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IN FOCUS

Familial thrombophilia and lifetime risk of venous thrombosis

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Summary *Background*: We started a large multicenter prospective follow-up study to provide reliable risk estimates of venous thrombosis in families with various thrombophilic defects. *Objectives*: This paper describes data collected at study entry on venous events experienced before study inclusion, i.e. the baseline data. *Patients/methods*: All individuals (probands, relatives) registered in nine European thrombosis centers with the factor (F)V Leiden mutation, a deficiency of antithrombin, protein C or protein S, or a combination of these defects, were enrolled between March 1994 and September 1997. As control individuals, partners, friends or acquaintances of the thrombophilic participants were included. Incidence and relative risk of objectively confirmed venous thrombotic events (VTEs) prior to entry were calculated for the relatives with thrombophilia and the controls. *Results*: Of the 846 relatives with thrombophilia (excluding probands), 139 (16%) had experienced a VTE with an incidence of 4.4 per 1000 person years. Of the controls, 15 of the 1212 (1%) controls had experienced a VTE with an incidence of 0.3 per 1000 person years. The risk of venous thrombosis associated with familial thrombophilia was 15.7 (95% CI 9.2–26.8) and remained similar after adjustment for regional and sex-effects (16.4; 95% CI 9.6–28.0). The highest incidence per 1000 person years was found in relatives with combined defects (8.4; 95% CI 5.6–12.2), and the lowest incidence was found in those with the FV Leiden mutation (1.5; 95% CI 0.8–2.6). *Conclusions*: Considerable differences in the lifetime risk of VTE were observed among individuals with different thrombophilia defects.

Keywords: genetic risk factors, thrombophilia, venous thrombosis.

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Introduction

In developed countries, venous thrombosis occurs in 1–2 per 1000 individuals per year [1,2] and commonly manifests as deep vein thrombosis (DVT), with or without pulmonary embolism (PE) [3]. Major complications in the clinical course of DVT are death from PE, development of a disabling post–thrombotic syndrome and recurrences [2,4–6]. Predisposing factors for venous thrombosis can be genetic or acquired, or both, and may lead to a life-long or temporary increase in the tendency to venous thrombosis (thrombophilia) [7]. As the clinical expression varies between individuals who are heterozygous for the same genetic thrombotic defect, as shown within genotypically identical family members [8], venous thrombosis is believed to be a multicausal disease [9,10]. The hypothesis of multicausal pathogenesis is underlined by the finding that the risk of venous thrombosis is higher in families with inherited thrombophilia than in individuals with the same defect without a positive family history [11,12]. This difference probably is the result of interaction within these families of the inherited defect with other genetic or acquired risk factors [11–13]. Several hereditary prothrombotic defects have been identified in the last four decades. The first was antithrombin deficiency, identified in

1965 [14]. Since then, several other hereditary defects have been identified as risk factors for venous thrombosis, such as protein C deficiency, protein S deficiency, factor (F)V Leiden and prothrombin 20210A [15–18].

Rational guidelines for optimal treatment policies in families with inherited thrombophilia are lacking due to few available studies of sufficient size. Therefore, we started a large multicenter prospective follow-up study to determine the natural history of venous thrombosis in family members of symptomatic patients with at least one inherited prothrombotic defect. With these risk estimates guidelines may be inferred for treatment and prevention of venous thrombosis in families with different kinds of inherited thrombophilia. Other endpoints such as arterial thrombotic disease (myocardial infarction [MI], stroke), death from various causes, major haemorrhage and fetal loss were also studied. The European Prospective Cohort on Thrombophilia (EPCOT) study combines data on individuals with familial thrombophilia over a large geographical area of eight European nations and therefore is the largest cohort of individuals with inherited thrombophilia, thus providing reliable risk estimates.

This paper will describe the data collected at study entry on the occurence of venous thrombosis in the EPCOT participants prior to entry, i.e. the baseline data on the history of venous thrombosis.

