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Recurrence Rate After a First Venous Thrombosis in Patients With Familial Thrombophilia

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Objective—Few comprehensive data are available on the recurrence rate of venous thrombosis in carriers of thrombophilic defects from thrombophilic families. We prospectively determined the recurrence rate after a first venous thrombotic event in patients with familial thrombophilia attributable to factor V Leiden or deficiencies of protein C, S, or antithrombin.

Methods and Results—Data were gathered during follow-up on the occurrence of risk situations, anticoagulation treatment, and events (eg, venous thrombosis, hemorrhage). Over a mean follow-up period of 5.6 years, 44 of the 180 patients with familial thrombophilia who did not use long-term anticoagulation experienced a recurrent venous thromboembolic event (5.0%/year; 95% CI 3.6 to 6.7) compared with 7 of the 124 patients on long-term anticoagulation (1.1%/year; 95% CI 0.4 to 2.2). Spontaneous events occurred less often in patients on long-term anticoagulation (57%) than in patients without long-term anticoagulation (75%). The highest recurrence rate was found among men with a deficiency in natural anticoagulants or multiple defects and women with antithrombin deficiency. Although long-term anticoagulation treatment decreased the incidence of recurrent events by 80%, it also resulted in a risk of major hemorrhage of 0.8% per year.

Conclusions—Extra care after a first event is required for men with a deficiency in natural anticoagulants or multiple defects and women with antithrombin deficiency. (*Arterioscler Thromb Vasc Biol.* 2005;25:1992-1997.)

Key Words: familial thrombophilia ■ incidence ■ prospective follow-up ■ recurrence ■ venous thrombosis

A prior history of venous thrombosis is a strong predictor for venous thrombosis, with recurrences in 3% to 13% of consecutive patients after 1 year and 12% to 28% after 5 years.¹⁻⁶ Patients with a first venous thrombotic event will receive oral anticoagulant treatment for at least 3 months after a deep vein thrombosis (6 months when the event was idiopathic) and at least 6 months after a pulmonary embolism. Decisions on extending anticoagulant treatment are based on the perceived risks of venous thromboembolism recurrence and anticoagulant-related bleeding. Whether long-term continuation of anticoagulant treatment should be considered after a first venous event in carriers of a thrombophilic defect from thrombophilic families is still uncertain, as few comprehensive data are available on whether inherited risk factors increase the risk of recurrence. As was shown by us previously, it is important to distinguish between unselected patients with a thrombophilic defect and individuals from

thrombophilic families, as the latter tend to have a much higher risk probably attributable to the concomitant presence of other risk factors within these families.^{7,8} To our knowledge, only 2 studies described the recurrence risk associated with familial deficiencies of protein C, protein S, and antithrombin: Pabinger et al found a high recurrence rate of 63% for patients with familial deficiencies of natural anticoagulant factors,⁹ and annual incidences calculated on available literature by Van den Belt et al ranged from 13% to 17% for patients with familial antithrombin deficiency and from 14% to 16% for patients with familial protein S deficiency.¹⁰ In the same article by Van den Belt et al, the results of a retrospective cohort study revealed a cumulative incidence of 10% after 1 year and 23% after 5 years for patients with inherited antithrombin-, protein S-, or protein C deficiency.¹⁰ For factor V Leiden contradicting results have been published about the risk of recurrent venous thrombosis.^{6,11-15} To our knowledge

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only 1 study focused on patients with a positive family history and concluded that the incidence of recurrent venous events depends on the presence of other thrombophilic disorders.¹⁶

We started the European Prospective Cohort on Thrombophilia (EPCOT-) study, a large prospective cohort study of individuals with familial thrombophilia, to obtain reliable risk estimates of the absolute risk of venous thrombosis in families with inherited thrombophilia. The aim of the current analysis was to determine the recurrence risk for participants with a hereditary thrombophilic defect and a history of one venous thromboembolic event before study entry. We focused on selected families with a clear thrombotic tendency, and the results could assist physicians in decisions on testing for thrombophilic abnormalities and choices about long-term anticoagulation after a first thrombosis.

