THROMBOSIS AND HEMOSTASIS

The risk of venous thrombosis in individuals with a history of superficial vein thrombosis and acquired venous thrombotic risk factors

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Key Points

- Superficial vein thrombosis combined with an acquired thrombotic risk factor increases the risk of venous thrombosis 10- to 100-fold.
- If confirmed, these findings have important implications for the future prevention of venous thrombosis.

Superficial vein thrombosis (SVT) increases the risk of venous thrombosis fourfold to sixfold. As most individuals with SVT do not develop venous thrombosis, additional risk factors may explain the risk of developing a venous thrombosis. In the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis study, we assessed the risk of venous thrombosis in individuals with previous SVT and a mild thrombotic risk factor (smoking or overweight/obesity), a strong risk factor (surgery, hospitalization, plaster cast immobilization, or malignancy), or a reproductive factor in women (oral contraception, postmenopausal hormone therapy, or pregnancy/puerperium). Individuals with previous SVT alone had a 5.5-fold (95% confidence interval [CI], 4.4-6.8) increased risk of venous thrombosis. This was 9.3 (95% CI, 7.2-12.1) combined with a mild thrombotic risk factor, 31.4 (95% CI, 14.6-67.5) with a strong risk factor, and 34.9 (95% CI, 19.1-63.8) in women with a reproductive risk factor. The highest separate risk estimates were found for SVT with surgery (42.5; 95% CI, 10.2-177.6), hospitalization (49.8; 95% CI, 11.9-209.2), or oral contraception (43.0; 95% CI, 15.5-119.3 in women). In conclusion, the risk of venous thrombosis is markedly increased in individuals with previous SVT who have an acquired thrombotic risk factor. (*Blood*. 2013;122(26):4264-4269)

Introduction

Superficial vein thrombosis (SVT) is an inflammatory process that can obstruct the superficial veins of the legs.[1] In the past it was viewed as a benign, self-limiting disorder. However, in recent years it has been shown that individuals with SVT have a fourfold to sixfold higher risk of venous thrombosis than individuals without SVT.[2-6] Most individuals with SVT do not develop venous thrombosis, which suggests that additional risk factors must be present in order to trigger a deep venous event.

Previous research has shown genetic thrombophilia to weakly elevate the risk of venous thrombosis in individuals with a history of SVT.[5,7] However, no information is available on the risk of venous thrombosis in individuals with a history of SVT who encounter an acquired risk factor for venous thrombosis. Information on this topic may be useful to identify which individuals with this condition are at high risk of a deep venous event, particularly because these acquired factors are often transient. Therefore, the aim of our study was to assess the risk of venous thrombosis in individuals with previous SVT who encounter either a mild risk factor for venous thrombosis (ie, smoking or overweight), a strong risk factor for venous thrombosis (surgery, hospitalization, plaster cast immobilization, or malignancy), or a female reproductive risk factor (oral contraception, postmenopausal hormone therapy, or pregnancy and the puerperium).

Methods

Study design

This study was performed within the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study, a large case-control study on risk factors for venous thrombosis. Details of this study have been described previously.[8] Briefly, between March 1999 and September 2004, 4956 consecutive patients with a first symptomatic episode of venous thrombosis or pulmonary embolism were included from 6 anticoagulation clinics in The Netherlands (Amersfoort, Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht). Detailed diagnostic information was obtained from hospital discharge reports and general practitioners. Deep vein thrombosis was objectively confirmed using Doppler ultrasonography. Pulmonary embolism was confirmed by a ventilation perfusion lung scan, a spiral computed tomography scan, or angiogram. Partners of patients were invited to participate as controls if they were aged 18 to 70 years and had no history of venous thrombosis. In total, 3297 partners

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Table 1. Clinical characteristics

