

Thrombophilia, Clinical Factors, and Recurrent Venous Thrombotic Events

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THE INCIDENCE RATE OF A FIRST venous thrombosis is 1 to 2 events per 1000 patient-years.¹⁻³ Venous thrombosis manifests mainly as deep venous thrombosis (DVT) and pulmonary embolism. Environmental risk factors include immobilization, surgery, malignancies, pregnancy, puerperium, and exogenous female hormones.⁴ Genetic abnormalities increasing the risk of a thrombotic event have been known for several decades and include deficiencies of the natural anticoagulants antithrombin, protein C, and protein S. Additional biochemical risk factors for a thrombotic event are factor V Leiden, prothrombin G20210A, high levels of factors VIII, IX, or XI, homocysteine, and fibrinogen.⁵⁻¹¹ Knowledge of the risk of a thrombotic event recurrence and its determinants is relevant for clinical policy regarding screening for thrombophilia, duration of anticoagulant treatment, and prophylactic strategies in circumstances of increased risk.

Estimates of the 5-year cumulative incidence of recurrent thrombotic events are around 25%.^{12,13} One study¹⁴ reported a high recurrence rate of 20% (17 cases) in a total of 83 patients during a 10-month follow-up. While estimates of the overall risk of a thrombotic event recurrence vary, reports on contributing factors are contradictory. Several studies have been published linking factor V Leiden, the pro-

Context Data on the recurrence rate of venous thrombotic events and the effect of several risk factors, including thrombophilia, remain controversial. The potential benefit of screening for thrombophilia with respect to prophylactic strategies and duration of anticoagulant treatment is not yet known.

Objectives To estimate the recurrence rate of thrombotic events in patients after a first thrombotic event and its determinants, including thrombophilic abnormalities.

Design, Setting, and Patients Prospective follow-up study of 474 consecutive patients aged 18 to 70 years without a known malignancy treated for a first objectively confirmed thrombotic event at anticoagulation clinics in the Netherlands. The Leiden Thrombophilia Study (LETS) was conducted from 1988 through 1992 and patients were followed up through 2000.

Main Outcome Measures Recurrent thrombotic event based on thrombophilic risk factors, sex, type of initial thrombotic event (idiopathic or provoked), oral contraceptive use, elevated levels of factors VIII, IX, XI, fibrinogen, homocysteine, and anticoagulant deficiencies.

Results A total of 474 patients were followed up for mean (SD) of 7.3 (2.7) years and complete follow-up was achieved in 447 (94%). Recurrence of thrombotic events occurred in 90 patients during a total of 3477 patient-years. The rate of thrombotic event recurrence was 25.9 per 1000 patient-years (95% confidence interval [CI], 20.8-31.8 per 1000 patient-years). The incidence rate of recurrence was highest during the first 2 years (31.9 per 1000 patient-years; 95% CI, 20.3-43.5 per 1000 patient-years). The risk of thrombotic event recurrence was 2.7 times (95% CI, 1.8-4.2 times) higher in men than in women. Patients whose initial thrombotic event was idiopathic had a higher risk of a thrombotic event recurrence than patients whose initial event was provoked (hazard ratio [HR], 1.9; 95% CI, 1.2-2.9). Women who used oral contraceptives during follow-up had a higher thrombotic event recurrence rate (28.0 per 1000 patient-years; 95% CI, 15.9-49.4 per 1000 patient-years) than those who did not (12.9 per 1000 patient-years; 95% CI, 7.9-21.2 per 1000 patient-years). Recurrence risks of a thrombotic event by laboratory abnormality ranged from an HR of 0.6 (95% CI, 0.3-1.1) in patients with elevated levels of factor XI to an HR of 1.8 (95% CI, 0.9-3.7) for patients with anticoagulant deficiencies.

Conclusions Prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent thrombotic event. Testing for prothrombotic defects has little consequence with respect to prophylactic strategies. Clinical factors are probably more important than laboratory abnormalities in determining the duration of anticoagulation therapy.

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thrombin G20210A mutation, and the recurrence of a thrombotic event.¹⁴⁻²⁵ Most studies showed little effect of carriage of these mutations on the risk of recurrence.^{14-20,23} However, in some studies a 4- to 5-fold higher risk of a

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thrombotic event recurrence has been noted in carriers compared with non-carriers.^{21,22,24,25} A recent critical review²⁶ of 4 studies highlighted hazard ratios (HRs) ranging from 1.1 to 4.1 in carriers of factor V Leiden compared with noncarriers. In studies comparing carriers of prothrombin G20210A with noncarriers, HRs of a thrombotic event recurrence varied from 0.9 to 4.9.

