Superficial thrombophlebitis and risk for recurrent venous thromboembolism

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Objective: **Superficial thrombophlebitis (ST) is a frequent and potentially serious disease if complicated with venous thromboembolism (VTE). Data on risk factors and incidence rates for ST are scarce. It is also unknown whether ST is a risk factor for recurrence of VTE.**

Methods: **After discontinuation of secondary thromboprophylaxis for a first spontaneous VTE, we prospectively observed 615 patients on average for 30 ± 26 months. Patients with natural coagulation inhibitor deficiency, lupus anticoagulant, or cancer, who were pregnant, or were receiving long-term antithrombotic therapy were excluded. The study outcomes were occurrence of symptomatic ST or objectively documented recurrent symptomatic VTE.**

Results: **ST developed in 45 patients (7.3%) with a first VTE. High factor VIII concentration emerged as an independent risk factor for ST (relative risk [RR], 2.0; 95% confidence interval [CI], 1.0-5.2), compared with lower levels after adjustment for age and sex; factor V Leiden and prothrombin G20210A concentration; hyperhomocysteinemia; high body mass index; and duration of oral anticoagulation therapy. VTE recurred in 12 (27%) of 45 patients with ST and in 67 (12%) of 570 patients without ST. In patients with VTE, subsequent ST emerged as an independent risk factor for recurrent VTE. Patients with ST had twofold higher RR (2.1; 95% CI, 1.0-4.2) for recurrence than did patients without ST after adjustment for putative confounding variables.**

Conclusion: **Patients with a first spontaneous VTE and subsequent ST are at increased risk for recurrent VTE. High factor VIII concentration is an independent risk factor for ST. (J Vasc Surg 2003;37:834-8.)**

Superficial thrombophlebitis (ST) of the lower limbs is common, affecting 3% to 11% of the general population.[1] ST is regarded as a benign disease that usually has a self-limited clinical course.[2] Its complications, however, can be serious or even fatal; an association with deep vein thrombosis (DVT)[3-6] and pulmonary embolism (PE)[7] has been reported.

In patients with varicose veins, ST frequently is triggered by minor trauma, but data on risk factors for ST in these patients or in patients without varices are otherwise limited.[2] A higher rate of ST has been noted among patients with natural coagulation inhibitor deficiency[8-11] and among carriers of the factor V Leiden mutation.[11,12] Data on the significance of prothrombin G20210A as a risk factor for ST are controversial.[11,12] Incidence of ST seems to be higher in overweight persons, and high body mass index (BMI) has been described as an independent risk factor.[12]

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Competition of interest: none.

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Risk for recurrence in patients with venous thromboembolism (VTE) has been extensively studied, and ranges from 5% to 40% during the first years after discontinuation of secondary thromboprophylaxis, depending on the presence of acquired or congenital risk factors.[13,14] The risk for subsequent ST in patients with a history of VTE, however, has not been investigated. Most important, it is unknown whether patients with a history of VTE and subsequent ST are at higher risk for recurrent VTE than those without ST.

We prospectively observed patients with a first spontaneous VTE to evaluate the incidence of and risk factors for subsequent ST. We then compared risk for recurrent VTE after a first VTE in patients with and without subsequent ST.

MATERIALS AND METHODS

Patient population. All patients enrolled in the Austrian Study on Recurrent Venous Thromboembolism (AUREC) were eligible for the present analysis. AUREC is an ongoing prospective study involving four thrombosis centers in Vienna, Austria. Patients (older than 18 years) with a first objectively documented VTE treated with oral anticoagulant therapy for at least 3 months were included. Patients with VTE secondary to trauma, surgery, or pregnancy, or who had natural coagulation inhibitor deficiency, lupus anticoagulant, or cancer, or who needed long-term antithrombotic therapy for reasons other than VTE were excluded.

All patients had initially been given unfractionated or low molecular weight heparin in therapeutic doses. Patients entered the study at the time of discontinuation of oral

anticoagulant therapy. Patients were seen at 3-month intervals during the first year and then every 6 months. Patients were instructed to report any symptoms of ST or VTE.

The study was approved by the ethics committee of the University of Vienna, and written informed consent was provided by all patients.

