THROMBOSIS AND HEMOSTASIS

Factors that predict thrombosis in relatives of patients with venous thromboembolism

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Key Points

- Unprovoked venous thromboembolism (VTE) and VTE at young age are independent predictors of VTE in patient relatives.
- Factor V Leiden or the prothrombin 20210A gene variant in patients with VTE was not an independent predictor of VTE in patient relatives.

When counseling first-degree relatives of patients with venous thromboembolism (VTE), it is important to know whether factors other than thrombophilia influence their risk for thrombosis. We assessed the risk for VTE in 915 first-degree relatives of patients with provoked VTE, compared this with the risk in 1752 first-degree relatives of patients with unprovoked VTE, and then combined data from the 2 groups of relatives to identify predictors of thrombosis. There had been 123 VTEs in 2617 first-degree relatives (0.12 per 100 person-years). The risk for VTE in first-degree relatives was higher if the index cases had an unprovoked compared with a provoked VTE (odds ratio [OR], 2.38; 95% confidence interval [CI], 1.43-3.85), if the index case was younger (OR, 0.97 per year older; 95% CI, 0.96-0.99), and if an additional family member had VTE (OR, 2.71; 95% CI, 2.22-3.31). Among first-degree relatives of an index case with factor V Leiden or the prothrombin 20210A gene variant, the presence of these abnormalities also predicted thrombosis (OR, 4.42; 95% CI, 1.35-14.38). We conclude that thrombosis at a young age and unprovoked VTE predict VTE in first-degree relatives, and that the influence of these 2 factors is additive. (*Blood*. 2014;124(13):2124-2130)

Introduction

Venous thromboembolism (VTE) is a multifactorial disease caused by hereditary and acquired risk factors.[1-3] Because there is often a hereditary component to the occurrence of VTE, thrombosis occurs more often in the first-degree relatives (ie, parents, siblings, children) of patients with VTE than in the general population.[4-9] The increased risk for thrombosis in relatives is incompletely explained by the presence of known thrombophilias, as the risk for thrombosis in first-degree relatives is increased even if patients do not have a detectable defect.[8,9]

We previously showed that the risk for thrombosis in first-degree relatives of patients with a first unprovoked VTE tends to be higher if the patient had factor V Leiden or the prothrombin 20210A gene variant compared with neither abnormality.[9] However, a more striking finding was that relatives of younger index cases (<45 years) had a much higher risk for thrombosis than relatives of older index cases. We suspect that patients who have unprovoked VTE at a young age often have undetected hereditary thrombophilias and that these defects increase the risk for thrombosis in their relatives.

The risk for thrombosis is uncertain in relatives of patients with provoked VTE (eg, recent surgery or cancer). Hereditary thrombophilias are associated with provoked VTE, but less commonly than with unprovoked VTE.[10-12] Therefore, it is reasonable to suspect that the risk for thrombosis is lower in first-degree relatives of patients with provoked than those with unprovoked VTE. To test this hypothesis, we assessed the risk for thrombosis in first-degree relatives of patients with provoked VTE in the current study and compared that risk with the risk we previously observed in the first-degree relatives of patients with unprovoked VTE. We also wanted to determine whether, similar to in first-degree relatives of patients with unprovoked VTE,[9] there was a higher risk for thrombosis in family members of patients who had provoked VTE at a young age. We then combined individual patient data from the current and previous study[9] to increase our ability to identify characteristics of patients and first-degree relatives that predicted the risk for thrombosis in relatives. This information is important for counseling of first-degree relatives of patients with thrombosis.

Methods

Study design and population

Using a cross-sectional design and predefined criteria (see following), we determined whether there was a history of previous VTE in the first-degree