A 6-fold increased risk of a thrombotic event recurrence was reported for patients with high plasma levels of factor VIII.²⁷ A slightly increased risk of a thrombotic event recurrence was reported for patients with high levels of factor IX.²⁸ No recurrence data are available for elevated levels of factor XI or fibrinogen, which have been shown to increase the risk for a first event.^{9,11} Hyperhomocysteinemia increases the risk of a thrombotic event.¹⁰ It was also found to be prevalent in patients with a recurrent thrombotic event.^{29,30}

Two reviews^{31,32} pointed out that the contradictory results on contributing factors of thrombotic event recurrence may have resulted from (1) differences in study design, (2) lack of proper inception cohorts, (3) incomparability of anticoagulation profiles, (4) differences in quality of documentation of events, or (5) differences in the interpretation of clinical outcomes and laboratory tests. A particular issue may be that selected subgroups of patients were studied, ie, those referred to specialized centers for thrombophilia work-up, who may well have harbored additional, yet unknown defects that could have affected risks. Most study cohorts were small and followed up for only a short period.

We set out to determine the risk of a recurrent thrombotic event in 474 patients who had participated in a large population-based case-control study of risk factors for a first DVT. Many risk factors for a thrombotic event were investigated and these patients were followed up for up to 12 years. In particular, we examined the effect of several thrombophilic risk factors on the risk of recurrence, as well as the effect of sex, oral contraceptive use, and whether the first event was idiopathic or provoked.

METHODS

We included 474 consecutive patients with a first, objectively confirmed episode of DVT. Patients were diagnosed between January 1, 1988, and December 30, 1992, and were participants in the Leiden Thrombophilia Study (LETS),^{11,33} which was a case-control study of the etiology of DVT. In the Netherlands, patients with a thrombotic event are treated at anticoagulation clinics, which are regionally organized. Therefore, all patients living in a certain area are monitored by the same clinic, irrespective of the hospital they were admitted to or the physician who started the treatment. Patients participating in LETS were identified from the files at the anticoagulation clinics in Leiden, Amsterdam, and Rotterdam. Ninety percent of eligible patients were willing to participate in LETS. Patients older than 70 years and those with malignancies were excluded. There were no major differences at baseline in characteristics between the patient groups from the 3 clinics; 453 patients had a DVT and 21 had a thrombosis in the arm. LETS was approved by the medical ethics committee of the Leiden University Medical Center and has been described elsewhere.^{11,33}

Patients were initially seen at least 3 months after the discontinuation of oral anticoagulant treatment, except in cases when this treatment could not be stopped (n=48). Patients were seen in person by one of us (T.K.) between October 1990 and January 1994. The median time between a thrombotic event and venipuncture was 19 months (range, 6-68 months). At the examination, information on acquired risk factors was collected and a venous blood draw was performed. Information was also collected on surgery, trauma, immobilization, use of oral contraception shortly before the diagnosis of a thrombotic event, family history, and reproductive history.

Blood was collected from the antecubital vein and placed in 0.106 M of trisodium citrate. Plasma was prepared by centrifugation for 10 minutes at 2000g at room temperature and stored at -70°C

in a 1.5-mL container. DNA was extracted by standard salting-out methods. When a deficiency of protein C, protein S, or antithrombin was suspected, patients were asked to have blood redrawn to confirm the diagnosis and then were informed of their deficiency.³⁴ In subsequent years, we investigated resistance to activated protein C with factor V Leiden (1994) and prothrombin G20210A (1996) in all participants and informed the patients if they had an abnormal result.^{5,6,35} None of the other test results (on levels of factors VIII, IX, or XI, homocysteine, and fibrinogen) were communicated to the patients.⁷⁻¹¹