Characteristics	Patients	Controls
Total	4290	5754
Mean age (range), y	49 (18-70)	47 (18-70)
Male (%)	1966 (46)	2650 (46)
Normal weight, BMI ≤ 25 kg/m^2 (%)	1540 (37)	2732 (50)
Overweight, BMI 25-30 kg/m^2 (%)	1743 (42)	2041 (37)
Obesity, BMI ≥30 kg/m^2 (%)	858 (21)	747 (14)
Nonsmoker (%)	1466 (35)	2280 (40)
Ever smoker (%)	2785 (65)	3416 (60)
VT		
DVT only (%)	2476 (58)	
PE only (%)	1410 (33)	
DVT and PE (%)	404 (9)	
Risk factors for VT		
Family history of VT (%)	1126 (30)	810 (16)
Surgery (%)	706 (17)	166 (3)
Hospitalization (%)	746 (17)	154 (3)
Plaster cast immobilization (%)	190 (4)	31 (1)
Travel ≥4 h (%)	676 (16)	1003 (17)
Malignancy (%)	387 (9)	104 (2)
Female hormonal risk factors		
OC use, in women aged ≤50 y (%)	988 (68)	647 (38)
HT, in women aged >50 y (%)	53 (6)	53 (4)
Pregnancy/puerperium, in women aged ≤50 y (%)	155 (11)	81 (5)

Continuous variables denoted as mean (range), categorical variables as number (%). Data were missing for some participants in some subgroups.

DVT, deep vein thrombosis; HT, postmenopausal hormone therapy; OC, oral contraception; PE, pulmonary embolism; VT, venous thrombosis.

participated. From January 2002 to September 2004, 3000 additional age- and sex-matched controls were recruited by random digit dialing (RDD). The study was approved by the medical ethics committee of the Leiden University Medical Center and all participants provided written informed consent in accordance with the Declaration of Helsinki.

Data collection

Participants completed a detailed questionnaire on risk factors for venous thrombosis. Items covered in the questionnaire included surgery, pregnancy and puerperium, plaster cast immobilization, and hospitalization in the 3 months before the index date, oral contraception or postmenopausal hormone therapy use in the month before the index date, and malignancy in the 5 years before the index date. The index date was defined as the date of diagnosis of venous thrombosis for patients and their partners and the date of completing the questionnaire for the random control subjects. Self-reported information was also obtained on weight, height, smoking status, family history of venous thrombosis, and previous SVT. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height squared (m^2). Smokers were divided into current, previous, and never smokers. If the difference between the age at the index date and the age of smoking cessation was 1 year or less, the person was considered to be a current smoker. A positive family history was defined as having at least 1 parent or sibling with a history of venous thrombosis. Participants were classified as having previous SVT if they answered a question on whether they had experienced an episode of SVT at any time before the onset of venous thrombosis (for patients) or before enrollment in the MEGA study (controls) with "yes." No information was obtained on the location of the SVT.

Statistical analysis

For the current analyses, only individuals for whom information on previous SVT was available from the questionnaire were included (93% of patients and 91% of controls). Odds ratios and 95% confidence intervals (CIs) for venous thrombosis were calculated in individuals with previous SVT and a mild thrombotic risk factor (smoking or overweight), a strong thrombotic risk factor (surgery, hospitalization, plaster cast immobilization, or malignancy), and in women with previous SVT and a female reproductive risk factor (oral contraception, postmenopausal hormone therapy or pregnancy and the puerperium). The risk of venous thrombosis was also assessed for the combination of previous SVT and each risk factor separately.

For the separate analyses on oral contraception use and pregnancy and the puerperium, only premenopausal women aged 18 to 50 years were included. Postmenopausal hormone therapy was analyzed in women aged 50 years or older. All other factors were analyzed for all participants without age restrictions. Risk estimates were adjusted for the putative confounders, the selection of which is shown in the legends of the tables. The outcomes deep vein thrombosis, pulmonary embolism, and deep vein thrombosis with concomitant pulmonary embolism were combined in most analyses, but also analyzed separately.

As the same percentage of partner controls and RDD controls had previously experienced SVT (both 2%), the 2 control groups were pooled into a single control group of 5754 individuals for the main analyses. However, we also analyzed the 2 control groups separately to check for differences (for the comparison with partner controls this was done using conditional logistic regression). All statistical analyses were performed with SPSS for Windows (release 20.0; SPSS Inc.).