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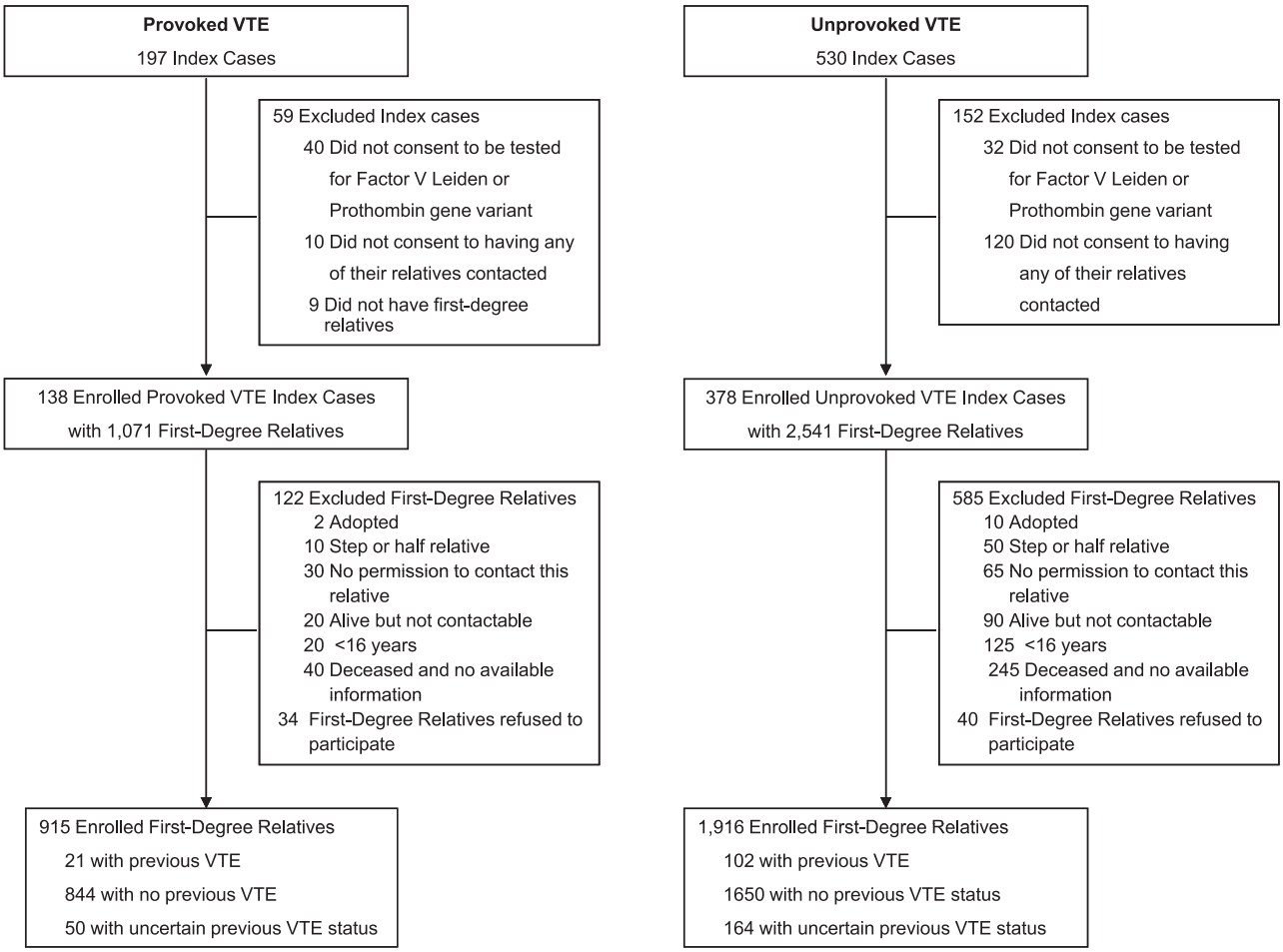

Figure 1. Enrolled index cases and first-degree relatives.

relatives of consecutive patients (index cases) with a first episode of provoked symptomatic proximal deep vein thrombosis or pulmonary embolism. Index cases were enrolled prospectively at 6 university hospitals (5 in Canada and 1 in France) when they were diagnosed with a first episode of acute symptomatic VTE. Index cases had to satisfy all of the following criteria: objectively confirmed proximal deep vein thrombosis (ie, ultrasonography) or pulmonary embolism (ie, lung scanning),[13] willingness to provide blood for testing for factor V Leiden and the prothrombin 20210A gene variant, have at least a single first-degree relative who could be evaluated for previous VTE, and willingness to provide written informed consent to participate in the study and to allow at least 1 of their first-degree relatives to be approached for the study. For thrombosis to be considered provoked, it had to have occurred either within 3 months of having major surgery, major leg trauma, or immobilization (confined to bed for at least 3 consecutive days) or in association with an active malignancy (ie, within the past 2 years).[9] Thrombosis that occurred in the absence of these risk factors was considered unprovoked.

First-degree relatives were eligible as study subjects if they were a biological child, full sibling, or biological parent of an index case and were at least 16 years of age, and if they provided informed consent. First-degree relatives who were dead could be included as study subjects provided the index case agreed and information about previous VTE was available. Research ethic boards of Brest Hospital Center (France) and Henderson General Hospital, McMaster University (Hamilton, ON, Canada) approved the study.

Previous VTE in first-degree relatives

Using a previously described algorithm,[9] first-degree relatives were classified as "have had VTE" if they satisfied either of the following 2 criteria: First, results of diagnostic testing were available that documented previous deep vein thrombosis (including thrombosis confined to the distal deep veins) or pulmonary embolism;[13] and second, the relatives had, in addition to a history of symptoms suggestive of VTE, at least 1 of the following[14]: a history of having been treated with anticoagulant therapy for at least 2 months without another indication,[14] a current ultrasound examination that showed that the proximal deep veins were not fully compressible or that there was reflux in a popliteal vein,[15] or current symptoms and signs suggestive of the postthrombotic syndrome (defined as a score of 5 or higher on the Villalta scale).[16] Relatives were classified as "have not had VTE" if they satisfied all of the following criteria: no known or suspected previous diagnosis of VTE, no unexplained anticoagulation in the past, and not currently having symptoms or signs suggestive of the postthrombotic syndrome (ie, had a score lower than 5 on the Villalta scale). Relatives were classified as "uncertain for previous VTE" if they did not satisfy the criteria for either previous or no previous VTE.