Laboratory Measurements

Details regarding the methods of measuring levels of the coagulation factors were described in detail in LETS.¹¹ The factor VIII activity was measured by a 1-stage coagulation assay.⁷ Factor IX antigen levels were measured by sandwich enzyme-linked immunosorbent assays using commercial polyclonal antibodies (Dako A/S, Glostrup, Denmark).⁸ Factor XI antigen levels were measured by using a monoclonal anti-factor XI capture antibody and polyclonal antifactor XI tagging antibody.⁹ The fibrinogen concentration was measured according to the Clauss method using a Dade reagent (Baxter, Miami, Fla). Protein C activity and antithrombin activity were measured with Coamate (Chromogenix, Mölndal, Sweden) on an ACL 200 (Instrumentation Laboratory, Milan, Italy).³⁴ Total protein S was measured by a polyclonal enzyme-linked immunosorbent assay.³⁴ All coagulation factors were expressed as units per deciliter, in which 1 U is the amount of coagulation factor present in 1 mL of pooled plasma. Fibrinogen levels were expressed as grams per liter. Total homocysteine concentration was measured in a nonfasting state by a modified method of automated high-performance liquid chromatography with reverse phase separation and fluorescent detection with a 232-401 sample processor (Gilson Inc, Middleton, Wis), an 8800 solvent-delivery system (Spectra-Physics, Mountain View,

Calif), and an LC 304 fluorometer (Spectra-Physics).¹⁰ Prothrombin G20210A and factor V Leiden (FV G1691A) genotypes were assessed by standard polymerase chain reaction.^{6,36}

Follow-up

All 474 patients gave informed consent for follow-up and for the collection of information from hospitals during a suspected thrombotic event recurrence. Follow-up started 90 days after the date of the initial thrombotic event that occurred in 1988-1992 (this 90-day period was defined as the period of initial anticoagulation) and ended on January 1, 2000. Information relevant to the follow-up after the thrombotic event was first gathered at the interview at baseline, and subsequently by repeated mailed questionnaires. The questionnaires were used as a screening tool for the occurrence of risk situations and recurrent thrombotic events, and also included items on relevant clinical circumstances such as anticoagulation (type, duration, indication), surgery, trauma, immobility, use of oral contraception, and pregnancies during the period covered by each questionnaire. Patients were further interviewed by telephone if they responded positively on any item from the questionnaire or if they did not respond to a questionnaire. Subsequently, confirmation of all relevant clinical information pertaining to recurrent thrombotic events or risk situations was obtained from the treating physicians.

Recurrent thrombotic events were confirmed and reports on diagnostic methods were obtained by collecting the discharge letters from the treating hospitals. Recurrent thrombotic events were adjudicated when they were objectively confirmed with Doppler ultrasound, venography, or impedance plethysmography. Recurrences of pulmonary embolism required a positive perfusion lung scan (at least 1 segmental perfusion defect), a ventilation-perfusion lung scan (intermediate or high probability), or a computerized tomographic scan.

Deep vein thromboses or pulmonary embolisms that occurred within the initial anticoagulation period (90 days) were not considered thrombotic event recurrences, but were considered a progression of the initial event (this occurred in 2 patients).

Idiopathic was defined as an initial thrombotic event that occurred in the absence of (1) pregnancy, (2) puerperium, (3) oral contraceptive use within 30 days, (4) trauma, surgery, immobilization, or use of a plaster cast within 3 months before the event. All others were classified as provoked.

Statistical Analysis

End of follow-up was at the first thrombotic event recurrence, date of death, date of emigration, or the end of the study, whichever occurred first. Observation time was calculated as the time at risk from the end of the anticoagulation treatment for the first thrombotic event to the end of follow-up. Incidence rates of recurrent thrombotic events were calculated as the number of events over the accumulated patient-time. Cumulative incidence was calculated by Kaplan-Meier survival analysis.

The Cox-proportional hazards model was used to evaluate risks between groups and was adjusted for age and sex. Anticoagulant therapy was entered in the model as a time-dependent covariate. Separate analyses were performed to assess the effect of prothrombotic abnormalities on the risk of recurrence (factor V Leiden, prothrombin G20210A, hyperhomocysteinemia, high levels of factors VIII, IX, or XI or of fibrinogen, and deficiencies of protein C, protein S, or antithrombin). We assessed the risk of thrombotic event recurrence by sex and by idiopathic or provoked classification of initial thrombotic event. The effect of oral contraceptive use was determined by calculating thrombotic event recurrence rates for women who used an oral contraceptive at any time (either continued use or restarted use) during the follow-up period, stratified by use at the time of the first event. In ad-

dition, we estimated the risk separately for a second contralateral compared with a second ipsilateral thrombotic event.

During the follow-up period, some patients experienced periods with an increased risk of a thrombotic event (trauma, immobilization, operations, oral contraception, pregnancy) or a decreased risk (oral anticoagulation treatment). To determine the effect of blood abnormalities on risk of thrombotic event recurrence without the interference of these episodes, we repeated the analysis while excluding all such periods.