Methods

As previously described,¹⁷ participants from 8 European countries were included between March 1994 and September 1997. Follow-up was until January 2001. The defects of interest were deficiencies of antithrombin, protein C, protein S, or factor V Leiden. We gathered information on the prothrombin G20210A variant as a second defect for 207 of the 304 patients (68%). The analysis includes only patients with 1 objectively confirmed deep venous thrombosis (DVT) or pulmonary embolism (PE) before inclusion in the study. For all patients, we calculated the absolute risk (incidence) and 95% confidence intervals¹⁸ of recurrent venous thrombosis and severe hemorrhage during follow-up. We calculated the recurrent event-free survival according to the number of observation years using the Kurtzke method.¹⁹ To determine the benefit of long-term anticoagulation, we calculated the relative risk of venous thrombosis by Cox-regression with and without adjustment for regional (center), age, and sex effects. (Please see <http://atvb.ahajournals.org> for a detailed method section.)

Results

Prospective data were collected on 304 patients with a history of 1 objectively confirmed DVT or PE before inclusion in the follow-up study. Of these subjects, 124 patients (69 probands and 55 relatives) were classified as being on long-term anticoagulation during prospective follow-up, while 180 patients (139 probands and 41 relatives) were not on long-term prophylactic anticoagulation. The total prospective follow-up time of the 304 patients was 1710 years (mean 5.6; range 1 to 7 years). During follow-up, 6 patients were lost-to-follow-up and 6 patients died as a result of heart disease (n=2), cancer (n=2), septic shock (n=1), and pneumonia (n=1).

Table 1 depicts the main characteristics at inclusion of the patients. Among those not on long-term anticoagulation, there were relatively fewer men and more probands than among those who received long-term anticoagulation. The latter can be explained by a low frequency of long-term anticoagulation among probands with factor V Leiden.

Recurrence Rates

Of the 180 patients who did not receive long-term anticoagulant treatment during prospective follow-up, 44 (24%) experienced a recurrent thrombotic event (Table 2) compared with 7 of the 124 (6%) patients on long-term anticoagulant treatment (Table 3). Of the patients who did not receive long-term anticoagulant treatment, 4 used aspirin and 2 used

TABLE 1. General Characteristics of the Thrombophilic Subjects With 1 Confirmed DVT or PE at Study Entry

	Patients (n=304)	
	No Long-Term Anticoagulation	Long-Term Anticoagulation
All, n	180	124
Men, n (%)	63 (35)	59 (48)
Probands, n (%)	139 (77)	69 (56)
Age at inclusion, mean years (range)	39 (14–78)	41 (20–72)
Age at 1st event, mean years (range)	32 (11–70)	33 (13–71)
Type of thrombophilia		
PC deficiency, n	37	32
PS deficiency, n	25	30
AT deficiency, n	11	26
FVL, n	79 (12 AA)	13 (4 AA)
Combined defects, n		
PC-PS	0	1
PC-FVL	6	7
PC-PT	3	4
PC-FVL-PT	2	0
PS-FVL	4	4
PS-PT	2	2
AT-FVL	2	3
AT-PT	2	1
FVL-PT	7	1†
Risk factors		
BMI, mean kg/m ² (range)	25 (17–47)	25 (17–34)
Cancer ever, %	2	0
Arterial disease, %	3	9
Thrombosis history		
DVT, n (%)	133 (74)	79 (64)
PE, n (%)*	47 (26)	45 (36)
Spontaneous DVT or PE, n (%)‡	105 (58)	62 (50)
History of STPs, n (%)	37 (21)	40 (32)
Time between 1st event and study entry, mean years (range)	6.4 (0–38)	7.3 (0–33)

PC indicates protein C deficiency; PS, protein S deficiency; AT, antithrombin deficiency; FVL, factor V Leiden; AA, homozygotes for factor V Leiden; PT, prothrombin G20210A; BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolism; STP, superficial thrombophlebitis.

*A DVT and PE were experienced at the same time by 29 patients without and 29 patients with long-term anticoagulation.

†Defined at entry as events in the absence of the following risk situations: surgery, cancer, hospitalization, plaster cast, immobilization, pregnancy, and traveling.