Study design

Participants and methods

A total of nine centers (Barcelona, Bologna, Frankfurt, Glasgow, Leiden, Malmö, Paris, Sheffield and Vienna) with long-standing interest in thrombophilia research from eight countries participated in the EPCOT-study. We included patients referred to these specialist clinics to create a large cohort of individuals with deficiencies in natural anticoagulants, which are rare, and to address the risk of venous thrombosis found in thrombophilic families compared with patients with a similar thrombophilia defect without a family history. Each center enrolled all registered probands (first of a family in whom thrombophilia was detected) with a deficiency of antithrombin, protein C or protein S, or FV Leiden, who had at least one relative with the same familial defect, and their registered relatives. Fewer individuals with FV Leiden were included than would be expected based on the frequency of this mutation; however, the FV Leiden mutation was identified more recently than the other defects of which carriers were collected over the past 15 years. As controls, partners or, if there were none, friends or acquaintances of the thrombophilic participants were included. Controls were excluded if they were known to have heritable thrombophilia or if they were related to a participant with an inherited thrombotic defect. There were no exclusion criteria for individuals with inherited thrombophilia: we included those who were symptomatic as well as those who were asymptomatic, and those who received anticoagulant treatment as well as those who did not. The study was approved by the Leiden University Hospital Medical Ethics Committee, and all participants in this study gave their informed consent.

Data collection

Inclusion took place between March 1994 and September 1997 with most of the participants (84% of controls and 88% of thrombophilic individuals) included in 1994 and 1995. Information was collected at inclusion, and annually during the prospective follow-up by standardized data collection forms. All data were collected by the responsible physician or another health professional at the participating centers by consulting another physician, by medical chart review or by telephone or mail contact with the patient. Completed forms were sent to the coordinating center with only the patient identifiers code to protect patient confidentiality. Data collected at study entry included information on general demographics, defect details (type, subtype, diagnostic methods, genetic confirmation), personal history with regard to thrombosis (dates, location, diagnostic test results), current medication (oral anticoagulants, oral contraceptives, hormone replacement therapy or other medication), other risk factors (e.g. obesity, varicose veins), obstetric history and family history of thrombosis. Data collection was identical for controls and thrombophilic individuals, except for items on the type and subtype of thrombophilia.

All centres performed the various assays according to their local protocol and participated in an external quality assessment scheme for thrombophilia testing. For the first 2 years this was the quality assurance scheme developed for the European Concerted Action on Thrombosis (ECAT/EQAS) (Leiden, the Netherlands) and for the subsequent years, the UK NEQAS quality assurance scheme (Sheffield, UK). Diagnostic criteria were based on those used in these centers, which for the deficiencies was based on repeated testing, and in some cases also on genotypic confirmation.

Recruitment was before identification of the G20210A mutation in the prothrombin gene. During prospective follow-up, we gathered information on the presence of this mutation as a second defect for 504 relatives and 424 probands included in the analyzes. Thus we only have information on the prothrombin G20210A mutation as a second defect in 64% of the participants with inherited thrombophilia.

Analysis and statistics

For the analysis of the baseline data collected at study inclusion on the history of venous thrombotic events prior to study entry, we included only probands and relatives from families in which thrombophilia testing was done because of the occurrence of venous thrombosis in the proband or family, and not when this was done solely for research purposes or family planning. This restriction was to avoid selection bias and to stay as close as possible to the real-life situation of an individual from a symptomatic thrombophilia family asking a physician for advice.

We were interested in the number, type, age at onset, event-free survival, incidence, and relative risk of venous thromboembolic events (VTEs) experienced before inclusion in the study. Only objectively confirmed events (by ultrasound, Duplex or venography for DVT, and by ventilation-perfusion scanning or angiography for PE) and confirmed events at other locations were counted as such; non-definite events, i.e. based on clinical or patient diagnosis were recorded but not considered in the analysis reported here, including superficial thrombophlebitis. Spontaneous venous thrombosis was defined as venous thrombosis without known precipitating risk factors (hospital admission, surgery, immobilization, plaster cast, uninterrupted travels over 8 h, pregnancy, delivery). Thrombotic events in which the only risk factor was use of oral contraceptives were also labeled as spontaneous.