For continuous phenotypes, we used the following cut-off values: 166 IU/dL for factor VIII; 129 IU/dL for factor IX; 121 IU/dL for factor XI; 4.1 g/L for fibrinogen; and 16.7, 19.8 or 20.3 μ mol/L for homocysteine (3 different cut-off levels were used as a consequence of different processing times in the 3 clinics). Patients were considered deficient for protein C or protein S when levels were below the lower limit of normal (67 U/dL or 33 U/dL when using oral anticoagulation at the blood draw). Patients were considered deficient of antithrombin when levels were repeatedly below 80 U/dL. All analyses were performed with SPSS version 11.0 (SPSS Inc, Chicago, Ill).

RESULTS

A total of 474 patients were followed up for a mean (SD) of 7.3 (2.7) years and complete follow-up was achieved for 447 patients (94%) for a total observation time of 3477 patient-years (FIGURE 1). Twenty-seven patients were lost from observation (22 untraceable, 4 refusals, 1 disabled) and were included until their last observation. Of the remaining 447 patients, 5 patients emigrated and 14 patients died during follow-up. Follow-up was complete until death for 6 patients. The other 8 patients died before the subsequent questionnaire was due and follow-up for a thrombotic event was considered complete up until the date of their last questionnaire. The response rates after each questionnaire varied between 96% and 99%.

The general characteristics of the cohort are listed in TABLE 1. There were more women (n = 272) than men (n = 202) included in this follow-up study. The mean (SD) age of the cohort was 45 (13.7) years. The overall mean age was 6 years higher in men, which differed markedly according to the type of initial thrombotic event. Idiopathic first events were more common in men, who were on average 5 years younger than women with an idiopathic first event. Most provoked first events occurred in women. In the patients with provoked events, men were on average 9 years older than women, in whom oral contraceptive use was a common determinant. Apart from elevated levels of factor IX (more frequent in women) and hyperhomocysteinemia (more frequent in men), prothrombotic factors were equally distributed between the sexes (Table 1).

During follow-up, 90 patients had a recurrent thrombotic event. Of these patients, 73 had a DVT in the leg, 4 had a thrombosis in the arm, 12 had a pulmonary embolism, and 1 had Budd-Chiari syndrome with an extension into the vena cava. Two patients who initially had a DVT later had an arm thrombosis. One patient who initially had an arm thrombosis later had a DVT. Two other patients with an initial arm thrombosis later had a thrombosis in the opposite arm as their recurrent thrombotic event. Of the 72 patients who had a DVT as their recurrent event, 41 were ipsilateral and 31 were contralateral.

Anticoagulant Use During Follow-up

Follow-up started 90 days after the first event. At this time point, 195 individuals had finished their initial anticoagulant treatment. Of the other 279 patients, 174 had a prolonged period of initial anticoagulation treatment, which was less than 3 months for the majority (n = 106; TABLE 2). All others had additional periods of oral anticoagulant use during follow-up. For 116 patients (67%), the total duration of oral anticoagulant use was less than 12 months. The main reasons for anticoagulant use

were prophylaxis of DVT during risk situations, such as surgery or pregnancy. Fifty-seven patients took an oral anticoagulant for more than 12 months in total, which was for cardiac reasons or arterial prophylaxis in 16 patients. The exact reasons for oral anticoagulant use were not known in 53 patients.

Of the 57 patients who took an oral anticoagulant for more than 12 months in total, 45 (79%) had 1 or more prothrombotic abnormalities. The mean (SD) duration of oral anticoagulant use during follow-up of 45 patients was 4.7 (2.5) years per patient compared with 3.1 (2.3) years in the 12 patients without any abnormality. This difference was due mostly to patients with anticoagulant deficiencies (protein C, protein S, and antithrombin) who received anticoagulation for a mean (SD) duration of 6.5 (0.9) years per patient. No major differences in prescription of anticoagulation were observed among carriers of the other prothrombotic risk factors, including factor V Leiden and prothrombin G20210A carriers compared with noncarriers.

