A lower risk of recurrent venous thrombosis in women compared with men is explained by sex-specific risk factors at time of first venous thrombosis in thrombophilic families

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Why men appear to have an increased risk of recurrent venous thrombosis compared with women is unknown. In a cohort study of families with thrombophilia, lifetime risk of recurrent venous thrombosis was assessed in men and women (n = 816). Adjusted relative risk of recurrence was 1.6 (95% CI, 1.3-2.0) in men compared with women. Women were younger at time of their first event (mean, 34 years vs 44 years; *P* < .001) and at time of recurrence (40 years vs 48 years, *P* < .001). After excluding provoked first and recurrent venous thrombosis, adjusted relative risk was 1.2 (95% CI, 0.8-1.7), although mean age at recurrence was comparable in men and women (50 years vs 49 years, *P* = .595). In women with a hormonal first event, median interval between first event and recurrence was 10.4 years versus 2.7 years in men (*P* < .001). This difference was not observed when only unprovoked events were considered (*P* = .938). The difference in lifetime risk of recurrent venous thrombosis between men and women in thrombophilic families can be explained by a younger age of women at time of first venous thrombosis due to hormonal risk factors, and a longer interval between a provoked first episode of venous thrombosis and recurrence in women. (Blood. 2009;114:2031-2036)

Introduction

Venous thrombosis is a major health problem. Annual incidence of first venous thrombosis ranges from 0.1% to 0.3% in the normal population,[1,2] whereas first recurrence rate is 3% to 5% per year, with a peak within the first 2 years after stopping anticoagulant treatment.[3-5] The duration of anticoagulant treatment after a first episode of venous thrombosis depends on the estimated risk of recurrence. Recent studies showed that men have a 1.6- to 3.6-fold higher risk of recurrent venous thrombosis than women.[6-9] For this reason, some authors proposed to continue anticoagulant treatment in men for a longer time than women.[6,7,9] In the most recent American College of Chest Physicians (ACCP) guideline on antithrombotic therapy for venous thrombotic disease, male sex is considered as a potential clinical predictor for recurrent venous thrombosis, that is, sex could be a factor in deciding which patients should receive prolonged anticoagulant treatment.[10] Although this treatment probably will prevent most recurrences, it is associated with major bleeding in approximately 3% of patients per year.[11-13] Therefore, this finding must be established and needs to be clarified. It is likely to assume a relationship between the risk of venous thrombosis and the hormonal state to explain the difference in risk of recurrent venous thrombosis between men and women. Because thrombophilic subjects are at higher risk of venous thrombosis and reveal venous thrombosis at younger age than the normal population,[14] hormonal effects on the risk of first and recurrent venous thrombosis may be enhanced in these subjects.

We performed a retrospective study in a large series of families with established thrombophilic defects (n = 6079), enabling a long follow-up time, to assess the lifetime risk of recurrent venous thrombosis in men and women and to clarify a possible difference in risk between men and women.

Methods

Data retrieval

We did a posthoc analysis of pooled data from individual subjects who enrolled in 1 of 5 large family cohort studies. These studies were performed by 3 university hospitals to assess the absolute risk of venous thrombosis associated with various thrombophilic defects as previously described.[14-21] Similarities and differences between these studies are described previously.[14] In brief, the first study was a single-center study and contained first-degree relatives (ie, offspring, siblings, and/or parents) of consecutive patients (probands) with documented venous thrombosis and established hereditary deficiencies of either antithrombin, protein C, or protein S.[15,16] As the number of antithrombin deficient probands was small, second-degree relatives (ie, grandparents and/or blood-related uncles or aunts) with a deficient parent were also identified. They were enrolled between April 1999 and July 2004. Three studies were multicenter studies of first-degree relatives of consecutive patients with venous thrombosis or premature atherosclerosis (< 50 years of age) and the presence of either the prothrombin 20210G>A mutation, high levels of factor (F)VIII at repeated measurements, or hyperhomocysteinemia.[17,19] Enrollment started in May 1998 and was completed in July 2004. The fifth study was a multicenter

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study of first-degree relatives of consecutive patients with venous thrombosis and FV Leiden enrolled between May 1995 and July 1998.[20,21] Approval was obtained by the institutional review boards of the 3 participating university hospitals.