‡One was homozygous for FVL.

heparin (short-term during surgery and pregnancy) at the time of the event. Thirty-three of the 44 events (75%) in those not on long-term anticoagulation occurred spontaneously, and the 11 remaining events occurred after traveling for more than 8 hours (n=5), during pregnancy (n=3), and after surgery (n=3). Of the women who experienced a recurrent event during pregnancy, 2 had received no prophylaxis during pregnancy and 1 had received low molecular weight heparin

TABLE 2. Incidence Rates (%/year) of a Recurrent DVT or PE in Patients Who Did Not Receive Long-Term Anticoagulant Treatment During Prospective Follow-Up

Patients	n	Time Between 1 st	DVT/PE, n	Person Years, n	Incidence Rate, %/Year (95% CI)	Incidence Rate Men, %/Year (95% CI)	Incidence Rate Women, %/Year (95% CI)
		Event and Study Entry, Mean Years (Range)					
All	180	6.4 (0–38)	44*	881.7	5.0 (3.6–6.7)	9.6 (6.3–13.9)	2.8 (1.7–4.5)
PC deficiency	37	6.3 (0–27)	10	195.0	5.1 (2.5–9.4)	10.8 (4.0–23.4)	2.9 (0.8–7.4)
PS deficiency	25	5.3 (0–16)	8	122.4	6.5 (2.8–11.8)	10.5 (3.9–22.9)	3.1 (0.4–11.0)
AT deficiency	11	9.3 (1–24)	6	57.4	10.5 (3.8–22.8)	11.6 (2.4–33.9)	9.5 (2.0–27.8)
FVL	79	5.3 (0–38)	13 (1 AA)	366.3	3.5 (1.9–6.1)	7.2 (2.9–14.9)	2.2 (0.8–4.8)
Multiple defects	28	9.4 (1–30)	7†	140.6	5.0 (2.0–10.3)	10.7 (3.5–24.9)	2.1 (0.3–7.7)

DVT indicates deep venous thrombosis; PE, pulmonary embolism; PC, protein C; PS, protein S; AT, antithrombin; FVL, factor V Leiden; AA, homozygotes for factor V Leiden; CI, confidence interval.

*Thirty-four experienced a DVT, 6 a PE, and 4 a DVT and PE concurrently.

†Three with protein C deficiency and factor V Leiden, 1 with protein C deficiency and the prothrombin 20210A variant, 1 with factor V Leiden and the prothrombin 20210A variant, 1 with protein C deficiency, factor V Leiden and the prothrombin 20210A variant, and 1 with antithrombin deficiency and the prothrombin 20210A variant.

(LMWH) daily from week 6 to 37 with an event around week 11 of the pregnancy. Of the 3 individuals with a recurrent event after surgery, 2 had received no prophylaxis during foot surgery and surgery for breast cancer, whereas 1 was considered to have had adequate prophylaxis. Of the patients on long-term anticoagulation, 4 of the 7 events (57%) occurred spontaneously (3 had their last international normalized ratio [INR] within the desired range of 2 to 3, whereas one patient used anticoagulation irregularly despite the prescription), 2 events occurred during or after pregnancy (with LMWH prophylaxis daily), and 1 individual who received adequate anticoagulation treatment experienced an event after strenuous exercise (karate). Thirteen of the 180 patients (7%) who did not use long-term anticoagulation experienced a superficial thrombophlebitic event during prospective follow-up (ie, as the only venous recurrent event or before a recurrent DVT or PE) compared with 9 of the 124 patients (7%) on long-term anticoagulation.

The recurrence rate was 5.0% per year (95% CI 3.6 to 6.7) in patients who were not on long-term anticoagulation and 1.1% per year (95% CI 0.4 to 2.2) in those on long-term

anticoagulation (Tables 2 and 3). Thus, the risk of recurrent events was 80% lower in the patients on long-term anticoagulation treatment (crude relative risk 0.2; 95% CI 0.1 to 0.4; unchanged when adjusted for center, sex, and age at inclusion). In patients who did not receive long-term anticoagulation treatment, the recurrence rate was much higher among men (9.6%/year; 95% CI 6.3 to 13.9) than among women (2.8%/year; 95% CI 1.7 to 4.5) (Table 2) with a relative risk of 3.0 (95% CI 1.6 to 5.6), which remained unchanged when adjusted for age (relative risk 3.1; 95% CI 1.6 to 5.9) or when we restricted the analysis to those with a first spontaneous venous thrombotic event (relative risk 3.1; 95% CI 1.4 to 7.1). Among the thrombophilic women who were not on long-term anticoagulation, measures to reduce the risk of recurrence associated with pregnancy or use of female hormones were frequently used: 25 of the 29 (86%) women who were pregnant during prospective follow-up received thromboprophylaxis during pregnancy or puerperium, and only 13 of the 100 (13%) women between the age of 15 and 50 used oral contraceptives, of whom 9 women used oral contraceptives which contained no estrogen. Among the thrombophilic