As probands were selected on having had venous thrombosis, we determined only the number and type of events, the age of onset and the age at which 50% of the probands had experienced venous thrombosis (median survival) prior to study entry. The probability of being free of events at any given age was analyzed by constructing Kaplan–Meier life tables. From these survival analyses we estimated the cumulative incidence of thrombosis with confidence intervals at age 30, 45 and 60.

The incidence of venous thrombotic events in relatives and controls was calculated by dividing the number of events by the total of observation years, i.e. the time between birth and the first event of interest, or until the end of study, i.e. the inclusion in the EPCOT study without a history of DVT, PE or other major event. The 95% confidence intervals (CIs) were calculated according to a Poisson distribution for the number of events [19]. Hazard ratios as an estimation of the relative risk were calculated by Cox-regression, with thrombosis as the dependent variable and presence of thrombophilia as an independent variable. Center (as stratum) and sex (as categorical variable) were entered in the Cox-regression model to adjust for regional and sex effects. Event-free survival, incidence and hazard ratios were calculated regardless of previous manifestations of superficial thrombophlebitis.

Results

A total of 2838 participants were enrolled in the cohort of whom 1626 had a thrombophilic defect (672 probands, 954 relatives of probands) and 1212 were controls (900 partners, 312 friends). In total, 600 probands and 846 relatives met the criteria that they were initially investigated because of thrombosis themselves or because of thrombosis in a family member.

The main characteristics at inclusion of probands, relatives and controls are depicted in Table 1. Among individuals with thrombophilia, men were slightly underrepresented (40% in probands and relatives). At study entry, 19 (10%) of the protein C deficient relatives, 43 (22%) of the protein S deficiency relatives, 32 (22%) of the antithrombin deficient relatives, 11 (5%) of the relatives with factor V Leiden and 22 (23%) of the relatives with combined defects received lifelong anticoagulation.

Table 1 General characteristics of the probands, relatives and controls at baseline

	Thrombophilic individuals		
	Probands	Relatives	Controls
All (*n*)	600	846	1212
Men (*n*)	237	339	627
Women (*n*)	363	507	585
PC deficiency (*n*)	126[a]	188	N/A
PS deficiency (*n*)	93	193	N/A
AT deficiency (*n*)*	102	145	N/A
FVL (*n*)	175[b]	225[c]	N/A
Combined defects (*n*)	104	95	N/A
PC deficiency-PS deficiency (*n*)	2	2	N/A
FVL-PC deficiency (*n*)	22[d]	22	N/A
FVL-PS deficiency (*n*)	23[d]	24	N/A
FVL-AT deficiency (*n*)	11	9	N/A
PT20210A-PC deficiency (*n*)	11	12	N/A
PT20210A-PS deficiency (*n*)	8	6[e]	N/A
PT20210A-AT deficiency (*n*)	5	6	N/A
PT20210A-FVL (*n*)	19[f]	13[g]	N/A
PT20210A-FVL-PC deficiency (*n*)	2	1	N/A
PT20210A-FVL-PS deficiency (*n*)	1	0	N/A
Age at inclusion (mean (range))	41 (2–78)	39 (0–91)	42 (3–87)
< 18 years old (*n*)	5	73	36
18–45 years old (*n*)	355	470	695
> 45 years old (*n*)	240	303	481

Abbreviation: PC = protein C, PS = protein S, AT = antithrombin, FVL = factor V Leiden, PT20210A = prothrombin G20210A, N/A = not applicable.

[a]2 were homozygous; [b]31 were homozygous; [c]13 were homozygous; [d]1 was homozygous for FVL; [e]1 was homozygous for PT20210A; [f]4 were homozygous for FVL; [g]1 was homozygous for FVL and 1 was homozygous for PT20210A.