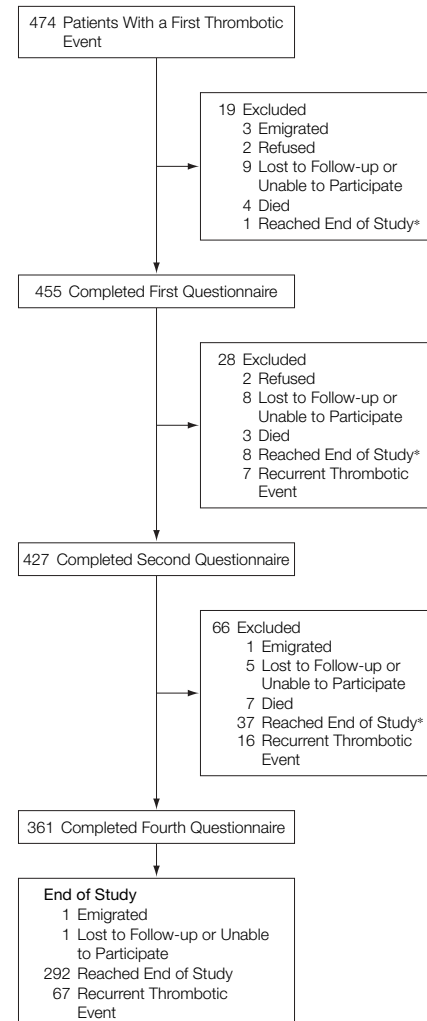
Risk of Recurrent Thrombotic Event

The overall incidence rate of recurrent thrombotic event was 25.9 per 1000 patient-years (95% CI, 20.8-31.8 per 1000 patient-years), corresponding to an annual risk of 2.6%. FIGURE 2 shows the cumulative incidence of recurrence over the 12-year follow-up period. The risk of recurrence was 12.4% after 5 years of follow-up (95% CI, 9.5%-15.4%) and 16.5% (95% CI, 13.1%-19.8%) after 7 years of follow-up. During the first 2 years after the discontinuation of the initial anticoagulant treatment, the incidence rate was highest (31.9 per 1000 patient-years; 95% CI, 20.3 to 43.5 per 1000 patient-years). Subsequently, the incidence rate decreased slowly with time (FIGURE 3).

Effect of Sex

Men had a 5-year cumulative incidence of thrombotic event recurrence of 19.3% (95% CI, 13.9%-24.8%) compared with 7.4% (95% CI, 4.3%-10.5%) in women. The cumulative in-

Figure 1. Flow of Patients During Follow-up



*A total of 9 individuals were lost during the study but later found. Thus, these individuals did not receive all 4 questionnaires, but information was complete during follow-up.

cidence after 7 years was 25.3% (95% CI, 19.3%-31.2%) in men compared with 9.9% (95% CI, 6.4%-13.5%) in women. The overall age-corrected HR for risk of thrombotic event recurrence in men compared with women was 2.7 (95% CI, 1.8-4.2).

Laboratory Abnormalities

Of all 474 patients, 319 (67%) had at least 1 laboratory abnormality at their first examination. After adjustment for age, sex, and anticoagulation, no clear excess risk of recurrence was observed

when we contrasted 319 patients with 1 or more prothrombotic abnormalities to those with none (HR, 1.4; 95% CI, 0.9-2.2) (TABLE 3). We did not observe an increased risk of recurrence for any of the following prothrombotic risk factors (using those without the specific abnormality as the reference group): factor V Leiden, prothrombin G20210A, elevated levels of factor VIII, elevated levels of factor IX, elevated levels of factor XI, and hyperhomocysteinemia (TABLE 4). Adjustment for age, sex, and periods of anticoagulation did not change these risk estimates (Table 4). In the patients with a deficiency of 1 of the natural anticoagulants protein C, protein S, or antithrombin, a mildly increased risk of a recurrent thrombotic event was observed (HR, 1.8; 95% CI,

0.9-3.7). Fibrinogen levels exceeding 4.1 g/L were also found to be associated with a slightly increased risk of thrombotic event recurrence (HR, 1.6; 95% CI, 1.0-2.6; after adjustment for age, sex, and anticoagulation, the HR was 1.7 [95% CI, 1.1-2.8]).

Only 1 of the 8 patients homozygous for factor V Leiden experienced a recurrence during a mean (SD) follow-up of 8 (3.5) years. Their 5-year cumulative incidence of 12.5% did not differ from all patients, while none of the 8 received long-term anticoagulant treatment.

Combinations of Thrombophilic Factors

Several patients had more than 1 of the abnormalities studied. Patients with 1

abnormality had a 1.2-fold increased risk of a thrombotic event recurrence compared with the 155 patients without an abnormality. In those with more than 1 abnormality, the recurrence rate increased 1.4-fold compared with those without an abnormality. After correction for age, sex, and periods of anticoagulation (Table 3), the HR increased to 1.6 in those with more than 1 abnormality, while it stayed the same in those with only 1 abnormality.