Subjects

All relatives, identified by pedigree analysis, were 15 years of age or older and were contacted through the probands. All participants provided written informed consent in accordance with the Declaration of Helsinki. As the objective of the present study was recurrent venous thrombosis, all probands and relatives with venous thrombosis, who were 15 years of age or older, were included without introducing bias. Physicians at the thrombosis outpatient clinics of the participating centers collected detailed information about previous episodes of venous thrombosis, exposure to exogenous risk factors for venous thrombosis, and anticoagulant treatment using a validated questionnaire,[22] and by reviewing medical records. Clinical data were collected before laboratory testing. Probands and relatives were tested for currently known thrombophilic defects, including hereditary antithrombin, protein C, protein S type I and protein S type III deficiency, FV Leiden, prothrombin 20210G>A, elevated levels of factors VIII, IX, XI, and TAFI, and hyperhomocysteinemia. Laboratory tests and definitions of abnormal results have been described in detail elsewhere.[14,15] A first episode of venous thromboembolism was initially treated with (low molecular weight) heparin, followed by vitamin K antagonists for 3 to 6 months. Afterward, thromboprophylaxis was recommended at exposure to exogenous risk factors (ie, surgery, immobilization for more than 7 days, pregnancy, and 6 weeks after delivery). Oral contraceptives and hormonal replacement therapy were strongly discouraged after venous thrombosis had occurred. If subjects were on long-term anticoagulant treatment with vitamin K antagonists at time of enrollment, blood samples were taken after treatment had been interrupted; meanwhile nadroparin was given subcutaneously. Due to the retrospective study design, follow up ended at date of enrollment. Hence, anticoagulant treatment of first and eventual recurrent venous thrombosis was not influenced by the presence or absence of thrombophilic defects, as demonstrated at enrollment.

Definitions

The first episode of venous thrombosis was considered established if proximal deep vein thrombosis was confirmed by compression ultrasound or venography; and pulmonary embolism, by ventilation/perfusion lung scanning, spiral CT scanning, or pulmonary angiography, or when the patient had received full-dose heparin and a vitamin K antagonist for at least 3 months without objective testing at a time when these techniques were not yet available. Superficial phlebitis and isolated calf vein thrombosis were not classified as a thrombotic event. Recurrence was considered established if it was demonstrated by objective techniques at another site than the first event, or at the same site if previously repeated tests showed no residual venous thrombosis. If recurrence of deep vein thrombosis at the same site was suspected, but objective tests were not conclusive, it was diagnosed when the patient revealed pronounced signs and symptoms of recurrence without preceding postthrombotic syndrome, or when pulmonary embolism was objectively demonstrated. If these criteria were not fulfilled, anticoagulant treatment was withheld and the event was not classified as recurrent venous thrombosis. Venous thrombosis (either first or recurrent) was defined as provoked if it had occurred at or within 3 months after exposure to exogenous risk factors, including surgery, trauma, immobilization for more than 7 days, pregnancy, postdelivery period, the use of oral contraceptives or hormonal replacement therapy, or malignancy. In the absence of these risk factors, venous thrombosis was classified as unprovoked. Venous thrombosis was considered associated with hormonal risk factors when women were pregnant, were in the postdelivery period, used oral contraceptives, or were on hormonal replacement therapy at time of or within 3 months before onset of venous thrombosis.