TABLE 3. Incidence Rates (%/year) of a Recurrent DVT or PE in Patients on Long-Term Anticoagulant Treatment During Prospective Follow-Up

Patients	n	Time Between 1 st	DVT/PE, n	Person Years, n	Incidence Rate, %/Year (95% CI)
		Event and Study Entry, Mean Years (Range)			
All patients	124	7.5 (0–36)	7*	652.0†	1.1 (0.4–2.2)
PC deficiency	32	6.7 (0–29)	1	172.1	0.6 (0.0–3.2)
PS deficiency	30	6.2 (0–20)	1	172.8	0.6 (0.0–3.2)
AT deficiency	26‡	6.7 (0–26)	4	146.9	2.7 (0.7–7.0)
FVL	13	7.3 (1–24)	0	43.4	0.0 (0.0–8.5)
Multiple defects	23	11.2 (0–36)	1§	116.8	0.9 (0.0–4.8)

DVT indicates deep venous thrombosis; PE, pulmonary embolism; PC, protein C; PS, protein S; AT, antithrombin; FVL, factor V Leiden; CI, confidence interval.

*Five patients experienced a DVT, 1 a PE, and 1 a cerebral venous event.

†The follow-up time regardless of treatment was 687.3 years. None of the individuals received treatment for less than a year.

‡One individual received antithrombin concentrate as anticoagulation therapy.

§This individual was protein S deficient and factor V Leiden carrier.

TABLE 4. Incidence Rates (%/Year) in Subgroups

	Incidence, %/Year (95% CI)	
	No Long-Term Anticoagulation (n=180)	Long-Term Anticoagulation* (n=124)
Probands	5.6 (4.0–7.7)	1.4 (0.5–3.3)
Relatives	3.1 (1.3–6.5)	0.7 (0.1–2.4)
History spontaneous events	5.7 (3.8–8.2)	1.2 (0.3–3.2)
No history spontaneous events	4.0 (2.2–6.6)	0.9 (0.2–2.7)
History of concurrent DVT/PE	8.5 (4.4–14.8)	1.1 (0.1–4.1)
History of DVT or PE only	4.3 (3.0–6.1)	1.0 (0.3–2.4)

CI indicates confidence interval; DVT, deep venous thrombosis; PE, pulmonary embolism.

*Incidence was in percentage per year on thromboprophylaxis.

women who were on long-term anticoagulation, 10 of the 50 (20%) women between the age of 15 and 50 used oral contraceptives, of whom 9 women used estrogen-containing oral contraceptives.

The lowest recurrence rates, although the confidence intervals were wide, were found in patients with factor V Leiden (3.5%/year without and 0.0%/year with long-term treatment), and the highest recurrence rates were found in patients with antithrombin deficiency (10.5%/year without and 2.7%/year with long-term treatment) (Tables 2 and 3). However, when we calculated the incidences for men and women separately, we found among those not on long-term anticoagulation high and similar recurrence rates for men with protein C, protein S, or antithrombin deficiency and men with multiple defects (10.5 to 11.6%/year; Table 2). For men with factor V Leiden we found a lower rate (7.2%/year; Table 2). For women, except for those with antithrombin deficiency (9.5%/year), the recurrence rates were much lower (2.1 to 3.1%/year; Table 2).