Factor V Leiden and the prothrombin 20210A gene variant

After first-degree relatives had completed assessments for previous VTE, their index cases were categorized as positive for factor V Leiden or the prothrombin 20210A gene variant or negative for both.[9] Personnel who were unaware of the index case's family history of VTE or the participant's past history of VTE performed these assays in a central laboratory in either France or Canada.

Statistical methods

The number of first-degree relatives of index cases with a provoked VTE who needed to be studied was based on 80% power to detect a 50% lower prevalence of thrombosis in relatives of patients with provoked compared

Table 1. Characteristics of index cases and relatives according to whether index case had provoked or unprovoked VTE

Characteristics	Total	Index case had provoked VTE			Index case had unprovoked VTE			*P*‡
		Subtotal	FVL or PGM	No FVL and no PGM	Subtotal	FVL or PGM	No FVL and no PGM	
Index cases, n	507	138	20	118	369	105	264	
Female, n (%)	248 (49)	63 (46)	11 (17)	52 (82)	185 (50)	50 (48)	135 (51)	.37
Age at diagnosis, mean (SD)	58.8 (17.7)	64.0 (16.2)	61.0 (17.9)	64.5 (15.9)	56.8 (17.9)	53.0 (18.1)	58.3 (17.6)	<.001
Number of FDR per index case, mean (SD)	6.9 (3.0)	7.4 (3.0)	7.3 (2.9)	7.6 (3.1)	6.7 (3.1)	6.5 (2.5)	6.8 (3·3)	.04
Number of included FDR per index case, mean (SD)	5.6 (2.9)	6.7 (2.9)	6.7 (2.8)	6.6 (3.5)	4.8 (2.8)	4.8 (2.6)	4.8 (2.8)	.001
Pulmonary embolism, n (%)*	278 (55)	86 (62)	11 (55)	75 (64)	192 (52)	51 (49)	141 (53)	.04
Provoking risk factor, n	—	138	20	118	—	—	—	
Surgery, n (%)	—	39 (28)	5 (25)	34 (29)	—	—	—	
Trauma, n (%)	—	13 (9)	4 20)	9 (7)	—	—	—	
Immobilization, n (%)	—	44 (32)	3 (15)	41 (35)	—	—	—	
Cancer, n (%)	—	42 (30)	8 (40)	34 (29)	—	—	—	
Thrombophilia, n (%)	125 (25)	20 (15)	20	—	105 (29)	105	—	.001
FVL heterozygote, n (%)	80 (64)	—	12 (60)	—	—	68 (65)	—	
FVL homozygote, n (%)	4 (3)	—	1 (5)	—	—	3 (3)	—	
PGM heterozygote, n (%)	35 (28)	—	7 (35)	—	—	28 (27)	—	
PGM homozygote, n (%)	1 (1)	—	—	—	—	1 (1)	—	
FVL heterozygote and PGM heterozygote, n (%)	4 (3)	—	—	—	—	4 (4)	—	
FVL homozygote and PGM heterozygote, n (%)	1 (1)	—	—	—	—	1 (1)	—	
FDR, n	2617	865	123	742	1752	502	1250	
Female, n (%)	1323 (51)	442 (51)	59 (48)	383 (52)	881 (50)	256 (51)	625 (50)	.7
Alive, n (%)	1819 (70)	591 (68)	86 (70)	505 (68)	1228 (70)	372 (74)	856 (68)	.36
Age, mean (SD)†	55.6 (18.2)	57.5 (18.3)	56.0 (18.5)	57.7 (18.3)	54.9 (18.1)	54.4 (18.1)	54.7 (18.1)	<.001
Relationship to the index case								
Parent, n (%)	773 (30)	225 (26)	31 (25)	194 (26)	549 (31)	162 (32)	387 (31)	.02
Sibling, n (%)	1039 (40)	362 (42)	50 (41)	312 (42)	677 (39)	195 (39)	482 (39)	
Child, n (%)	804 (30)	278 (32)	42 (34)	236 (32)	526 (30)	145 (29)	381 (31)	

FDR, first-degree relatives; FVL, factor V Leiden; PGM, prothrombin 20210A gene variant; VTE, venous thromboembolism; SD, standard deviation.

*Presentation of VTE; all patients with confirmed symptomatic pulmonary embolism are included, whether or not they were also diagnosed with deep vein thrombosis.