Results

A total of 10 044 participants, 4290 patients with venous thrombosis and 5754 controls without venous thrombosis, provided information on previous SVT and were eligible for analysis. Their clinical characteristics are depicted in Table 1. The mean age at enrollment was 49 years (range, 18-70 years) in patients and 47 years (range, 18-70 years) in controls. Patients were more likely to be overweight/obese (63% vs 51%) and more likely to smoke (65% vs 60%) than control subjects. Overall, 414 patients (10%) and 110 controls (2%) reported previously experiencing SVT. In both patients and controls, a history of SVT was more common in women than in men (11% of women vs 8% of men in patients, and 3% vs 1% in controls).

Individuals with previous SVT had a 5.5-fold (95% CI, 4.4-6.8) increased risk of venous thrombosis compared with individuals without previous SVT. In addition, in the absence of previous SVT, all studied acquired risk factors were associated with an increased risk of venous thrombosis (Table 2). When individuals with both previous SVT and an acquired risk factor for venous thrombosis were studied, the odds ratios for venous thrombosis were 9.3 (95% CI, 7.2-12.1) for previous SVT and a mild thrombotic risk factor, 31.4 (95% CI, 14.6-67.5) for previous SVT and a strong thrombotic risk factor, and 34.9 (95% CI, 19.1-63.8) in women with previous SVT and a reproductive risk factor (Table 3).

In a subsequent analysis, we analyzed the joint effect of previous SVT and each acquired risk factor for venous thrombosis separately (Table 2). The risk estimates for smoking and overweight combined with previous SVT were similar to the overall risk estimate for mild risk factors: odds ratios of 6.3 (95% CI, 4.6-8.7) and 8.0 (95% CI, 5.8-11.0), respectively. Within the strong risk factors, particularly high risk estimates were found for patients with previous SVT undergoing surgery, odds ratio 42.5 (95% CI, 10.2-177.6), or during hospitalization, odds ratio 49.8 (95% CI, 11.9-209.2). For women aged <50 years with previous SVT, the risk of venous thrombosis was highest for those who used oral contraception, odds ratio 43.0 (95% CI, 15.5-119.3) (Table 3). The combination of previous SVT and postmenopausal hormone therapy