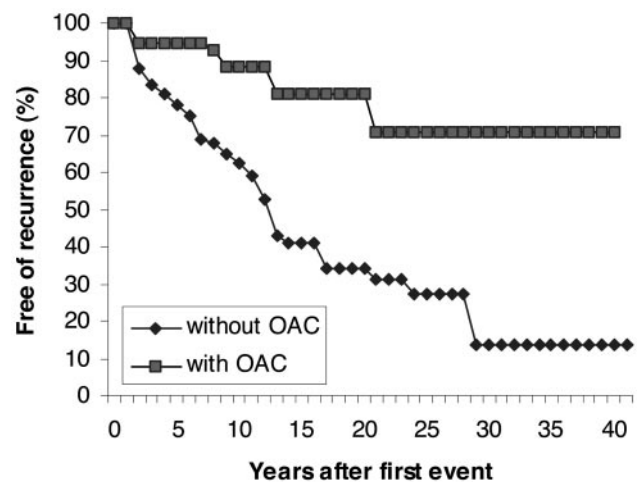
Besides a difference in the recurrence rate among men and women who received no long-term anticoagulation, we found, although confidence intervals were wide, a higher recurrence rate in the probands, and in the patients with a spontaneous first event than in the other patients. The annual incidence of spontaneous events per type of defect was 6.9% (95% CI 2.8 to 14.3) for protein C deficiency, 8.9% (95% CI 2.9 to 20.9) for protein S deficiency, 9.3% (95% CI 1.9 to 27.1) for antithrombin deficiency, 3.6% (95% CI 1.7 to 6.9) for factor V Leiden, and 7.4% (95% CI 2.4 to 17.2) for combined defects. Among the 105 individuals with a spontaneous first venous thrombotic event, a recurrent event occurred mostly also spontaneously (23/29; 79%) or during traveling for more than 8 hours (4/29; 14%). We also found a higher risk among those with a concurrent DVT and PE as first event (Table 4). Of the recurrent events in those with a concurrent DVT and PE as a first event (n=12), most second events were a DVT (n=10) and 2 second events were a concurrent DVT and PE again. Of the individuals without long-term treatment with a DVT as first event (n=133), 23 experienced a DVT (82%) as recurrent event, 3 a PE, and 2 a concurrent DVT and PE. Of individuals without long-term treatment with a PE as first event (n=18), 1 had a DVT as

second event and 3 (75%) a PE. Although we can offer no explanation for these observations, they are in line with previous publications of different risk factors for DVT and PE.^{20,21}

In patients on long-term anticoagulation, the overall recurrence rates were independent of sex (recurrence rates of 1.0%/year for men and 1.2%/year for women) and the etiology of the first event (spontaneous or not; Table 4). However, in those on long-term anticoagulation with antithrombin deficiency all recurrences occurred in women (incidence 5.1%; 95% CI 1.4 to 12.9; 2 DVTs during pregnancy for which they received LMWH, 1 spontaneous DVT and 1 spontaneous cerebral sinus thrombosis), whereas the remaining 3 events in the group on long-term anticoagulation with other defects occurred in men.

The influence of risk situations on the risk of venous thrombosis was difficult to determine as short-term prophylaxis was prescribed frequently in patients who were not on long-term anticoagulation: in 6 of the 11 individuals wearing a plaster cast, in 7 of the 83 patients who traveled, and in 39 of the 71 patients undergoing surgery or hospitalization.

The Figure shows the recurrence-free survival curve according to the number of observation years. For the subjects who were not on long-term anticoagulation, five individuals were included in the same year as their first event occurred, and 28 individuals entered the study in 1994 or 1995 and had experienced their first event in, respectively, 1993 or 1994. After 2 years of observation, these 5 and 28 individuals were followed prospectively for, respectively, 2 years and 1 year, and 12% of these 33 individuals had experienced a recurrent event (Figure). After 5 years of observation, an additional 10% of the subjects had experienced an event (Figure). Recurrence-free survival was higher for subjects who were on long-term anticoagulation: after 2 years of observation, 7 and 11 individuals were followed prospectively for, respectively, 2 years and 1 year, and 6% of these 18 individuals had experienced a recurrent event (Figure). After 5 years of observation, no additional subjects had experienced an event (Figure)



Percentage of individuals who were free of a recurrent venous event according to the number of years after a first event (calculated using the Kurtzke method).

Risk from Prophylactic Anticoagulation

Two women who did not use long-term anticoagulation experienced a severe hemorrhage during delivery while receiving short-term heparin treatment to prevent thrombosis during pregnancy. Five patients experienced a severe hemorrhage during the use of long-term anticoagulation (3 gastrointestinal hemorrhages and 2 postoperative bleeding episodes after a hysterectomy or a thrombectomy) requiring hospital admission for an emergency diagnosis or for treatment. One additional patient experienced a postoperative hemorrhage after the removal of a melanoma but had stopped oral anticoagulation 2 weeks before during treatment with penicillin for erysipelas. The incidence of severe hemorrhages associated with the use of oral anticoagulation was 0.8% per year (95% CI 0.3 to 1.8; 5 events on 638 years of anticoagulation).