†Age at enrolment was not available for 101 relatives, mostly because these persons were dead (information obtained from relatives). For all analyses, the age of these relatives was assumed to be the same as the average age of other enrolled relatives in the corresponding category as follows: 49 years for alive men with VTE, 47 years for alive women with VTE, 47 years for alive men without VTE, 49 years for alive women without VTE, 62 years for deceased men without VTE, 70 years for deceased women without VTE, 75 years for deceased men with VTE, and 59 years for deceased women with VTE.

‡*P* value for the comparisons of all FDR of index cases who had provoked VTE with all FDR of index cases who had unprovoked VTE.

with unprovoked VTE,[10-12] while accepting a 2-sided α error of 0.025, assuming a prevalence of previous thrombosis of 5.7% in the 1752 relatives of patients with unprovoked VTE.[9] This yielded a sample size of 875 for the number of relatives of patients with provoked VTE who needed to be evaluated (including those classified as "uncertain for previous VTE").

The average annual incidence of VTE was calculated by dividing the number of first episodes of VTE by the total number of years of observation (expressed as events per 100 person-years). For each study participant, the period of observation was from 16 years of age until their age at the time of the first VTE, death, or when they were assessed at enrolment (whichever occurred latest). The influence of the index case's characteristics (factor V Leiden or prothrombin 20210A gene variant vs neither, age at diagnosis, female vs male, deep vein thrombosis vs pulmonary embolism) and the first-degree relative's characteristics (age during the observation period [assessed as a time-dependent variable], female vs male, parent vs sibling vs child, dead vs alive when assessed) on the risk for VTE in the first-degree relatives was investigated using a logistic regression. If the study subject had more than 1 first-degree relative with a history of VTE (ie, other than the index case), we introduced a random intercept to account for the clustering effect within families (intrafamily correlation) into a generalized linear mixed model.[17] Associations between the characteristics of the index case or the first-degree relative, and the risk for thrombosis in the first-degree relative, were assessed as follows: first, single characteristics were assessed using univariable analysis, and second, a multivariable model was fitted that contained only those characteristics associated with a significance level of $P < .1$ in the univariable analysis.[18] Statistical analyses were performed using SPSS software (version 20.0; IBM Corporation, Armonk, NY) with the exception of the random coefficient logistic modeling, which was done using SAS PROC GLIMMIX (version 9.1; SAS, Inc., Cary, NC).

Comparison with first-degree relatives of patients with unprovoked VTE and analysis of combined data from the 2 groups of relatives

To compare findings and combine individual patient data, we used the same study design, definitions of VTE (proximal deep vein thrombosis alone and pulmonary embolism; provoked and unprovoked thrombosis), and statistical methods in the current study as we used in our previous study that assessed VTE in first-degree relatives of patients with a first unprovoked VTE.[9]

Results

Between January 2006 and January 2012, 197 patients with a provoked VTE were assessed, of whom 40 did not consent to be tested for factor V Leiden and the prothrombin 20210A gene variant, 9 did not have any first-degree relatives, and 10 did not consent to having their relatives contacted (Figure 1). The remaining 138 index cases with provoked VTE had 915 first-degree relatives who were enrolled (Figure 1). Among these 915 relatives, the assessment of previous

Table 2. VTE in relatives according to if the index case had factor V Leiden or the prothrombin 20210A gene variant

Findings in relatives	Total	No FVL and no PGM in index cases	Any FVL or PGM in index cases
Index cases had provoked VTE, n	865	742	123
Person-years of observation, n	36 511	31 475	5 036
Previous VTE, n	21*	19	2
Incidence per 100 person-years (95% CI)	0.06 (0.04-0.09)	0.06 (0.04-0.09)	0.04 (0.01-0.15)
Unadjusted odds ratio (95% CI)	—	Reference	0.63 (0.15-2.74)
Adjusted odds ratio (95% CI)†	—	Reference	0.61(0.14-2.66)
Index cases had unprovoked VTE, n	1 752	1 250	502
Person-years of observation, n	68 066	48 866	19 200
Previous VTE, n	102‡	62	40
Incidence per 100 person-years (95% CI)	0.15 (0.12-0.18)	0.13 (0.10–0.16)	0.21 (0.15-0.28)
Unadjusted odds ratio (95% CI)	—	Reference	1.68 (1.09-2.59)
Adjusted odds ratio (95% CI)†	—	Reference	1.48 (0.94-2.33)
All index cases, n	2 617	1 992	625
Person-years of observation, n	104 577	80 341	24 236
Previous VTE, n	123	81	42
Incidence per 100 person-years (95% CI)	0.12 (0.10-0.14)	0.10 (0.08-0.12)	0.17 (0.13-0.23)
Unadjusted odds ratio (95% CI)	—	Reference	1.70 (1.16-2.50)
Adjusted odds ratio (95% CI)†	—	Reference	1.34 (0.89-2.01)

CI, confidence interval; FVL, factor V Leiden; PGM, prothrombin 20210A gene variant; VTE, venous thromboembolism.