Table 2. Effect of lifestyle-related risk factors with SVT on the risk of VT

		Patients, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
SVT history	**Mild VT risk factor**				
Negative	No	529 (10)	1219 (17)	Reference	Reference
Negative	Yes	3347 (80)	4425 (81)	1.7 (1.6-1.9)	1.7 (1.5-1.9)
Positive	No	38 (1)	20 (0.5)	4.4 (2.5-7.6)	4.0 (2.3-6.9)
Positive	Yes	376 (9)	90 (1.5)	9.6 (7.5-12.4)	9.3 (7.2-12.1)
SVT history	**Smoking***				
Negative	No	1329 (31)	2231 (39)	Reference	Reference
Negative	Yes	2510 (59)	3357 (59)	1.2 (1.1-1.4)	1.2 (1.1-1.3)
Positive	No	139 (3)	51 (1)	4.7 (3.3-6.8)	3.5 (2.4-5.2)
Positive	Yes	275 (7)	59 (1)	7.3 (5.4-9.9)	6.3 (4.6-8.7)
SVT history	**Overweight/Obesity†**				
Negative	No	1423 (34)	2692 (49)	Reference	Reference
Negative	Yes	2319 (56)	2728 (49)	1.6 (1.5-1.7)	1.6 (1.5-1.7)
Positive	No	132 (3)	50 (1)	4.9 (3.4-7.0)	4.3 (2.9-6.3)
Positive	Yes	282 (7)	60 (1)	9.0 (6.6-12.2)	8.0 (5.8-11.0)
SVT history	**Strong VT risk factor‡**				
Negative	No	2668 (62)	5319 (92)	Reference	Reference
Negative	Yes	1208 (28)	325 (6)	7.4 (6.5-8.4)	7.3 (6.4-8.4)
Positive	No	301 (7)	103 (1.5)	5.8 (4.6-7.3)	5.7 (4.5-7.2)
Positive	Yes	113 (3)	7 (0.5)	32.2 (15.0-69.1)	31.4 (14.6-67.5)
SVT history	**Surgery§**				
Negative	No	3233 (75)	5480 (95)	Reference	Reference
Negative	Yes	643 (15)	164 (3)	6.6 (5.5-7.9)	5.9 (4.9-7.1)
Positive	No	351 (8)	108 (2)	5.4 (4.2-6.8)	4.6 (3.6-5.9)
Positive	Yes	63 (2)	2 (0)	46.7 (11.4-191.4)	42.5 (10.2-177.6)
SVT history	**Hospitalization§**				
Negative	No	3188 (74)	5492 (95)	Reference	Reference
Negative	Yes	688 (16)	152 (3)	7.6 (6.3-9.1)	6.7 (5.6-8.1)
Positive	No	356 (8)	108 (2)	5.5 (4.3-7.0)	4.7 (3.6-6.0)
Positive	Yes	58 (2)	2 (0)	44.9 (10.9-184.6)	49.8 (11.9-209.2)
SVT history	**Plaster cast‖**				
Negative	No	3696 (86)	5614 (97)	Reference	Reference
Negative	Yes	180 (4)	30 (1)	9.4 (6.2-14.3)	9.8 (6.5-14.9)
Positive	No	404 (9)	109 (2)	5.5 (4.3-7.0)	4.8 (3.7-6.1)
Positive	Yes	10 (1)	1 (0)	13.3 (1.7-104.7)	14.6 (1.8-120.0)
SVT history	**Malignancy†**				
Negative	No	3519 (82)	5544 (95)	Reference	Reference
Negative	Yes	357 (8)	100 (2)	5.4 (4.2-6.7)	5.4 (4.3-6.9)
Positive	No	384 (9)	106 (2)	5.6 (4.4-7.1)	4.8 (3.7-6.2)
Positive	Yes	30 (1)	4 (1)	10.4 (3.6-29.9)	11.1 (3.8-32.2)

Mild risk factors defined as smoking or obesity; strong risk factors as surgery, hospitalization, plaster cast immobilization, or malignancy. All ORs for SVT alone and SVT combined with a lifestyle-related risk factor were adjusted, where applicable, for age, sex, BMI, smoking, malignancy, family history of VT, and female hormone use. All ORs for the separate risk factors were adjusted for age and sex.

OR, odds ratio; VT, venous thrombosis.

*BMI-adjusted risk factors for all ORs.

†Smoking-adjusted risk factors for all ORs.

‡Smoking- and BMI-adjusted risk factors for all ORs.

§Smoking-, BMI-, and malignancy-adjusted risk factors for all ORs.

‖Physical activity–adjusted risk factors for all ORs.

among women aged >50 years yielded an odds ratio of 5.8 (95% CI, 1.6-21.6). Although pregnancy and puerperium alone increased the risk of venous thrombosis: odds ratio 2.4 (95% CI, 1.8-3.2), it was not possible to calculate the combined effect with previous SVT, as there were no control subjects with this combination of risk factors.

In a final analysis, we viewed patients with deep vein thrombosis, patients with pulmonary embolism, and patients with both deep vein thrombosis and pulmonary embolism separately (Table 4). The combination of previous SVT and a mild thrombotic risk factor increased the risk of deep vein thrombosis alone (odds ratio, 11.5; 95% CI, 8.7-15.4), and the risk of deep vein thrombosis with concomitant pulmonary embolism (odds ratio, 14.2; 95% CI, 8.3-24.4), more than the risk of pulmonary embolism alone (odds ratio, 6.0; 4.3-8.5). For strong risk factors, no such differential effect on deep vein thrombosis and pulmonary embolism was found, with odds ratios of 32.8 (95% CI, 15.0-71.7) for deep vein thrombosis alone, 34.7 (95% CI, 13.6-88.5) for deep vein thrombosis with concomitant pulmonary embolism, and 27.8 (95% CI, 12.2-63.0) for pulmonary embolism alone. Women with reproductive risk factors seemed to have a particularly high risk of deep vein thrombosis with pulmonary embolism, odds ratio 55.0 (95% CI, 24.1-125.2), especially when using oral contraception: a 100.4-fold (95% CI, 24.2-416.0) increased risk (Table 5). The reproduction-associated odds ratios for deep vein thrombosis alone and pulmonary embolism alone were also increased: 40.1 (95% CI, 21.4-75.2) and 21.0 (95% CI, 10.7-41.3), respectively. Again, due to small numbers, it was not possible to assess the combined