*Six probands and 14 relatives showed only low antithrombin activity, 2 relatives were identified by DNA-testing only, and 5 probands and 7 relatives had only activity levels measured.

Thrombotic history

Probands Of all included probands, 532 (89%) had experienced an objectively confirmed venous thrombosis prior to study entry (Table 2). The remaining 68 probands (11%) had been identified because of superficial thrombophlebitis ($n = 58$), or were the first in the family in whom a defect was demonstrated with no personal but only a family history of venous thrombosis ($n = 10$). Of all probands with a personal history of thrombosis, 288 (54%) had experienced one or more recurrencies before study entry. The mean age at the first venous thrombosis was 30 years (range 0–71) and ranged per type of defect from 26 years in patients with antithrombin deficiency to 33 years in patients with FV Leiden (Table 2). Of all probands, 50% had experienced venous thrombosis before the age of 29 (Fig. 1). Spontaneous venous thrombotic events, i.e. venous events without known precipitating risk factors or during use of oral contraceptives only, occurred in 220 of the 362 (61%) probands for whom this information was available.

Table 2 Description of objectively confirmed venous events before study entry

	Thrombophilic individuals		
	Probands ($n = 600$)	Relatives ($n = 846$)	Controls ($n = 1212$)
Individuals with venous events before baseline (*n*)	532	139	15
DVT (*n*)	359	89	9
PE (*n*)	154	45	3
Other VT (*n*)	19	5	3
PC deficiency (*n*)	110	22	N/A
PS deficiency (*n*)	84	50	N/A
AT deficiency (*n*)	90	25	N/A
FVL (*n*)	152[a]	14[b]	N/A
Combined defects (*n*)	96[c]	28	N/A
Age at onset all major events (mean (range))	30 (0–71)	36 (13–71)	41 (24–68)
PC deficiency	32 (11–71)	42 (23–71)	N/A
PS deficiency	29 (2–68)	37 (13–71)	N/A
AT deficiency	26 (0–53)	34 (17–64)	N/A
FVL	33 (14–68)	38 (17–61)	N/A
Combined defects	28 (3–69)	28 (13–59)	N/A

Abbreviations: DVT: deep venous thrombosis; PE: pulmonary embolism with or without DVT; VT: venous thrombosis; PC: protein C; PS: protein S; AT: antithrombin; FVL: FV Leiden; N/A: not applicable.
[a]30 were homozygous; [b]2 were homozygous; [c]6 were homozygous for FVL.

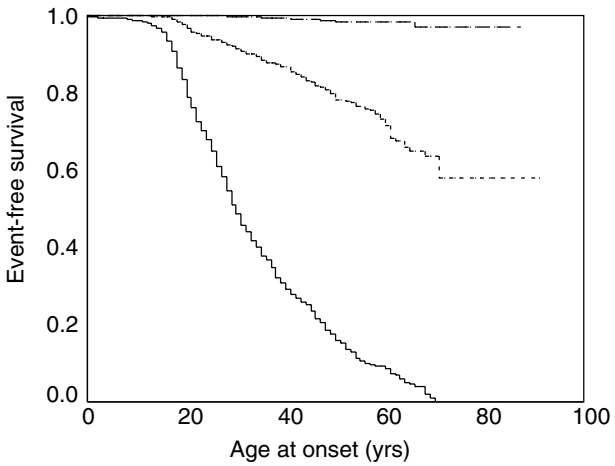

Fig. 1. Venous event-free survival of the probands (solid line), relatives (short dashed line) and controls (long dashed line) until study entry.

Relatives and controls Of all included relatives, 139 (16%) had experienced an objectively confirmed venous thrombosis compared with 15 (1%) in the controls (Table 2) prior to study entry. The percentage of relatives with a venous event varied per type of defect from 6% in those with the FV Leiden mutation to 29% in individuals with combined defects (Table 3). Recurrencies were present before baseline in 58 (42%) relatives with a history of venous thrombosis, and in only 2 (13%) of the controls with a history of venous thrombosis.