*Of the 21 episodes of VTE in first-degree relatives of index cases with provoked VTE, 2 were unprovoked, 3 were associated with cancer, 9 were provoked by major reversible risk factors, 0 were provoked by minor reversible risk factors, and risk factors were uncertain in 7.

†Adjusted for intrafamily clustering, age of index cases, age of first-degree relatives during the period of observation, sex of first-degree relatives, and whether the first-degree relatives were dead or alive at enrolment.

‡Of the 102 episodes of VTE in first-degree relatives of index cases with unprovoked VTE, 21 were unprovoked, 5 were associated with cancer, 36 were provoked by major reversible risk factors (ie, recent surgery, plaster cast immobilization of the leg or immobilization for more than 72 hours), 20 were provoked by minor reversible risk factors (ie, air travel, pregnancy, or estrogen therapy), and risk factors were uncertain in 20.

VTE was uncertain in 50 (Figure 1). Therefore, analyses included 865 first-degree relatives who could be categorized as either "have had VTE" or "have not had VTE."

First-degree relatives of patients with provoked VTE

Age of the index case. There was an inverse relationship between the age of index cases and the risk for VTE in family members. For each year that the index case was younger, the incidence of VTE increased by 3.0% in the first-degree relatives (corresponding to an adjusted OR of 0.97 per year that the index case was older [95% CI, 0.96-0.999; $P = .04$]). When the age of index cases was divided into quartiles, the incidence of VTE was almost 5 times higher in the first-degree relatives of index cases in the youngest (index cases < 47 years) compared with the oldest (index cases > 72 years) quartile (adjusted OR, 4.97; 95% CI, 1.24-19.99; $P = .024$).

Factor V Leiden or the prothrombin 20210A gene variant in the index cases. Among the 138 index cases with provoked VTE, 20 (14.5%) had factor V Leiden, the prothrombin 20210A gene variant, or both abnormalities, and 118 (85.5%) had neither abnormality (Table 1). The 20 index cases with 1 or both abnormalities had 123 first-degree relatives, and among these individuals, there were 2 episodes of VTE, corresponding to an incidence of 0.04 events per 100 person-years (95% CI, 0.01-0.15 events) (Table 2). The 118 index cases with neither abnormality had 742 first-degree relatives; among these, there were 19 episodes of VTE, corresponding to an

Table 3. Predictors of VTE in all first-degree relatives

	Univariable (each variable separately)		Multivariable (only variables with $P < .1$ in the univariable model)	
Characteristic	**Odds ratio**	***P***	**Odds ratio**	***P***
Index case				
Unprovoked vs provoked *	2.50 (1.54-4.00)	<.001	2.38 (1.43-3.85)	.001
FVL and/or PGM vs neither	1.70 (1.16-2.50)	.007	1.34 (0.89-2.01)	.16
Age at diagnosis (per year)†	0.98 (0.97-0.99)	<.001	0.97 (0.96-0.99)	<.001
Female vs male	0.96 (0.67-1.38)	.81		
Pulmonary embolism vs deep vein thrombosis	0.91 (0.63-1.31)	.61		
First-degree relatives				
Female vs male	1.62 (1.12-2.35)	.011	1.37 (0.94-2.02)	.11
Age (per year)	1.04 (1.03-1.05)	<.001	1.06 (1.04-1.07)	<.001
Relationship to index case		<.001		.33
Parent	4.76 (2.58-8.76)	<.001	0.59 (0.18-1.90)	.37
Sibling	3.37 (1.81-6.16)	<.001	0.94 (0.43-2.10)	.89
Child	Reference		Reference	
Dead vs alive	0.69 (0.45-1.06)	.09	0.44 (0.28-0.72)	.001

CI, confidence interval; DVT, deep vein thrombosis; FVL, factor V Leiden; PE, pulmonary embolism; PGM, prothrombin 20210A gene variant; VTE, venous thromboembolism.

*For provoked vs unprovoked: univariable odds ratio, 0.40 (95% CI, 0.25-0.65); multivariable odds ratio, 0.42 (95% CI, 0.26-0.70).

†When age was divided into quartiles with the fourth quartile (>72 years) as the reference, the adjusted odds ratio for VTE was 1.40 (95% CI, 0.81-2.41; $P = .22$) in the third quartile (62-72 years), 1.47 (95% CI, 0.83-2.60; $P = .18$) in the second quartile (48-61 years), and 3.49 (95% CI, 1.98-6.14; $P < .001$) in the first quartile (<47 years).