Because factor V Leiden is the most common genetic abnormality, we studied its combinations with other prothrombotic defects in more detail. Sixty-three patients had factor V Leiden and 1 of the other prothrombotic risk factors (prothrombin G20210A, elevated levels of factors VIII, IX, or XI, fibrinogen, homocysteine, or deficiencies of protein C, protein S, or antithrombin), while 29 patients carried factor V Leiden without any additional abnormality. The thrombotic event recurrence rate was 27.9 per 1000 patient-years (95% CI, 14.9-47.8 per 1000 patient-years) in those with factor V Leiden and any other abnormality and 33.9 per 1000 patient-years (95% CI, 13.6-69.9 per 1000 patient-years) in those with factor V Leiden without any other abnormality.

In patients with a combination of factor V Leiden and elevated levels of fibrinogen, a high recurrence rate of 69.8 per 1000 patient-years (95% CI, 25.6-152.1 per 1000 patient-years) was found. Other combinations of biochemical risk factors (prothrombin G20210A, elevated levels of factors VIII, IX, or XI, or homocysteine, deficiencies of protein C, protein S, or antithrombin) with factor V Leiden did not show an additional increased risk.

Table 1. Patient Characteristics*

	Men (n = 202)	Women (n = 272)	All (n = 474)
Age, mean (SD), y†	49 (12.8)	43 (14.0)	45 (13.7)
First thrombotic event			
Idiopathic	163 (81)	96 (35)	259 (55)
Mean (SD) age, y	49 (13.1)	54 (10.7)	51 (12.5)
Provoked‡	39 (19)	176 (65)	215 (45)
Mean (SD) age, y	46 (11.3)	37 (11.6)	39 (12.1)
Prothrombotic risk factors			
Factor V Leiden	40 (20)	52 (19)	92 (19)
Prothrombin G20210A	13 (6)	16 (6)	29 (6)
Anticoagulant deficiency§	13 (6)	12 (4)	25 (5)
High level of factor			
VIII (>166 IU/dL)	44 (22)	66 (24)	110 (23)
IX (>129 U/dL)	29 (14)	57 (21)	86 (18)
XI (>121 U/dL)	37 (18)	55 (20)	92 (19)
Hyperfibrinogenemia (>4.1 g/L)	39 (19)	48 (18)	87 (18)
Hyperhomocysteinemia	39 (19)	44 (16)	83 (18)

*Values are expressed as number (percentage) unless otherwise indicated. Cut-off points are in parentheses unless otherwise indicated.

†At start of follow-up.

‡Defined as pregnancy, puerperium, or use of oral contraceptives within 30 days, or trauma, surgery, immobilization, or use of a plaster cast within 3 months before the event.

§Deficiency of protein C (<0.67 [0.33] IU/mL), protein S (<0.67 [0.33] IU/mL), or antithrombin (<0.80 U/mL).

||Cut-off points: more than 16.7 μ mol/L (Leiden), 19.8 μ mol/L (Amsterdam), 20.3 μ mol/L (Rotterdam).

Table 2. Oral Anticoagulant Use During Follow-up

Oral Anticoagulant	Use During Follow-up*				Total
	None	<3 Months	3-12 Months	>12 Months	
Initial use					
<90 d	195	16	6	21	238
≥90 d	0	0	0	0	0
Continuous use after first event	0	106	51	17	174
Restart	0	13	30	19	62
Total	195	135	87	57	474

*Ninety days after first event.

Ipsilateral vs Contralateral Recurrent DVTs

The incidence rate of an ipsilateral second DVT (n=41) was 12.4 per 1000 patient-years (95% CI, 8.9-16.9 per 1000 patient-years), while the incidence rate of a contralateral second DVT (n=31) was only slightly lower at 9.5 per 1000 patient-years (95% CI, 6.5-13.5 per 1000 patient-years).