Statistical analysis

The absolute risk of recurrent venous thrombosis was calculated over the period from the end of anticoagulant treatment after the first episode of venous thrombosis until either the date of first recurrence or the end of study. We compared the risk of recurrence between men and women; the risk of unprovoked recurrence after an unprovoked first event between men and women; and the risk of recurrence in women after a first event associated with or without hormonal risk factors at time of the first thrombotic event. To account for age, we also stratified men and women in an age group of 55 years or younger at time of first venous thrombosis, and an age group that was older than 55 years at time of first event. Dichotomizing patients within these age groups has an additional advantage, as most women are postmenopausal at age of 55 years or older.[23] Incidences and 95% confidence intervals (95% CIs) were calculated under the Poisson distribution assumption. Freedom of recurrent venous thrombosis was analyzed by the Kaplan-Meier method. As our study cohort consisted of subjects from thrombophilic families, and consequently were prone to have multiple thrombophilic defects,[14] we adjusted for thrombophilic defects, including antithrombin, protein C or protein S deficiency, factor V Leiden, high factor VIII, and prothrombin 20210G>A. Only 17 relatives with first venous thrombosis had no thrombophilic defect, whereas all probands had at least one thrombophilic defect. This small number precluded an additional sensitivity analysis comparing carriers of thrombophilia with noncarriers.

Continuous variables were expressed as mean values and standard deviations and categoric data, as counts and percentages. Differences between groups were evaluated by the Student *t* test or Mann-Whitney *U* test, depending on the normality of data for continuous data and by Fisher exact test for categoric data. A 2-tailed *P* value of less than .05 indicated statistical significance.

Statistical analyses were performed using SAS software, Version 9.1 (SAS Institute Inc).

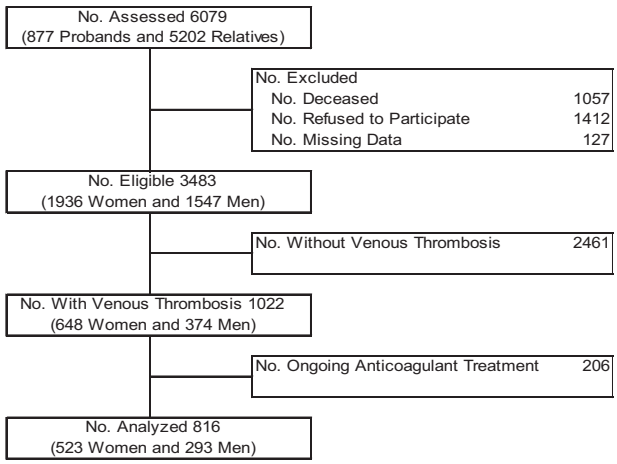

Figure 1. Flow diagram of the study cohort.

Results

Our study cohort contained 877 probands, with a total number of 5202 relatives, who were 15 years of age or older (Figure 1). Of relatives, 1057 were deceased before the start of the study, whereas another 1412 relatives did not participate because of various reasons, including refusal or inability to give informed consent, or residence outside The Netherlands. Another 127 subjects were excluded because of missing data. Of the remaining 3483 subjects, 1022 had experienced a first venous thrombosis. Two-hundred six subjects were not evaluable, because they were still on oral anticoagulant treatment after their first event at date of enrollment. Of these 206 subjects, 101 men had first venous thrombosis at a mean age of 45 years (SD, 16), compared with 33 years (SD, 15) in

Table 1. Characteristics of men and women with a first episode of venous thrombosis

	Women, n = 523	Men, n = 293	*P*
First venous thrombosis			
Mean age at onset, (SD), y	34 (15)	44 (15)	< .001
Unprovoked, no. (%)	133 (25)	217 (74)	< .001
Condition that provoked thrombosis, no. (%)			
Oral contraceptives, no. (%)	114 (22)		
Pregnancy/puerperium, no. (%)	121 (23)		
Surgery, trauma, immobilization, no. (%)	148 (28)	74 (25)	.39
Malignancy, no. (%)	7 (1)	2 (1)	.50
Prevalence thrombophilic defects*			
Antithrombin deficiency, less than 70 IU/dL, no. (%)	22 (4)	11 (4)	.89
Protein C deficiency, less than 65 IU/dL, no. (%)	49 (11)	38 (15)	.14
Protein S deficiency, less than 65 IU/dL, no. (%)	58 (13)	34 (13)	.85
FV Leiden, no. (%)	249 (48)	127 (43)	.26
FVIII more than 150 IU/dL, no. (%)	281 (61)	166 (64)	.39
Prothrombin 20210G>A, no. (%)	88 (17)	48 (17)	.999