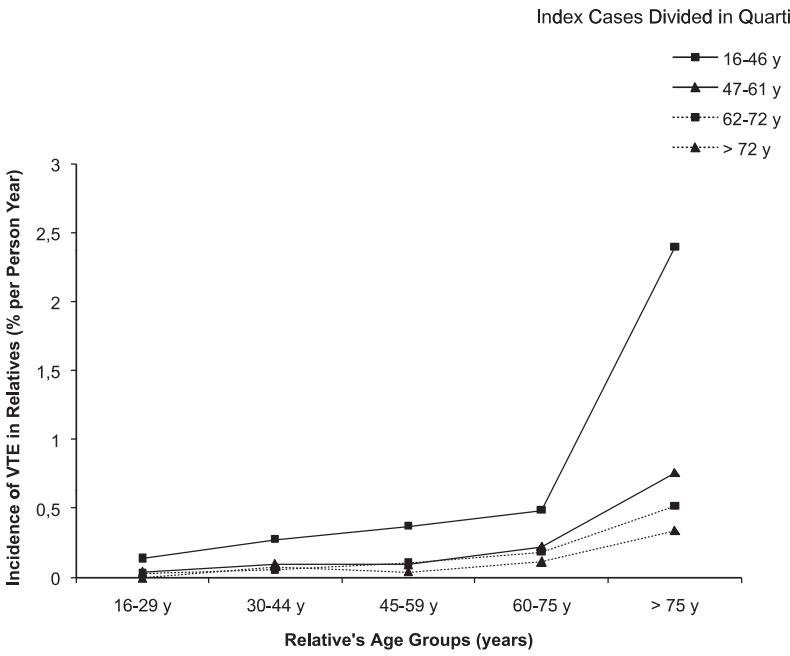

Figure 2. Incidence of VTE in all relatives according to age of index cases.

incidence of 0.06 events per 100 person-years (95% CI, 0.04-0.09 events) (Table 2). The adjusted OR for VTE in the relatives of index cases with 1 or both abnormalities compared with the relatives of index cases with neither abnormality was 0.61 (95% CI, 0.14-2.66) (Table 2).

Whether first-degree relatives had factor V Leiden or the prothrombin 20210A gene variant when these abnormalities were present in their index case. The 20 index cases with provoked VTE who had factor V Leiden, the prothrombin 20210A gene variant, or both abnormalities had 60 relatives who were tested for the same abnormality as in the index case. One of the 31 relatives who had the same abnormality as their index case had a history of VTE, but there were no episodes of VTE in the 29 relatives who did not have the same abnormality as their index case (supplemental Table 1).

Comparisons of the 2 groups of first-degree relatives

The incidence of VTE in relatives of index cases with provoked VTE was lower than in relatives of index cases with unprovoked VTE (adjusted OR, 0.42; 95% CI, 0.26-0.70) (Tables 2 and 3).

Analysis of combined data from the 2 groups of first-degree relatives

Index case characteristics and risk for thrombosis in first-degree relatives. In multivariable analyses, both unprovoked vs provoked VTE in the index case (adjusted OR, 2.38; 95% CI, 1.43-3.85) and VTE at a younger age in the index case (adjusted OR, 0.97 per year older; 95% CI, 0.96-0.99 per year older) were independent predictors of the risk for thrombosis in the patient's first-degree relatives (Table 3; Figure 2). Presence of factor V Leiden or prothrombin 20210A gene variant in index cases was associated with a higher risk for VTE in first-degree relatives in univariable analysis, but this association was no longer statistically significant in the multivariable analysis (Table 3). Sex of the index case, and whether the index event was a deep vein thrombosis or a pulmonary embolism, were not predictive of thrombosis in the index case's relatives.

Influence of number of other first-degree relatives with thrombosis. Among the 507 index cases, 405 (120 provoked; 285 unprovoked) had no other first-degree relative with a history of VTE, 82 (15 provoked; 67 unprovoked) had 1 other first-degree relative with VTE, 19 (3 provoked; 16 unprovoked) had 2 other first-degree relatives with VTE, and 1 (unprovoked) had 3 other first-degree relatives with VTE (Table 4). The risk for VTE was higher if, in addition to the index case, study participants had another first-degree relative (ie, 2 or more relatives vs 1 relative) with a history of VTE (adjusted OR, 2.71; 95% CI, 2.22-3.31) (Table 4). The increase in the risk for VTE associated with having 2 or more first-degree relatives with VTE, as opposed to just the index case, did not appear to differ according to whether the index case had provoked (adjusted OR,

Table 4. Risk of VTE according to the number with thromboses in the family

Number with VTE in the family*	Number of families, n	Number of included FDR, n	Size of families, mean (SD)	Annual incidence of VTE in FDR, percentage 100 person-years (95% CI)	Adjusted OR, estimate (95% CI)†	*P*
1	405	1998	7.8 (3.0)	0.41 (0.37-0.45)	Reference	<.001
2	82	462	8.1 (3.3)	0.79 (0.68-0.92)	2.47 (1.98-3.09)	<.001
3	19	145	9.7 (3.1)	0.88 (0.67-1.13)	3.54 (2.49-5.04)	<.001
4	1	12	15	0.75 (0.18-1.60)	5.17 (1.55-17.28)	<.001
≥2	102	619	8.5 (3.3)	0.81 (0.70-0.91)	2.71 (2.22-3.31)	<.001

Includes the families of index cases with provoked VTE (n = 138) and unprovoked VTE (n = 369).
CI, confidence interval; FDR, first-degree relatives; OR, odds ratio; SD, standard deviation; VTE, venous thromboembolism.
*Includes the index case; therefore, all families had at least a single person with VTE.
†Adjusted for age during the observation period and the number of members in each family.