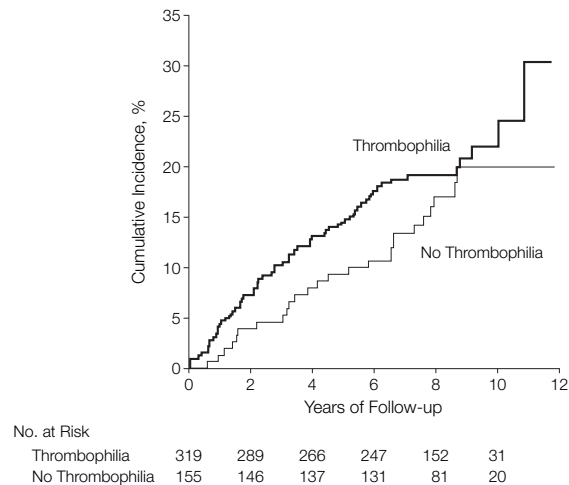
The incidence rate of an ipsilateral recurrent DVT in patients with a prothrombotic risk factor was 13.0 per 1000 patient-years (95% CI, 8.6-18.7 per 1000 patient-years), while the incidence rate of a contralateral recurrent DVT was 9.8 per 1000 patient-years (95% CI, 6.1-15.0 per 1000 patient-years). In patients without prothrombotic risk factors, the incidence rate of an ipsilateral recurrent DVT was 11.4 per 1000 patient-years (95% CI, 6.1-19.6 per 1000 patient-years), while the incidence of a contralateral recurrent DVT was 9.0 per 1000 patient-years (95% CI, 4.3-16.5 per 1000 patient-years).

Initial Idiopathic and Provoked Thrombotic Events

The recurrence rate was highest in those with an idiopathic first thrombotic event at 33.2 per 1000 patient-years (95% CI, 25.4-42.6 per 1000 patient-years) compared with patients with a provoked first thrombotic event in whom the recurrence rate was 17.7 per 1000 patient-years (95% CI, 11.9-25.4 per 1000 patient-years) (HR, 1.9; 95% CI, 1.2-2.9). In both men and women, the risk of thrombotic event recurrence was higher in those who had had an idiopathic first thrombotic event, but the effect was slightly higher in women (TABLE 5). Likewise, the effect of sex on the risk of thrombotic event recurrence was the same irrespective of type (idiopathic or provoked) of thrombotic event, with a higher risk in men than in women (Table 5).

In patients with an idiopathic first event, the recurrence rates were equal in those with prothrombotic abnormalities (33.6 per 1000 patient-years; 95% CI, 24.3-45.2 per 1000 patient-years) and without an abnormality (32.4 per 1000 patient-years; 95% CI, 19.2-51.2 per 1000 patient-years) for a HR adjusted for sex, age, and anticoagulation of 1.2 (95% CI, 0.7-2.2). In patients with a nonidiopathic first thrombotic event, the recurrence rate was somewhat higher among those with prothrombotic abnormalities (20.9 per 1000 patient-years; 95% CI, 12.9-31.9 per 1000 patient-years) compared with

Figure 2. Cumulative Incidence of Recurrent Thrombotic Events



Patients with and without thrombophilia during the period from the end of the initial anticoagulation period (90 days) until January 1, 2000. The crude hazard ratio of thrombophilia compared with no thrombophilia was 1.3 (95% confidence interval, 0.8-2.0); the hazard ratio adjusted for age, sex, and oral anticoagulation as a time-dependent covariate was 1.4 (95% confidence interval, 0.9-2.2).

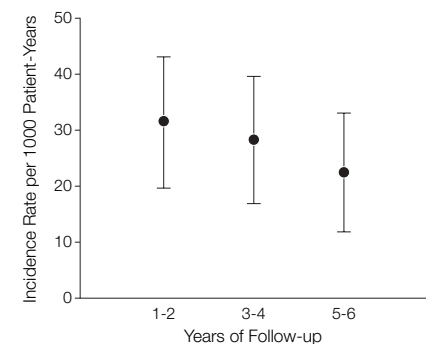
those without an abnormality (12.6 per 1000 patient-years; 95% CI, 5.4-24.8 per 1000 patient-years) for a HR adjusted for sex, age, and anticoagulation of 1.7 (95% CI, 0.7-3.8).

Oral Anticonceptive Use

A substantial number of women (n = 128, 47%) used oral contraceptives at the time of the first thrombotic event, most of whom discontinued use after the event. However, 58 women continued or restarted use of an oral contraceptive during follow-up. Eleven thrombotic event recurrences occurred during use of oral contraception or within 1 month after cessation. The recurrence rate in women who did not use oral contraceptives during follow-up was 12.9 per 1000 patient-years (95% CI, 7.9-21.2 per 1000 patient-years), while it was 28.0 per 1000 patient-years (95% CI, 15.9-49.4 per 1000 patient-years) in women who used oral contraceptives at some point during the follow-up period (either continuing or restarting).