Table 3. Effect of female reproductive risk factors with SVT on the risk of VT

		Patients, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
SVT history	**Reproductive risk factors**				
Negative	No	857 (37)	2177 (70)	Reference	Reference
Negative	Yes	1212 (53)	843 (27)	3.7 (3.2-4.1)	5.0 (4.3-5.8)
Positive	No	124 (5)	72 (2)	4.4 (3.2-5.9)	4.0 (2.9-5.4)
Positive	Yes	128 (5)	12 (1)	27.1 (14.9-49.2)	34.9 (19.1-63.8)
SVT history	**OC use**				
Negative	No	416 (33)	1046 (44)	Reference	Reference
Negative	Yes	902 (57)	642 (54)	3.7 (3.1-4.3)	4.0 (3.3-4.7)
Positive	No	41 (3)	18 (1)	5.2 (2.9-9.4)	5.1 (2.8-9.5)
Positive	Yes	86 (7)	5 (1)	49.4 (18.0-135.9)	43.0 (15.5-119.3)
SVT history	**HT use**				
Negative	No	706 (81)	1264 (91)	Reference	Reference
Negative	Yes	41 (6)	50 (4)	1.3 (0.8-2.1)	1.5 (0.9-2.4)
Positive	No	108 (12)	58 (4)	3.4 (2.3-4.8)	3.1 (2.1-4.5)
Positive	Yes	12 (1)	3 (1)	5.8 (1.6-21.3)	5.8 (1.6-21.6)
SVT history	**Pregnancy**				
Negative	No	1171 (81)	1607 (94)	Reference	Reference
Negative	Yes	147 (10)	81 (4)	2.5 (1.9-3.3)	2.4 (1.8-3.2)
Positive	No	119 (8)	23 (2)	6.8 (4.2-10.9)	5.6 (3.4-9.2)
Positive	Yes	8 (1)	0	NA	NA

All ORs for SVT alone and SVT combined with a reproductive risk factor were adjusted for age, BMI, smoking, malignancy, and family history of VT. The overall OR, and the ORs for OC and HT were adjusted for age, BMI, smoking, and family history of VT. The OR for pregnancy was adjusted for age.

HT, postmenopausal hormone therapy; OC, oral contraception; OR, odds ratio; VT, venous thrombosis.

effect of pregnancy and puerperium and SVT on the risk of venous thrombosis. However, the event numbers were in accordance with the findings for other risk factors as 6 of the 8 patients with this combination of risk factors had deep vein thrombosis. All analyses in which patients were compared with partner controls or RDD controls separately yielded similar results confirming the appropriateness of pooling the control groups (data not shown).

Discussion

In a large case-control study with over 10 000 participants we found that individuals with previous SVT had a markedly increased risk of venous thrombosis in the presence of acquired thrombotic risk factors. This risk was 9.3-fold (95% CI, 7.2-12.1) increased in individuals with a mild thrombotic risk factor (smoking or overweight), 31.4-fold (95% CI, 14.6-67.5) increased in individuals with a strong thrombotic risk factor (surgery, hospitalization, plaster cast immobilization, or malignancy), and 34.9-fold (95% CI, 19.1-63.8) increased in women with a reproductive risk factor (oral contraception, postmenopausal hormone therapy, or pregnancy and the puerperium).

In this study, the risk of deep vein thrombosis with or without concomitant pulmonary embolism in individuals with previous SVT seemed to be higher than the risk of pulmonary embolism alone. These findings are in line with the results of previous research showing some risk factors for venous thrombosis to have a differential effect on deep vein thrombosis and pulmonary embolism, suggesting that the etiology of these 2 diseases is not always the same.[9] However, CIs were wide and overlapped for the different subtypes of venous thrombosis. Therefore, this finding should be interpreted with caution.