2.78; 95% CI, 1.79-4.33) or unprovoked (adjusted OR, 2.53; 95% CI, 2.02-3.18) VTE, had factor V Leiden or prothrombin 20210A gene variant (adjusted OR, 2.73; 95% CI, 1.89-3.94), or did not have 1 or both of these abnormalities (OR, 2.68; 95% CI, 2.11-3.41).

Influence of whether relatives had thrombophilia present in their index case

The prevalence of factor V Leiden, the prothrombin 20210A gene variant, or both abnormalities was higher in index cases of unprovoked compared with provoked VTE (28.4% vs 14.5%; $P < .001$) (Table 1). A total of 125 index cases (20 provoked and 105 unprovoked) had 1 or both abnormalities, and among their first-degree relatives tested for the same abnormality, that abnormality was present in 149 and absent in 136 (supplemental Table 1). VTE occurred more often in relatives who had the same abnormality as their index case compared with those who did not have the abnormality that was present in their index case (adjusted OR, 4.42; 95% CI, 1.35-14.38).

Discussion

First, we found that the risk for VTE in the first-degree relatives of patients with a provoked VTE is less than half the risk in first-degree relatives of patients with unprovoked VTE. Second, we found that thrombosis at a younger age was associated with a higher risk for VTE in patients' first-degree relatives compared with thrombosis that occurred at an older age: the risk for VTE in a patient's first-degree relatives was about 3 times as high if thrombosis occurred before 45 years compared with after 72 years. The influence of these 2 factors on the risk for VTE in first-degree relatives was additive and occurred independent of the presence of factor V Leiden or the prothrombin 20210A gene in index cases. Third, the risk for thrombosis in first-degree relatives was higher if, in addition to the index case, VTE had occurred in other family members, with more than a doubling with 1 additional and more than a tripling with 2 additional effected relatives. Last, as is well recognized, if the index case had factor V Leiden or the prothrombin 20210A gene, the risk for thrombosis in first-degree relatives was markedly influenced by whether they had the same mutation.[5-9]

We are not aware of previous studies that compared the risk for VTE between first-degree relatives of patients with provoked vs unprovoked VTE. We previously reported that unprovoked VTE at a young age is associated with a heightened risk for VTE in patient's relatives.[9] We now show that this is also true for the first-degree relatives of patients with provoked VTE at a young age. Consistent with our analyses, the Swedish Multigenerational Registry reported a higher risk for VTE in siblings of younger compared with older patients with a spectrum of VTE types, and that the risk for VTE also increased with the number of family members with thrombosis.[19]

The strengths of our study include the prospective enrolment of unselected cases of provoked and unprovoked VTE, use of a standardized approach to determine whether first-degree relatives had a history of VTE, adjustment for potential confounding factors (eg, age of relatives during the observation period and within-family clustering), and blinding of assessors to first-degree relatives' or index cases' factor V Leiden and prothrombin 20210A gene variant status.[20] Limitations of our study include that index cases were not evaluated for hereditary thrombophilias other than factor V Leiden and the prothrombin G20210A gene variant (eg, deficiencies of protein C, protein S, and antithrombin); that follow-up of first-degree relatives was retrospective rather than prospective, which increases the potential for misclassification of VTE events and the occurrence of survivor bias; and that we were unable to adjust for factors that may vary over time, such as obesity. A sensitivity analysis in which all "uncertain for VTE" first-degree relatives of both provoked and unprovoked index cases were assumed to either "have had VTE" or "not have had VTE" had little effect on the comparison of VTE risk between the first-degree relatives of provoked vs unprovoked index cases (data not shown). It is also possible that inclusion of estrogen-associated VTE among the unprovoked index cases could have diluted the comparison of VTE risk between first-degree relatives of unprovoked vs provoked cases. We were unable to assess this directly, but we think this is unlikely because findings for this comparison in the relatives of younger women were similar to those for the overall study (data not shown).

The findings of this study have potentially important clinical and pathophysiological implications. First, all patients with VTE, but particularly those with unprovoked VTE, unprovoked or provoked VTE at a young age, or a family history of VTE, should inform their first-degree relatives that they have a heightened risk for thrombosis. Relatives can then remind healthcare providers that they should receive VTE prophylaxis when they are in high-risk situations (eg, after surgery), and they can factor this heightened risk into decision making around the use of estrogens, which will further increase their risk for thrombosis.[21] Second, our findings support that known and unknown hereditary thrombophilias contribute to both provoked and unprovoked VTE, particularly in younger patients and in those with unprovoked VTE and a family history of thrombosis.