*Numbers of women/men tested for antithrombin, protein C, protein S, factor V Leiden, elevated FVIII, and prothrombin 20210G>A were 513/288, 452/254, 461/254, 517/290, 462/258, and 506/281, respectively.

the remaining 105 women ($P < .001$). Unprovoked events occurred in 58 men (57%) compared with 18 women (17%; $P < .001$). Clinical characteristics of 816 evaluable subjects (523 women and 293 men) are shown in Table 1. Women were younger at time of their first event than men (mean age, 34 years vs 44 years; $P < .001$). Of first events, 133 (25%) were unprovoked in women and 217 (74%), in men ($P < .001$); 114 (22% in women) were associated with oral contraceptives or hormonal replacement therapy; 121 (23% in women) were associated with pregnancy or puerperium; and 148 were associated with surgery, trauma, or immobilization in women (28%) versus 74 in men (25%; $P = .39$). Thrombophilic defects were equally divided between men and women.

Venous thrombosis recurred in 337 subjects. Mean age at first recurrence was 42 years (SD, 17); 227 recurrences (67%) were unprovoked. Mean observation period was 6.6 years; total observation time was 5395 years. Women were younger at time of recurrence than men (mean, 40 years vs 48 years; $P < .001$; Table 2). Overall, absolute risk of recurrence was 5.1% per year (95% CI, 4.4-5.8) in women and 9.3% per year (95% CI, 7.8-10.9) in men. Crude relative risk of recurrence was 1.7 (95% CI, 1.4-2.1) in men compared with women. In subjects with unprovoked first venous thrombosis and recurrence, crude relative risk was 1.2 (95% CI, 0.8-1.7), whereas mean age at time of first event (46 years vs 44 years, $P = .38$) and recurrence (49 years vs 50 years, $P = .60$) was comparable in men and women. Adjustments for various thrombophilic defects by stepwise Cox regression did not change outcomes. When we restricted the analysis to only probands, relative risk of recurrent venous thrombosis was 1.6 (95% CI, 1.2-2.1) in men compared with women. In probands with unprovoked first venous thrombosis and recurrence, this risk was 1.1 (95% CI, 0.7-1.6).

In women, crude relative risk of recurrence after first venous thrombosis associated with hormonal risk factors (oral contraceptives, and pregnancy or puerperium) compared with women with nonhormonal first venous thrombosis was 0.6 (95% CI, 0.5-0.9), and adjusted for thrombophilic deficiencies it was 0.7 (95% CI, 0.5-0.97; Table 3). This risk was not altered after we confined the analysis to women who had unprovoked first venous thrombosis compared with women who had first venous thrombosis associated with oral contraceptives (Table 4).

Table 2. Recurrence rates of venous thrombosis in men and women

	Overall venous thrombosis*		Unprovoked venous thrombosis†	
	Women	Men	Women	Men
No. of subjects	523	293	122	207
No. of recurrences	198	139	46	90
Mean age at onset of recurrence, y	40	48‡	49	50§
Observation period, y	3896	1499	615	998
Annual incidence, % (95% CI)	5.1 (4.4-5.8)	9.3 (7.8-10.9)	7.5 (5.5-10.0)	9.0 (7.3-11.1)
Relative risk (95% CI)	Reference	1.7 (1.4-2.1)	Reference	1.2 (0.8-1.7)
Relative risk adjusted for				
Antithrombin deficiency	Reference	1.7 (1.3-2.1)	Reference	1.2 (0.8-1.8)
Protein C deficiency	Reference	1.7 (1.3-2.1)	Reference	1.4 (0.9-2.1)
Protein S deficiency	Reference	1.6 (1.3-2.1)	Reference	1.3 (0.8-2.0)
FV Leiden	Reference	1.7 (1.3-2.1)	Reference	1.2 (0.8-1.7)
FVIII more than 150 IU/dL	Reference	1.6 (1.3-2.0)	Reference	1.2 (0.8-1.7)
Prothrombin 20210G>A	Reference	1.6 (1.3-2.0)	Reference	1.2 (0.8-1.7)

CI indicates confidence interval.
*Overall indicates any first venous thrombosis and any recurrence.
†Unprovoked indicates unprovoked first venous thrombosis and unprovoked recurrence.
‡$P < .001$.
§$P = .60$.