In individuals with previous SVT, it is possible that local changes may promote the migration of thrombi in superficial veins toward the deep venous system.[2,3] However, in up to 10% of individuals with previous SVT who develop deep vein thrombosis, this occurs in the contralateral leg,[10] indicating that systemic hypercoagulability also plays a role in the development of venous thrombosis after SVT.[9]

Despite an increasing amount of research, many physicians still view SVT as a benign, self-limiting disorder.[2,3] Our findings provide evidence to the contrary. In a previous population-based cohort study, the incidence rates of venous thrombosis were 0.74 per 1000 person-years for individuals aged 18 to 70 years (the age groups included in our study) and 0.46 per 1000 person-years in women aged 18 to 50 years (the age group at which oral contraception is targeted).[11] Multiplying these numbers with the relative risks found in our study suggests that ~1 in 32 individuals undergoing surgery, 1 in 27 hospitalized individuals, and 1 in 51 oral contraception users with previous SVT develop venous thrombosis each year. Therefore, awareness of the risk of venous thrombosis in these individuals seems of clinical importance. For instance, in future, it may be necessary to include a history of SVT in prediction models for venous thrombosis, or to advise patients with previous SVT to avoid transient risk factors for venous thrombosis (eg, oral contraceptives) as much as possible. However, confirmation of our results is necessary before any definite recommendations can be made.

There are some aspects of our study that warrant comment. A strength of our research is that data were collected in the same manner for all participants and that all venous thrombotic events were objectively diagnosed. A limitation is that, due to small numbers, some risks could not be estimated and others resulted in wide CIs. For the same reason, it was not possible to view different levels of exposure to the acquired risk factors (ie, different types of surgery, different indications for hospitalization, or different types of oral contraception or postmenopausal hormone therapy) separately or to assess the risk estimates separately for individuals with and without genetic thrombophilia. Another limitation is that information on SVT was collected as a yes/no

Table 4. Effect of lifestyle-related risk factors with SVT on the risk of VT subtypes