Diagnosis of venous thromboembolism. The diagnosis of DVT was made on the basis of positive findings at venography or color duplex scanning. The diagnosis was established at venography when one of three criteria was fulfilled: constant filling defect seen on two views; abrupt discontinuation of the contrast medium-filled vessel at a constant level of the vein; or absence of filling in the entire deep vein system, without compression, with or without venous flow through collateral veins. The diagnosis was established at duplex scanning if one of two criteria was met: visualization of an intraluminal thrombus in a deep vein, or incomplete compressibility or absence of compressibility.

Diagnostic criteria for PE were positive findings at ventilation-perfusion lung scanning according to the criteria of the Prospective Investigation of Pulmonary Embolism Diagnosis[15] or at spiral computed tomography (CT) if one or more low-attenuation areas were noted that partly or completely filled the lumen of an opacified vessel.

Study end points. End points of the study were symptomatic ST or recurrence of symptomatic VTE. Symptomatic ST was diagnosed on the basis of clinical findings such as painful induration and redness of a superficial vein in the lower extremity. Only patients with a high clinical probability of recurrent DVT underwent duplex scanning (n = 9) or venography (n = 1). Recurrent DVT was confirmed at venography or duplex scanning, in patients with proximal DVT of the contralateral leg only; and at ventilation-perfusion lung scanning or spiral CT in patients with symptomatic PE. Findings had to meet the same criteria as for diagnosis of venous thromboembolism. In patients undergoing venography, DVT was considered to have recurred if the patient had a thrombus in the leg other than the one with the previous thromboembolic event; a thrombus in another deep vein in the same leg as affected by the previous event; or a thrombus in the same venous system as affected by the previous event, with proximal extension of the thrombus, if the upper limit of the original thrombus had been visible, or with a constant filling defect surrounded by contrast medium if the original thrombus had not been visible.

Laboratory analysis. After the patient had fasted overnight, venous blood was collected in a 1:10 dilution of 0.11M trisodium citrate. A portion of the blood was centrifuged for 20 minutes at 2000g. Another portion of the blood was immediately centrifuged at 1600g for 20 minutes at 4° C for measurement of homocysteine; the plasma was then snap-frozen and stored at −80° C. Genomic DNA was isolated from leukocytes with standard methods.

Determination of antithrombin, protein C, protein S, factor VIII, and homocysteine concentrations was performed as reported.[16] Screening for factor V Leiden and prothrombin G20210A was carried out as described.[17,18] The presence of lupus anticoagulant was assessed according to the criteria of the International Society on Thrombosis and Haemostasis.[19] Laboratory technicians were blinded to patient characteristics at all times.

Statistical analysis. Time to occurrence of ST or recurrent VTE (uncensored data) and follow-up time in patients without ST or without recurrent VTE (censored data) were analyzed with survival time methods.[20] The probability of ST or recurrent VTE was estimated with the Kaplan-Meier method.[21] To test for homogeneity between strata, we used the log-rank test and the generalized Wilcoxon test. Relative risk for recurrence was estimated with a Cox regression model with ST as a time-dependent covariable. Data were adjusted for age and sex; factor V Leiden and prothrombin G20210A concentration; hyperhomocysteinemia (dichotomized at the 95th percentile of normal) and high factor VIII concentration (dichotomized at a plasma level of 234 IU/dL); duration of oral anticoagulation therapy; and high BMI (>25 kg/m^2), calculated by dividing weight in kilograms by the square of height in meters.

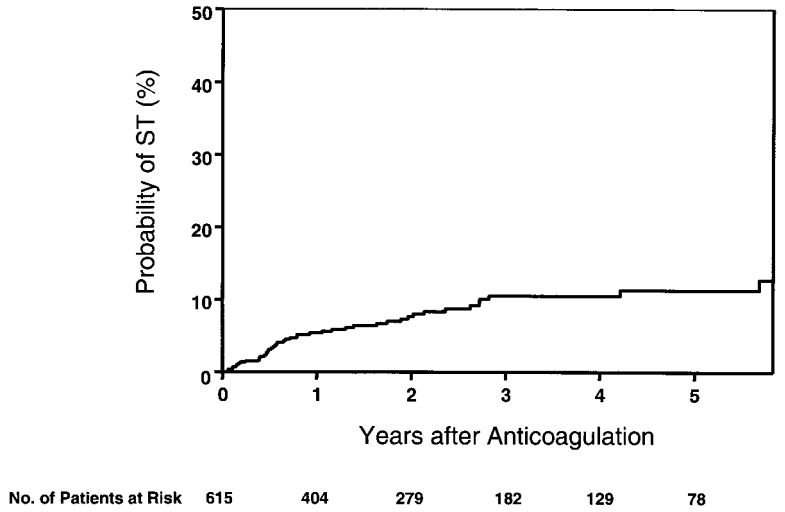
Categorial data were checked for homogeneity with contingency table analyses (χ^2 test). Simple descriptive statistics were computed to provide clear presentation of data. For numerical operations a SAS software package was used. Values are given as mean ± SD or median and range.