Discussion

In patients with familial thrombophilia, the recurrence rate of venous thrombosis after a first DVT or PE was 5.0% per year (95% CI 3.6 to 6.7) in the 180 patients who did not receive long-term anticoagulation during prospective follow-up. The recurrence rate of venous thrombosis was much higher in men than in women with a relative risk, adjusted for age, of 3.1 (95% CI 1.6 to 5.9), which is in accordance with a recent article by Kyrle et al who reported a relative risk of recurrence of 3.6 (95% CI 2.3 to 5.5) for men compared with women.²² The lower risk in women may be partly explained by more extensive preventive measures in women, which included frequent use of anticoagulant prophylaxis during pregnancy and avoidance of estrogen-containing oral contraceptives. A similar sex difference has been observed in nonthrombophilic patients followed after a first venous thrombosis.^{6,23} The incidence was also high for patients in whom the first event had been a spontaneous event, as previously reported by others.^{24–26} In addition, we found a higher recurrence rate in patients who had experienced a DVT and PE concurrently as a first event than in those with a DVT or PE as first event. For factor V Leiden carriers the recurrence rate (3.5% per year) was similar to the incidences found in several prospective and retrospective studies on unselected patients with factor V Leiden of \approx 5% per year.^{6,11–14} The risk of a recurrent event in unselected patients with a first thrombotic event is reported to be highest in the first year after a first event (3% to 13% after 1 year compared with 12% to 28% after 5 years).^{1–6} However, as most symptomatic individuals in the present study did not enter the study in the same year as they had experienced their first event, our rates cannot readily be compared with these rates found in other studies. When we took the year of a first event into account, we found that 12% of the subjects who did not receive long-term anticoagulation had experienced a recurrent event after 2 years. After 5 years of observation, an additional 10% had experienced a recurrent event. We did not include individuals with a nonobjectively confirmed recurrent venous event only; however, these were few (n=4).

The recurrence rate was 80% lower in the 124 patients using long-term anticoagulation treatment with an incidence of recurrent events of 1.1% per year (95% CI 0.4 to 2.2). De

Stefano et al found a low annual incidence of 1.4% for individuals with antithrombin-, protein S-, or protein C deficiency in a retrospective study in which most individuals received life-long prophylaxis.²⁷ Their finding is similar to the recurrence rate found in the present study for patients with protein C-, protein S-, or antithrombin deficiency receiving long-term anticoagulation (1.2%/year; 95% CI 0.4 to 2.7), although the recurrence rate for antithrombin deficiency remained high (2.7% per year). The reduction of the recurrence rate with 80% was offset by a risk of severe hemorrhages during use of long-term anticoagulation of 0.8% per year (95% CI 0.3 to 1.8), which is similar to the incidence of major hemorrhages of 1% to 3% found in other studies.^{28,29}

The strength of our study is its size attributable to the collaboration of several European thrombosis centers, which made the restriction to patients with 1 venous thrombotic event possible. However, because this study was an observational study and not randomized, incomparability between the groups of patients who did and did not receive long-term anticoagulation cannot be ruled out. It is difficult to imagine, however, how selective prescription would have led to the overestimation of the effect of anticoagulation. This study therefore demonstrates that long-term anticoagulation is effective in reducing the risk of recurrent thrombosis in patients with familial thrombophilia, except in women with antithrombin deficiency, who still showed a high recurrence rate of 5.1% with long-term anticoagulation after the first event. Although randomized studies may still be desirable to demonstrate the efficacy of long-term anticoagulant treatment of thrombophilic patients, the low prevalence of familial thrombophilia may render this infeasible. In addition, the overall risk of recurrence was similar to the risk found in consecutive patients with a first venous thrombosis who generally do not receive long-term anticoagulation to prevent a recurrent event, because of the risk of major hemorrhage. Therefore, for most patients with familial thrombophilia, especially patients with factor V Leiden, there seems to be little justification for long-term treatment after a first event, although the availability of anticoagulants with a better risk-benefit profile could change the balance. The highest recurrence rates were found among men with a deficiency in natural anticoagulants or multiple defects and women with antithrombin deficiency. As a substantial proportion of recurrent events occurred during risk situations, efforts could be aimed at preventing these secondary events.

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