		Patients, n (%)	Controls, n (%)	DVT only OR (95% CI)	DVT with PE OR (95% CI)	PE only OR (95% CI)
SVT history	**Mild VT risk factor***					
Negative	No	529 (10)	1219 (17)	Reference	Reference	Reference
Negative	Yes	3347 (80)	4425 (81)	1.7 (1.5-2.0)	1.8 (1.3-2.5)	1.6 (1.4-1.9)
Positive	No	38 (1)	20 (0.5)	4.1 (2.2-7.7)	7.4 (2.5-21.8)	3.2 (1.5-6.8)
Positive	Yes	376 (9)	90 (1.5)	11.5 (8.7-15.4)	14.2 (8.3-24.4)	6.0 (4.3-8.5)
SVT history	**Smoking***					
Negative	No	1329 (31)	2231 (39)	Reference	Reference	Reference
Negative	Yes	2510 (59)	3357 (59)	1.2 (1.1-1.4)	1.1 (0.8-1.3)	1.4 (1.2-1.6)
Positive	No	139 (3)	51 (1)	4.0 (2.6-6.2)	4.0 (1.9-8.3)	3.0 (1.8-5.0)
Positive	Yes	275 (7)	59 (1)	7.2 (5.1-10.1)	6.5 (3.7-11.5)	4.6 (3.0-7.0)
SVT history	**Overweight/Obesity†**					
Negative	No	1423 (34)	2692 (49)	Reference	Reference	Reference
Negative	Yes	2319 (56)	2728 (49)	1.6 (1.5-1.8)	1.9 (1.5-2.4)	1.4 (1.3-1.6)
Positive	No	132 (3)	50 (1)	4.2 (2.8-6.6)	5.2 (2.3-11.8)	4.0 (2.5-6.5)
Positive	Yes	282 (7)	60 (1)	10.1 (7.1-14.2)	12.9 (7.3-23.0)	4.7 (3.1-7.1)
SVT history	**Strong VT risk factor‡**					
Negative	No	2668 (62)	5319 (92)	Reference	Reference	Reference
Negative	Yes	1208 (28)	325 (6)	7.1 (6.2-8.2)	5.8 (4.5-7.6)	8.2 (7.0-9.6)
Positive	No	301 (7)	103 (1.5)	6.7 (5.2-8.5)	6.1 (4.0-9.4)	4.0 (2.9-5.5)
Positive	Yes	113 (3)	7 (0.5)	32.8 (15.0-71.7)	34.7 (13.6-88.5)	27.8 (12.2-63.0)
SVT history	**Surgery§**					
Negative	No	3233 (75)	5480 (95)	Reference	Reference	Reference
Negative	Yes	643 (15)	164 (3)	6.0 (4.9-7.4)	4.2 (2.9-6.1)	6.3 (5.0-7.8)
Positive	No	351 (8)	108 (2)	5.3 (4.0-6.9)	5.6 (3.5-8.8)	3.5 (2.5-4.9)
Positive	Yes	63 (2)	2 (0)	47.5 (11.2-201.4)	32.3 (6.0-173.2)	30.0 (6.4-141.0)
SVT history	**Hospitalization§**					
Negative	No	3188 (74)	5492 (95)	Reference	Reference	Reference
Negative	Yes	688 (16)	152 (3)	5.8 (4.7-7.2)	5.3 (3.7-7.6)	8.7 (7.0-10.8)
Positive	No	356 (8)	108 (2)	5.4 (4.1-7.1)	5.4 (3.3-8.6)	3.6 (2.5-5.0)
Positive	Yes	58 (2)	2 (0)	45.1 (10.4-195.3)	44.4 (8.7-226.0)	45.8 (10.0-208.8)
SVT history	**Plaster cast‖**					
Negative	No	3696 (86)	5614 (97)	Reference	Reference	Reference
Negative	Yes	180 (4)	30 (1)	11.8 (7.7-18.1)	9.5 (4.9-18.2)	6.8 (4.0-11.4)
Positive	No	404 (9)	109 (2)	5.5 (4.2-7.2)	5.8 (3.7-9.1)	3.5 (2.6-4.9)
Positive	Yes	10 (1)	1 (0)	20.6 (2.4-177.2)	27.0 (1.7-439.5)	2.7 (0.2-46.5)
SVT history	**Malignancy†**					
Negative	No	3519 (82)	5544 (95)	Reference	Reference	Reference
Negative	Yes	357 (8)	100 (2)	5.2 (4.0-6.7)	4.1 (2.6-6.5)	6.1 (4.6-8.0)
Positive	No	384 (9)	106 (2)	5.6 (4.3-7.3)	6.1 (3.9-9.6)	3.6 (2.6-4.9)
Positive	Yes	30 (1)	4 (1)	7.6 (2.4-24.3)	11.5 (2.6-51.1)	14.9 (4.7-47.3)

Mild risk factors defined as smoking or obesity, strong risk factors as surgery, hospitalization, plaster cast immobilization, or malignancy. All ORs for SVT alone and SVT combined with a lifestyle-related risk factor were adjusted, where applicable, for age, sex, BMI, smoking, malignancy, family history of VT, and female hormone use. All ORs for the separate risk factors were adjusted for age and sex.

DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; VT, venous thrombosis.

*BMI-adjusted risk factors for all ORs.

†Smoking-adjusted risk factors for all ORs.

‡Smoking- and BMI-adjusted risk factors for all ORs.

§Smoking-, BMI-, and malignancy-adjusted risk factors for all ORs.

‖Physical activity–adjusted risk factors for all ORs.

self-reported question in a questionnaire, and that the location or length of SVT was not asked for. Therefore, it was not possible to take the length or extension of the SVT, which may be associated with the risk of venous thrombosis,[12] into account, or to ascertain whether our results apply equally to patients with SVT of the leg and patients with SVT in other anatomic locations.

