presentation is low compared with the 5% rate among patients with venous thromboembolism (19–21). This difference may be related to the generally low rate of comorbid conditions among patients with SVT; in particular, few of these patients present with active cancer (6.0% vs. 10% to 11% in recent clinical trials on venous thromboembolism [14, 15]). Another noticeable difference between patients with SVT and those with DVT is the preponderance of outpatients, typically women, with varicose veins or a high body weight. In these patients, anticoagulant drugs (mainly low-molecular-weight hepa-

Table 3. **Variables Associated With Symptomatic Thromboembolic Events at 3 Months in Patients With Isolated Superficial Venous Thrombosis at Inclusion***

Characteristic	Patients, n	Hazard Ratio (95% CI)	P Value
Age			0.95
<75 y	466	1	
≥75 y	120	1.02 (0.47–2.21)	
Sex			0.002
Women	378	1	
Men	208	2.63 (1.42–4.86)	
History of DVT or PE			0.016
No	462	1	
Yes	109	2.18 (1.15–4.12)	
Chronic cardiac or respiratory insufficiency			0.171
No	549	1	
Yes	29	1.99 (0.74–5.32)	
Cancer			0.067
No	535	1	
Active	22	0.72 (0.17–3.10)	
Previous	25	3.12 (1.15–8.47)	
Anticoagulant drugs before inclusion			0.62
No	422	1	
Yes	157	1.18 (0.61–2.29)	
Varicose veins			0.049
Yes	506	1	
No	80	2.06 (1.01–4.25)	

DVT = deep venous thrombosis; PE = pulmonary embolism.
* All model variables presented. We included history of venous thromboembolism, cancer, advanced age (≥75 years), and use of anticoagulant drugs at the time of inclusion because they are well-known predictors for thromboembolism. We selected male sex, no varicose veins, and chronic cardiac or respiratory insufficiency from a larger pool of variables with a prevalence of at least 3% on the basis of association with thromboembolism indicated by univariate analysis ($P < 0.15$).

rins) were administered heterogeneously, in dosage regimens that ranged from prophylactic (in one third of patients) to therapeutic (in two thirds of patients), for various durations (range, 1 to 262 days). The variation by country in routine practice for treating this disease emphasizes the uncertainty regarding the best treatment; only 20% of patients with SVT were treated, mainly with nonsteroidal anti-inflammatory agents, in a recent retrospective study in the Netherlands (5). This highlights the urgent need to determine an optimal therapeutic strategy (7).

Our study has limitations. Our results only apply to patients referred by primary care physicians to vascular medicine specialists for confirmation of an SVT that was shown on compression ultrasonography to be at least 5 cm long. We recruited only patients with an SVT of at least this length to focus the study on patients with clinically significant disease (12, 22). Our exclusion criteria were very limited. We collected the data at the level of the vascular physician because we specifically wanted to investigate patients with confirmed disease, and this confirmation requires compression ultrasonography. Whether the prevalence of concomitant DVT or pulmonary embolism in patients with confirmed SVT would have been different if we had studied all patients who consulted primary care physicians for a suspicion of SVT is a matter of conjecture. However, we emphasize that the sample population investigated in the prospective part of our study may clearly be considered representative of patients with confirmed isolated SVT seen in routine practice. Although we had approximately half the patients with isolated SVT that our statistical analysis called for (634 of 1200)—because of the premature termination of enrollment by the steering committee—we nevertheless had a large number of patients. We prospectively followed up with our cohort, with close to 98% of patients completing the follow-up, and all thromboembolic events were objectively documented and adjudicated by a central committee. We chose the 3-month duration of follow-up to include all events likely to be related to the disease, with the risk for venous thromboembolism being highest during the 2 months after the index event (12).

In conclusion, our findings suggest that symptomatic SVT of the lower limbs is not entirely benign. Many patients have venous thromboembolism at the time of presentation, and those without venous thromboembolism are at some risk for complications at 3 months—including symptomatic pulmonary embolism and proximal DVT. Our findings also suggest that compression ultrasonography might be considered for patients with symptomatic SVT at presentation to evaluate the extent of the thrombosis and diagnose potential DVT, that physicians should suspect and test for pulmonary embolism in patients with suggestive symptoms, and that close follow-up of patients with isolated SVT might be advisable to detect early complications that involve the deep veins. Moreover, our findings suggest that clinical trials are warranted to investigate the benefits and risks of using systemic anticoagulant therapy for symptomatic relief of SVT (23–25) and primary prevention of DVT.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Decousus (e-mail, herve.decousus@chu-st-etienne.fr)

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