The mean age at the first venous thrombosis before study entry was 36 years (range 13–71) in the relatives and 41 years (range 24–68) in the controls (Table 2). Per type of defect, the age of onset ranged from 28 years in relatives with combined defects to 42 years in relatives with protein C deficiency (Table 2).

Spontaneous venous events occured before study entry in 54 of the 90 (60%) relatives and in 7 of the 14 (50%) controls for whom this information was available, with thrombotic events occuring during use of oral contraceptives considered as spontaneous events.

The incidence of venous events experienced before study entry in relatives was 4.4 (95% CI 3.7–5.2) per 1000 person years and in controls 0.3 (95% CI 0.2–0.5) per 1000 person years (Table 3). Per type of thrombophilia, the incidence was lowest in the relatives with the FV Leiden mutation (1.5 per 1000 person years) and highest for those with combined defects (8.4 per 1000 person years) (Table 3). The incidence regarding FV Leiden did not change after exclusion of homozygous individuals. The incidence was higher in men in the relatives (6.2 per 1000 person years for men and 3.2 per 1000 person years for women), but similar for both men and women in the controls (0.3 per 1000 person years for men and 0.2 per 1000 person years for women) (Table 3).

The probability of being free of venous events before study entry in the thrombophilic individuals (probands excluded) was 91% (95% CI 89–93%) at age 30, 82% (95% CI 79–86%) at age 45 and 70% (95% CI 65–76%) at age 60 (Fig. 1). Per type of defect, the probability of being free of venous events at age 45 was 87% with protein C deficiency, 74% with protein S deficiency, 80% with antithrombin deficiency, 94% with FV Leiden and 67% with combined defects. In the controls, the probability of being free of venous thrombosis at age 30, 45 and 60 was, respectively, 100%, 99% (95% CI 98–100%) and 98% (95% CI 97–99%) (Fig. 1).

The risk of venous thrombosis derived from the incidences of venous events experienced before study entry was 16 times higher in the relatives with thrombophilia compared with the controls (relative risk of 15.7; 95% CI 9.2–26.8) and remained similar after adjustment for center and sex (relative risk of 16.4; 95% CI 9.6–28.0) (Table 4). Per type of thrombophilia the relative risk differed greatly: the highest risk was found in the relatives with combined defects. For the relatives with single defects, the risk was highest in relatives with protein S deficiency (32.4; 95% CI 16.7–62.9) and lowest in the relatives with the FV Leiden mutation (4.3; 95% CI 1.9–9.7) (Table 4). Exclusion of homozygous individuals with the FV Leiden mutation did not affect these estimates. The relative risk was higher in men than in women: 18.1 (95% CI 9.0–36.3) and 13.9 (95% CI 6.0–32.4), respectively (Table 4).

Table 3 Incidence per 1000 person years of venous events before study entry in the controls and the relatives

	All (*n*)	Events (*n* (%))	Person years (years)	Incidence (per 1000 years (95% CI))
Controls	1212	15 (1)	51079	0.3 (0.2–0.5)
Men	627	9 (1)	26746	0.3 (0.2–0.6)
Women	585	6 (1)	24333	0.2 (0.1–0.5)
Age at inclusion > 18 years*	1171	15 (1)	29504	0.5 (0.3–0.8)
Age at inclusion > 45 years**	477	6 (1)	5712	1.1 (0.4–2.3)
Relatives	846	139 (16)	31660	4.4 (3.7–5.2)
PC deficiency	188	22 (12)	7059	3.1 (2.0–4.7)
PS deficiency	193	50 (26)	7059	7.1 (5.3–9.3)
AT deficiency	145	25 (17)	5034	5.0 (3.2–7.3)
FVL	225	14 (6)	9186	1.5 (0.8–2.6)
Combined defects	95	28 (29)	3322	8.4 (5.6–12.2)
Men	339	78 (23)	12634	6.2 (4.9–7.7)
Women	507	61 (12)	19026	3.2 (2.5–4.1)
Age at inclusion > 18 years*	743	126 (17)	16893	7.5 (6.2–8.9)
Age at inclusion > 45 years**	260	39 (15)	3593	10.9 (7.7–14.8)