In conclusion, the risk for VTE in the first-degree relatives of patients with a first VTE is strongly influenced by whether the VTE was provoked or unprovoked, the patient's age when the VTE occurred, and the number of relatives who have had thrombosis. The risk for VTE in first-degree relatives is about twice as high if the index case had an unprovoked compared with a provoked VTE, is about 3 times as high if the index case had VTE before about 50 years compared with later in life, and is at least twice as high if 2 rather than 1 family members have had VTE. This information compliments the results of thrombophilia testing when counseling family members about their risk for thrombosis.

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Authorship

Contribution: F.C. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; F.C. and C.K. conceived and designed the study; F.C., C.K., C.L., C.T., D.M., and J.A.J. analyzed and interpreted the data and drafted the article; F.C., C.L., C.K., J.A.J., S.R.K., J.S.G., P.S.W., J.D.D., C.T., and D.M. provided critical review of intellectual content; F.C., C.L., C.T., S.R.K., J.S.G., P.S.W., J.D.D., D.M., and C.K. provided study material or patients; F.C. and C.K. obtained funding; F.C., C.K., C.L., and D.M. provided administrative, technical, and logistic support; F.C., C.K., J.A.J., and C.T. collected and assembled data; and all authors approved the final manuscript.

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References

1. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation.* 2003; 107(23 Suppl 1):I9-I16.
2. Heit JA, O'Fallon WM, Petterson TM, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med.* 2002; 162(11):1245-1248.
3. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet.* 1999;353(9159):1167-1173.
4. Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. *Arch Intern Med.* 2009;169(6):610-615.
5. Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. *JAMA.* 2009; 301(23):2472-2485.
6. Couturaud F, Kearon C, Leroyer C, et al; Groupe d'Etude de la Thrombose de Bretagne Occidentale (G.E.T.B.O). Incidence of venous thromboembolism in first-degree relatives of patients with venous thromboembolism who have factor V Leiden. *Thromb Haemost.* 2006;96(6): 744-749.
7. van Sluis GL, Söhne M, El Kheir DY, Tanck MW, Gerdes VE, Büller HR. Family history and inherited thrombophilia. *J Thromb Haemost.* 2006; 4(10):2182-2187.
8. Sørensen HT, Riis AH, Diaz LJ, Andersen EW, Baron JA, Andersen PK. Familial risk of venous thromboembolism: a nationwide cohort study. *J Thromb Haemost.* 2011;9(2):320-324.
9. Couturaud F, Leroyer C, Julian JA, et al. Factors that predict risk of thrombosis in relatives of patients with unprovoked venous thromboembolism. *Chest.* 2009;136(6): 1537-1545.
10. Kearon C, Ginsberg JS, Anderson DR, et al; SOFAST Investigators. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. *J Thromb Haemost.* 2004; 2(5):743-749.
11. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med.* 1999; 340(12):901-907.
12. Kearon C, Julian JA, Kovacs MJ, et al; ELATE Investigators. Influence of thrombophilia on risk of recurrent venous thromboembolism while on warfarin: results from a randomized trial. *Blood.* 2008;112(12):4432-4436.
13. Tapson VF. Acute pulmonary embolism. *N Engl J Med.* 2008;358(10):1037-1052.
14. Frezzato M, Tosetto A, Rodeghiero F. Validated questionnaire for the identification of previous personal or familial venous thromboembolism. *Am J Epidemiol.* 1996;143(12):1257-1265.
15. Ginsberg JS, Shin A, Turpie AGG, Hirsh J. Detection of previous proximal venous thrombosis with Doppler ultrasonography and photoplethysmography. *Arch Intern Med.* 1989; 149(10):2255-2257.
16. Villalta S, Prandoni P, Cogo A, et al. The utility of non-invasive tests for detection of previous proximal-vein thrombosis. *Thromb Haemost.* 1995;73(4):592-596.
17. Zou G, Donner A. Confidence interval estimation of the intraclass correlation coefficient for binary outcome data. *Biometrics.* 2004;60(3): 807-811.
18. Hosmer DW, Lemeshow S. *Applied Logistic Regression.* New York: John Wiley & Sons; 1989.
19. Zöller B, Li X, Sundquist J, Sundquist K. Age- and gender-specific familial risks for venous thromboembolism: a nationwide epidemiological study based on hospitalizations in Sweden. *Circulation.* 2011;124(9):1012-1020.
20. Vandenbroucke JP, von Elm E, Altman DG, et al; STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med.* 2007;147(8):W163-94.
21. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ.* 2009;339:b2890.