RESULTS

Risk for ST in patients with VTE. The study population consisted of 615 patients with a first spontaneous VTE (367 DVT, 248 PE with or without DVT). After discontinuation of oral anticoagulation therapy, patients were followed up on average for 30 (±26) months. One hundred eighty-two patients were excluded because they had cancer (n = 11), required antithrombotic therapy for reasons other than VTE (n = 99), became pregnant (n = 17), or were lost to follow-up (n = 51). One patient died of gastric cancer, 1 died of septicemia, and 2 patients died of heart failure. Data for these patients were censored at exclusion or death.

ST subsequently developed in 45 of 615 patients (7.3%). In all patients, ST was treated with compression therapy and ambulation. In addition, 22 patients received low molecular weight heparin for 10 days, and 8 patients were given nonsteroidal antiinflammatory drugs. The median time between discontinuation of secondary thromboprophylaxis for VTE and subsequent ST was 8 months (range, 1-68 months).

With the Kaplan-Meier method, cumulative probability of ST in patients with a first spontaneous VTE was 7.3% (CI, 5.2%-10.1%), 10.6% (CI, 7.4%-13.7%), and 12.8% (CI, 8.3%-17.2%) at 2, 4, and 6 years, respectively, after discontinuation of secondary thromboprophylaxis (Figure). For comparison, cumulative probability of recurrent VTE was 10.7% (CI, 7.9%-13.5%), 17.9% (CI, 13.9%-22.0%), and 23.7% (CI, 18.0%-29.4%) at 2, 4, and 6 years, respectively.



Estimated risk for ST in 615 patients with a first spontaneous VTE (Kaplan-Meier method).

Table I. Characteristics of 615 patients with VTE with and without ST

	Without ST (n = 570)*		*With ST* (n = 45)*		
Characteristics	*n*	*%*	*n*	*%*	P
Sex (male)	256	45	22	50	NS
Age at VTE (y)	48 ± 17		56 ± 12		.003
VTE at inclusion in study					
DVT	340	60	27	60	NS
PE	230	40	18	40	NS
Duration of anticoagulation (mo)	8 ± 11		13 ± 29		NS
Factor V Leiden	183	33	16	36	NS
Prothrombin G20210A	43	8	5	11	NS
Hyperhomocysteinemia	143	27	10	23	NS
High factor VIII (>234 IU/dL)	52	10	11	24	.004
High Body mass index (>25 kg/m^2)	342	63	36	82	.007
Follow-up (mo)	29 ± 26		41 ± 28		.004
ST ipsilateral to first DVT	—		32	71	—

VTE, Venous thromboembolism; *ST,* superficial thrombophlebitis; *DVT,* deep venous thrombosis; *PE,* pulmonary embolism; *NS,* not significant.
*Plus or minus values are mean ± SD.

Characteristics of patients with and without ST are shown in Table I. Patients with ST were significantly older than patients without ST (56 ± 12 years vs 48 ± 17 years; $P = .003$) and were followed up longer (41 ± 28 months vs 29 ± 26 months; $P = .004$). The proportion of patients with high BMI (>25 kg/m^2) was significantly larger among patients with ST compared with those without ST (82% vs 63%; $P = .007$). Incidence of ST was comparable between patients with proximal or distal DVT (8.1% and 6.2%; $P = .8$).

High levels of factor VIII confer substantial risk for both first and recurrent VTE. We therefore investigated the role of factor VIII with regard to risk for ST. Compared with patients without ST, a significantly larger proportion of patients with ST had high factor VIII levels (24% vs 10%; $P = .004$). Compared with patients with low factor VIII levels, patients with high factor VIII levels had a fourfold relative risk for ST (RR, 4.0; CI, 2.0-8.6), which remained significant after adjustment for age and sex; factor V Leiden and prothrombin G20210A concentration; hyperhomocysteinemia; high BMI; and duration of oral anticoagulation therapy (RR, 2.0; CI, 1.0-5.2).