Furthermore, as the diagnosis of SVT was not objectively verified, we cannot rule out that patients wrongly reported symptoms signaling the onset of venous thrombosis to be SVT, or that patients recalled their exposure to SVT or acquired risk factors for venous thrombosis more accurately than controls. This would have led to an overestimation of the true risk estimates. However, a previous cohort study, in which SVT was confirmed with objective techniques, showed the risk of venous thrombosis to be strongly increased (odds ratio, 10.2; 95% CI, 2.0-51.6) in the first 6 months after SVT.[13] In addition, we also found up to 45-fold increased risks of pulmonary embolism, making large-scale misclassification improbable. Finally, we did not have information on the date of SVT. For this reason, it was not possible to calculate risk estimates for different time frames.

In summary, our study showed that individuals with previous SVT and an acquired thrombotic risk factor had a markedly increased risk of venous thrombosis. If confirmed, these findings have important implications for future venous thrombosis prevention strategies.

Table 5. Effect of female hormonal risk factors with SVT on the risk of VT

		Patients, n (%)	Controls, n (%)	DVT only OR (95% CI)	DVT with PE OR (95% CI)	PE only OR (95% CI)
SVT history	**Reproductive risk factor**					
Negative	No	857 (37)	2177 (70)	Reference	Reference	Reference
Negative	Yes	1212 (53)	843 (27)	6.1 (5.1-7.2)	6.9 (4.6-10.2)	3.4 (2.8-4.1)
Positive	No	124 (5)	72 (2)	5.2 (3.7-7.3)	4.7 (2.4-9.2)	2.4 (1.6-3.7)
Positive	Yes	128 (5)	12 (1)	40.1 (21.4-75.2)	55.0 (24.1-125.2)	21.0 (10.7-41.3)
SVT history	**OC use**					
Negative	No	416 (33)	1046 (44)	Reference	Reference	Reference
Negative	Yes	902 (57)	642 (54)	4.4 (3.6-5.4)	7.1 (4.1-12.5)	3.5 (2.7-4.5)
Positive	No	41 (3)	18 (1)	5.1 (2.5-10.5)	12.5 (3.6-43.3)	4.3 (1.9-10.0)
Positive	Yes	86 (7)	5 (1)	46.8 (16.5-133.0)	100.4 (24.2-416.0)	33.2 (10.9-101.5)
SVT history	**HT use**					
Negative	No	706 (81)	1264 (91)	Reference	Reference	Reference
Negative	Yes	41 (6)	50 (4)	1.7 (1.0-3.1)	2.0 (0.7-5.7)	0.8 (0.4-1.9)
Positive	No	108 (12)	58 (4)	3.9 (2.6-5.9)	3.1 (1.4-7.0)	2.2 (1.3-3.7)
Positive	Yes	12 (1)	3 (1)	8.9 (2.3-34.9)	NA	3.2 (0.5-19.8)
SVT history	**Pregnancy**					
Negative	No	1171 (81)	1607 (94)	Reference	Reference	Reference
Negative	Yes	147 (10)	81 (4)	2.4 (1.8-3.4)	1.3 (0.5-3.4)	2.6 (1.8-3.7)
Positive	No	119 (8)	23 (2)	5.8 (3.4-9.8)	7.4 (3.2-17.1)	4.8 (2.6-8.8)
Positive	Yes	8 (1)	0	NA	NA	NA

All ORs for SVT alone and SVT combined with a reproductive risk factor were adjusted for age, BMI, smoking, malignancy, and family history of VT. The overall OR, and the ORs for OC and HT were adjusted for age, BMI, smoking, and family history of VT. The OR for pregnancy was adjusted for age.

DVT, deep vein thrombosis; HT, postmenopausal hormone therapy; OR, odds ratio; PE, pulmonary embolism; VE, venous thrombosis.

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Authorship

Contribution: R.E.J.R. performed the statistical analyses and drafted the manuscript; W.M.L. designed the analyses and revised the manuscript; A.v.H.V. and F.M.H. revised the manuscript; F.R.R. was responsible for the MEGA study concept and design and revision of the manuscript; and S.C.C. designed the analyses and revised the manuscript.

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