Abbreviations: PC = protein C, PS = protein S, AT = antithrombin, FVL = FV Leiden, CI = confidence interval.
*Only person years above 18 years were counted. Individuals older than 18 years at baseline who had events before age 18 were excluded.
**Only person years above 45 years were counted. Individuals older than 45 years at baseline who had events before age 45 were excluded.

Table 4 Relative risk of venous events before study entry in the relatives

	Crude relative risk*	Adjusted** relative risk
All relatives vs. controls	15.7 (9.2–26.8)	16.4 (9.6–28.0)
PC deficiency	11.1 (5.7–21.4)	11.3 (5.7–22.3)
PS deficiency	26.1 (14.7–46.5)	32.4 (16.7–62.9)
AT deficiency	19.0 (10.0–36.1)	17.5 (9.1–33.8)
FVL	5.2 (2.5–10.8)	4.3 (1.9–9.7)
Combined defects	32.0 (17.1–60.0)	46.7 (22.5–97.1)
Men	19.2 (9.6–38.4)	18.1 (9.0–36.3)
Women	13.8 (5.9–31.8)	13.9 (6.0–32.4)
Age at inclusion > 18 years†	14.4 (8.4–24.6)	14.4 (8.4–24.6)
Age at inclusion > 45 years‡	10.2 (4.3–24.0)	10.3 (4.3–24.4)

Abbreviations: PC = protein C, PS = protein S, AT = antithrombin, FVL = FV Leiden.
*For every defect, we compared relatives with the defect with all controls.
**Adjusted for regional and sex-effects. For the relative risk per sex, the relative risk was only adjusted for regional effects.
†Only person years above 18 years were counted. Individuals older than 18 years at baseline who had events before age 18 were excluded.
‡Only person years above 45 years were counted. Individuals older than 45 years at baseline who had events before age 45 were excluded.

Discussion

To obtain reliable estimates of the risk of venous thrombosis associated with familial thrombophilia caused by various defects, we started a prospective collaborative multinational study including 1626 individuals with inherited thrombophilia and 1212 controls from eight European countries.

Data collected at study entry on the history of venous thrombosis prior to study inclusion showed a 16 times increased risk of VTEs for the individuals with inherited thrombophilia (only relatives of probands included) compared with the normal population (crude relative risk of 15.7 (95% CI 9.2–26.8), adjusted relative risk of 16.4 (95% CI 9.6 –28.0) adjusted for sex and regional effects). The incidence of venous events before study entry was 4.4 per 1000 person years in the relatives, compared with 0.3 per 1000 person years in the controls.

The highest incidence of events and the lowest age at onset before study entry were found in the relatives with combined defects (8.4 per 1000 person years; mean age at onset 28 years), as has been described by other authors [11,20–25], For single defects we found the highest risk with protein S deficiency (7.1 per 1000 person years), and the lowest for FV Leiden (1.5 per 1000 person years). Although there is one report that protein S deficiency confers the highest risk of VTE [26], several others have shown that the greatest venous thromboembolic risk is associated with antithrombin deficiency [23,24,27,28]. Whether there are real differences in the venous thrombotic risk in respect of antithrombin and protein S deficiency remains unresolved. The absence of a difference in our study might reflect differences in the distribution of, yet unknown, interacting second defects or the presence of the prothrombin G20210A mutation for which 36% of the participants could not be tested. It is, however, noteworthy, that a population study, in which selection or referral bias was excluded, also did not find a higher risk for antithrombin deficiency [29]. Another possible explanation for these conflicting results is that since antithrombin deficiency was the first thrombophilia to be discovered, affected individuals could have received prophylaxis more frequently than individuals with other types of thrombophilia. However, when the year of diagnosis of thrombophilia was taken as follow-up end-point instead of the age at which individuals were without venous events at study entry, the incidence was only slightly higher for individuals with antithrombin deficiency: 5.9% (95% CI 3.8–8.7).