Recurrence of venous thromboembolism. Of 615 patients, 79 (13%) had recurrent VTE, including 12 (27%; 5 DVT, 7 PE, respectively) of 45 patients with ST and 67 (12%; 47 DVT, 20 PE, respectively) of 570 patients without ST. Median time between ST and recurrent VTE was 17 ± 14 months (range 2 to 39) months.

The primary purpose of this study was to evaluate the influence of ST on risk for subsequent VTE, which implies

Table II. Relative risk for recurrent VTE in patients with ST

	Number of patients	*Number of recurrences*	*Univariate analysis*		*Multivariate analysis*	
			RR	*CI*	*RR*	*CI*
Without ST	570	67	1*		1*	
With ST	45	12	3.3	1.7-6.3	2.1	1.0-4.2

VTE, Venous thromboembolism; *ST,* superficial thrombophlebitis; *RR,* relative risk; *CI,* 95% confidence interval.
*Reference group.

a time-dependent association between ST and recurrent VTE. Hence, for calculation of RR for recurrent VTE, ST was taken as a time-dependent variable in the regression model. In this model, crude RR for recurrent VTE among patients with VTE and subsequent ST was 3.3 (CI, 1.7-6.3). ST remained a risk factor for recurrent VTE after adjustment for age and sex; factor V Leiden, prothrombin G20210A, and high factor VIII concentration; hyperhomocysteinemia; high BMI; and duration of anticoagulation therapy (RR, 2.1; CI, 1.0-4.2) (Table II).

DISCUSSION

In a large cohort of patients with a first spontaneous VTE, we prospectively evaluated the incidence of and risk factors for ST, and the association between ST and risk for subsequently recurrent VTE. Two years after discontinuation of secondary thromboprophylaxis, the probability for ST in patients with VTE was 7%. At this time, the probability for ST and recurrent VTE (11%) are comparable, but risk for ST becomes progressively lower thereafter. At 6 years, risk for recurrent VTE is almost twice as high as risk for ST (24% vs 13%).

A high factor VIII concentration is a potent risk factor for a first VTE as well as recurrent VTE.[16,22-24] High factor VIII concentration is also an independent risk factor for ST (adjusted RR, 2.0, compared with patients with lower levels). Although this association has been established in patients with a history of VTE, it can be assumed that a high factor VIII concentration is also a risk factor for ST in persons without prior VTE. Factor V Leiden did not emerge as a risk factor for ST in our patients. This finding is in contrast to two studies in which factor V Leiden conferred a twofold to sixfold higher risk for ST.[11,12] In both studies, however, the study cohort consisted of patients without a history of VTE. In confirmation of the Swiss study, the proportion of patients with excess body weight was also significantly greater among patients with ST compared with those without ST.[12]

The principal finding of our study was that patients with a first spontaneous VTE and subsequent ST were at threefold increased risk for recurrent VTE compared with patients without ST. When confounding variables were considered in the logistic regression model, RR was somewhat reduced, mainly because of high factor VIII concentration. However, ST still remained an independent risk factor for recurrent VTE in patients with thrombosis.

The diagnosis of symptomatic ST was established on the basis of characteristic clinical signs and symptoms. Only patients with a high clinical probability of recurrent VTE underwent duplex scanning or venography. ST is frequently associated with DVT and PE.[3-7,25] However, we consider it unlikely that the higher risk for recurrence in patients with ST could have resulted from recurrent VTE that was overlooked at the time of ST, for the following reasons. Concomitant DVT was ruled out at duplex scanning or venography in one fourth of patients. Most important, all patients were closely followed up until resolution of symptoms of ST. Within 2 months after the diagnosis, no patients had VTE and no patients with ST had symptoms of PE.

Patients with a first spontaneous VTE and subsequent ST are at increased risk for recurrent VTE. High factor VIII concentration, which is a risk factor for recurrent VTE, is also an independent risk factor for ST. The results of an ongoing interventional trial will show whether prolonging secondary thromboprophylaxis is beneficial in patients with high factor VIII concentration and a first VTE.

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