Table 3. Recurrence rates of venous thrombosis in women with a nonhormonal versus hormonal first event

	Nonhormonal first venous thrombosis	Hormonal first venous thrombosis
No. of subjects	273	201
Mean age at onset of first event, y	40	30‡
No. of recurrences*	81	68
Mean age onset recurrent event, y	47	40§
Observation period, y	1604	2074
Annual incidence, % (95% CI)	5.1 (4.0-6.3)	3.3 (2.5-4.2)
Crude relative risk (95% CI)	Reference	0.6 (0.5-0.9)
Adjusted relative risk (95% CI)†	Reference	0.7 (0.5-0.97)

Hormonal event indicates venous thrombosis associated with oral contraception, pregnancy or puerperium, or hormonal replacement therapy.

CI indicates confidence interval.

*Recurrences associated with hormonal risk factors were excluded.

†Adjusted for antithrombin, protein C, and protein S deficiency.

‡$P < .001$

§$P = .003$.

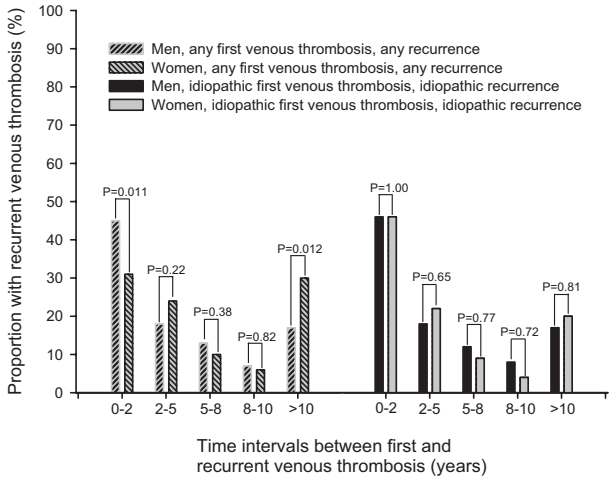

Figure 2. Time intervals between end of anticoagulant treatment for first venous thrombosis and recurrence.

Women revealed recurrence after a longer time period than men ($P = .003$), which was mainly due to hormonal risk factors ($P < .001$). In women with a hormonal first event, median interval between end of anticoagulant treatment for first event and recurrence was 10.4 years versus 2.7 years in men ($P < .001$). This difference between women and men was not observed when only unprovoked events were considered ($P = .94$). After stratifying the time interval between end of anticoagulant treatment and onset of recurrence, men had a higher recurrence rate within the first 2 years than women (45% vs 31%, $P = .011$), whereas 30% of women had a recurrent event more than 10 years after the end of anticoagulant treatment compared with 17% in men ($P = .012$; Figure 2). These differences were not observed when provoked first and recurrent venous thrombotic events were excluded from analysis.

To account for age, we classified women and men aged younger or older than 55 years at onset of first venous thrombosis. In the age group where first events occurred at age 55 years or younger, adjusted relative risk of recurrence was 1.6 (95% CI, 1.3-2.1) in men compared with fertile women, whereas men were older at recurrence than women (mean age, 45 vs 38 years; $P < .001$). In the other age group, comparing postmenopausal women to men, adjusted relative risk was 1.3 (95% CI, 0.7-2.6), whereas mean age at recurrence was comparable (mean age 67 vs 70 years; $P = .35$).