The annual risk of thrombophilia-associated venous thrombosis before study entry was sex-dependent: the incidence was higher in male relatives than in female relatives, but similar for both male and female controls. As many venous thrombotic events in young women can be attributed to oral contraception, the low percentage of asymptomatic thrombophilic women using oral contraceptives (16%; age 15–35) compared with asymptomatic female controls (37%; age 15–35) offers a likely explanation for a lower risk in women with thrombophilia compared with control women. Another explanation is that female relatives were referred to a thrombosis clinic for investigation before hormone prescription or pregnancy, whereas men were only referred when they were symptomatic.

Labelling events as provoked or unprovoked is difficult and mostly dependent on the researcher's definition of a provoked event, e.g. we labeled events occuring during oral contraceptive use as unprovoked, as oral contraceptive use is a generally weak and very common risk factor during which anticoagulation treatment is mostly not considered. Studies including detailed, reliable information on risk factors could give insight in the risk of venous thrombosis associated with these risk factors.

We have included over 1500 individuals with familial thrombophilia from eight European countries, so our study yields reliable and generalizable results. It should be noted, however, that in this study follow-up was counted only for those entered in the cohort, i.e. individuals with any of these defects who died before the start of the study were not included. This implies that we may have underestimated the risk of thrombosis. However, in previous studies we have shown that the mortality of antithrombin deficiency [30], protein C deficiency [31] and FV leiden [32] does not exceed the population risk. We also only counted objectively confirmed manifestations of venous thrombosis to avoid selection bias, which means that we may have excluded inadequately diagnosed or missed events, and thus could have underestimated the risk. However, only a fraction of all reported events were not objectively confirmed. We also did not have full details on thromboprophylaxis prior to recruitment. The incidence of VTEs may thus have been reduced in the relatives if short-term thromboprophylaxis was used to cover surgery, trauma or pregnancy. After diagnosis of a hereditary thrombotic defect, thromboprophylaxis may be more likely to be offered even to asymptomatic relatives and oral contraception with estrogen-containing preparations is discouraged at least in some countries. However, incidences per defect were only slightly higher or remained similar to the incidences shown in Table 3 when the year of diagnosis of thrombophilia was taken as the study end-point instead of the age at which individuals were without venous events at study entry. The risk of venous thrombosis might have been overestimated when mostly symptomatic relatives were referred to a thrombosis clinic for investigation. In addition, the risk for individuals with single defects might have been overestimated when they were carriers of the prothrombin G20210A mutation but could not be tested for this particular mutation in our study.

It is important to note that our results concern individuals from thrombophilic families registered at specialized clinics, and hence the results may be generalized to such individuals, but not to unselected individuals with the same defect, as we have previously shown that these individuals have a lower risk of thrombosis [11,12].

While more detailed data will result from the prospective follow-up, this study showed that individuals with familial thrombophilia have an increased risk of venous thrombosis with a high risk of spontaneous thrombosis and recurrencies. Since 70% of the individuals with thrombophilic defects were free of thrombosis at age 60, it is unlikely that long-term anticoagulation started at a young age would have benefits outweighing the risks of this treatment especially in those with a single genetic prothrombotic defect.

Contributors

F.R. Rosendaal designed and coordinated the study together with F.E. Preston, I.D. Walker and J. Fontcuberta (the study steering committee). The first author, C.Y. Vossen, performed the analyses and wrote the manuscript. All other authors were involved in designing the study and involved in collecting patient data and reviewing the manuscript.

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