Table 4. Recurrence rates of venous thrombosis in women with an idiopathic first event versus oral contraceptives or hormonal replacement therapy–associated event

	Unprovoked venous thrombosis*	Oral contraceptive venous thrombosis†
No. of subjects	122	109
No. of recurrences†	46	29
Mean age onset recurrent event, y	49	32§
Observation period, y	615	679
Annual incidence, % (95% CI)	7.5 (5.5-10.0)	4.3 (2.9-6.1)
Crude relative risk (95% CI)	Reference	0.6 (0.4-0.96)
Adjusted relative risk (95% CI)‡	Reference	0.6 (0.4-0.9)

CI indicates confidence interval.

*Unprovoked indicates unprovoked first venous thrombosis and unprovoked recurrence.

†Oral contraceptive indicates first venous thrombosis associated with oral contraceptives or hormonal replacement therapy, unprovoked recurrence.

‡Adjusted for antithrombin, protein C, and protein S deficiency.

§$P < .001$.

To account for possible misclassification, as not all events were confirmed by objective techniques because these were not available at the time of event onset, we repeated the analysis in men and women who had first venous thrombosis and recurrence diagnosed with objective techniques. In this analysis, crude relative risk of recurrence was 2.0 (95% CI, 1.5-2.8) in men compared with women, whereas it was 1.0 (95% CI, 0.7-1.6) for unprovoked first and recurrent events.

Discussion

Men had a higher risk of recurrent venous thrombosis than women. They were of older age at onset of first event and had recurrence after a shorter time interval. This finding is in line with other studies that reported on this issue.[6-9] However, no differences in risk of recurrence, age at onset of first and recurrent venous thrombosis, respectively, and time interval between first and recurrent event were demonstrated between men and women when provoked events were excluded from analysis. Therefore, our study shows that the higher risk of recurrence in men is likely due to provoked events rather than an unknown thrombophilic abnormality, as previously suggested.[6,24] Of all first events in women, almost half were associated with oral contraception or pregnancy/puerperium. This explains the younger age of women at onset of first venous thrombosis. Women had recurrences after a longer time interval than men. Of women in whom first venous thrombosis was associated with hormonal risk factors, more than 50% had a recurrence 10.4 years or longer after the end of anticoagulant treatment for the first event, whereas this interval was less than 2.7 years in men. Because oral contraceptives were discouraged and thromboprophylaxis was recommended during puerperium and pregnancy after prior venous thrombosis, the risk of recurrence in women was modified and age became the main determinant of recurrence, thus clarifying the longer interval. Overall, men were older at time of first venous thrombosis and had a 1.7-fold higher risk of recurrence compared with women. A meta-analysis showed a 1.6-fold higher risk of recurrent venous thrombosis in men compared with women, but could not account for age with multivariate analysis.[9] When we excluded provoked events from analysis, the risk of recurrence in men compared with women dropped to 1.2 (95% CI, 0.8-1.7), whereas differences in age at

onset of first venous thrombosis and recurrence, respectively, were no longer observed. Pengo and Prandoni reported a similar relative risk of recurrence in men compared with women (1.21; 95% CI, 0.95-1.55), excluding provoked venous thrombosis.[25] Recurrence rates may be influenced by thromboprophylaxis at exposure to risk factors for venous thrombosis after prior venous thrombosis. Despite guidelines, its dosage and duration vary widely.[26,27] As a consequence, provoked recurrent venous thrombosis is prone to confounding,[28] which we reduced by excluding these events from analysis. When we accounted for age by dividing men and women in an age group of 55 years or younger and an age group older than 55 years at onset of first venous thrombosis, both the relative risk of recurrence and the difference in age at recurrence declined in the latter group. This result provides supportive evidence that the difference in risk of recurrence between men and women is mainly due to hormonal risk factors, as most women are postmenopausal at age of 55 years or older.[23]

The Austrian study that first reported on a higher risk of recurrence in men than women included women who had first venous thrombosis associated with oral contraceptives (39% of the female study population).[6] In an accompanying editorial comment, it was discussed that this study had a potential weakness because men were older than women.[24] In our study, women in whom first venous thrombosis was associated with hormonal risk factors had a 40% decreased risk of recurrence, and were 10 and 7 years younger at time of first event and recurrence, respectively, compared with women in whom first venous thrombosis was not associated with hormonal risk factors. This suggests that the higher risk of recurrence in men compared with women in the Austrian study[6] could be due to oral contraceptive use in younger women with first venous thrombosis.

Our study showed that 31% of women experienced recurrent venous thrombosis more than 10 years after the end of anticoagulant treatment for their first event compared with 17% of men. These women would have been missed in the prospective studies that observed an increased risk of recurrence in men, because of their maximum follow-up time (1.5 to 8 years).[6-8,29-31] Indeed, one prospective study with a maximum follow-up of 10 years (n = 1626) found a relative risk of recurrence that was 1.2 (95% CI, 0.9-1.4),[32] whereas it was 1.3 (95% CI, 1.1-1.6) in the second, retrospective, study with a follow-up time of maximum 25 years (n = 1719).[3]

Some methodological aspects of our study warrant comment. Because the study was performed in thrombophilic families, we cannot exclude that male sex is a risk factor for recurrent venous thrombosis in nonthrombophilic families. However, in a previous study we demonstrated that only subjects with hereditary deficiencies of antithrombin, protein C, or protein S are at increased risk of recurrence.[14] Adjustment for these and other thrombophilic defects did not change our relative risk estimates. Moreover, as thrombophilic defects were equally divided among men and women, it is less likely that relative risk estimates in men compared with women were influenced by the study design. Nevertheless, absolute risk estimates and cumulative recurrence rates in this study cannot be extrapolated to the general population. Absolute risk estimates are also biased because we included probands whose end point was either first or recurrent venous thrombosis. However, as probands were consecutive patients with venous thrombosis, relative risk estimates are not influenced by this study design as being a proband is not related to sex. The retrospective design and the pooling of different studies may be considered as a methodological drawback. Possibly, data of population-based studies, with a long follow-up period (for example studies reported by Heit et al,[3] Prandoni et al,[32] or Lazkovics et al[33]), may find similar results if the analysis would be restricted to women with unprovoked first venous and recurrent thrombosis. Second, referral bias may have been introduced by the setting of university hospitals, but it was probably reduced by testing consecutive patients with thrombosis for thrombophilic defects. Third, we cannot provide detailed information on mortality in our study population. However, an excess of fatal events in relatives with antithrombin, or protein C or protein S deficiency is not likely as these deficiencies were not associated with a reduced life expectancy in previous studies,[34,35] whereas the overall mortality due to recurrent venous thrombosis is low.[36,37] Finally, subjects with clinical suspicion of venous thrombosis, who were treated with heparin and vitamin K antagonists for more than 3 months at a time when objective testing was not available yet, might have overestimated our recurrence rates. However, one should expect a similar effect in men and women. Moreover, our results were not influenced when only objectively confirmed events were considered. Hence, it is less likely that primary outcomes were biased by events that could not be confirmed by objective techniques.

We conclude that the difference in observed lifetime risk of recurrent venous thrombosis between men and women in thrombophilic families can be explained by a younger age of women at time of first venous thrombosis due to hormonal risk factors, and a longer interval between a provoked first episode of venous thrombosis and recurrence in women.

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Authorship

Contribution: S.M., K.H., M.H.P., H.R.B., and J.v.d.M conceived the study concept and design; W.M.L. and N.J.G.M.V. acquired the data and provided administrative, technical, or material support; W.M.L., N.J.G.M.V., M.H.P., and J.v.d.M. analyzed and interpreted the data; W.M.L. drafted the paper; W.M.L., N.J.G.M.V., S.M., K.H., M.H.P., H.R.B., and J.M. critically revised the paper for important intellectual content; W.M.L., N.J.G.M.V., and M.H.P. performed statistical analysis; S.M. and H.R.B. obtained funding; and S.M., K.H., M.H.P., H.R.B., and J.v.d.M. supervised the study. W.M.L. 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.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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