Among women who did not use oral contraceptives during follow-up, the recurrence rate was slightly higher in women who had never used an oral contraceptive (16.2 per 1000 per 1000 patient-years; 95% CI, 8.7-30.2 per

Figure 3. Incidence Rate of Recurrent Thrombotic Event



Error bars indicate 95% confidence intervals.

1000 patient-years) compared with women who used oral contraceptives at the time of the first thrombotic event (9.7 per 1000 patient-years; 95% CI, 4.3-21.5 per 1000 patient-years) (TABLE 6). Among women who used oral contraceptives during follow-up, the risk of thrombotic recurrence was more or less equal in women who had also used an oral contraceptive at the time of the first thrombotic event (27.3 per 1000 patient-years; 95% CI, 14.7-50.7 per 1000 patient-years) compared with those who had not used oral contraceptives

at the time of their first event (32.5 per 1000 patient-years; 95% CI, 8.1-130.0 per 1000 patient-years). These rates were higher when only the years that the oral contraceptives were actually used were taken into account (Table 6).

Two of the 11 thrombotic events that arose during oral contraceptive use oc-

curred within 2 weeks after starting use. Two events occurred after 1 year of use, and the other events happened after a longer period of use, varying between 3 and 9 years. Of the 58 women who used oral contraceptives during follow-up, 15 had factor V Leiden. Only 1 thrombotic event recurrence occurred

in this group (17.2 per 1000 patient-years; 95% CI, 2.4-122.0 per 1000 patient-years).

Rate of Spontaneous Recurrences

To determine the effect of prothrombotic abnormalities on recurrence risk without the interference of episodes with an increased or decreased risk of thrombosis, we repeated the analysis while excluding all postoperative periods (4 weeks following surgical interventions), pregnancy and puerperium (6 weeks following delivery), periods of oral contraceptive use, and all periods of anticoagulation treatment. This left 66 events over 2862 patient-years, for an incidence rate of 23.1 per 1000 patient-years (95% CI, 17.8-29.3 per 1000 patient-years). For those with prothrombotic abnormalities (factor V Leiden, prothrombin G20210A, hyperhomocysteinemia, deficiencies of the protein C, protein S, or antithrombin, elevated levels of the factor VIII, factor IX, factor XI, or fibrinogen), the incidence rate was 24.8 per 1000 patient-years (95% CI, 18.2-33.1 per 1000 patient-years). For those patients without a prothrombotic abnormality, the incidence rate was 19.8 per 1000 patient-years (95% CI, 12.1-30.6 per 1000 patient-years) (HR, 1.2; 95% CI, 0.7-2.1). The effects of each of the prothrombotic defects separately on the risk of spontaneous recurrence were again equal to those found in the overall analysis (Table 4).

COMMENT

In a large cohort of patients followed up for a prolonged time after a first venous thrombotic event, we found an annual risk of thrombotic event recurrence of 2.6%. The cumulative risk of recurrence was 12.4% after 5 years and 16.5% after 7 years of follow-up. Although the incidence rate was slightly higher in the first 2 years, at an annual rate of 3.2%, the risk of thrombotic event recurrence persisted at a high level of more than 2% during the following years. Others have reported higher recurrence rates of approximately 25% after 5 years of follow-

Table 3. Recurrence Rate for Number of Prothrombotic Laboratory Abnormalities in 474 Patients

	Abnormality			
	None	1	>1	Any
Incidence rate (95% CI)*	22 (14-32)	25 (17-37)	30 (21-42)	28 (22-36)
Hazard ratio (95% CI)†	Referent	1.2 (0.7-2.0)	1.4 (0.8-2.3)	1.3 (0.8-2.0)
Hazard ratio (95% CI)‡	Referent	1.2 (0.7-2.1)	1.6 (1.0-2.7)	1.4 (0.9-2.2)

Abbreviation: CI, confidence interval.

*Per 1000 patient-years.

†Relative to those without an abnormality (crude ratio).

‡Relative to those without an abnormality and adjusted for age, sex, and anticoagulation as a time-dependent covariate.

Table 4. Recurrence Rates for Prothrombotic Laboratory Abnormalities in 474 Patients

Abnormality	No. of Recurrences	Incidence Rate (95% CI)*	Hazard Ratio (95% CI)†	Hazard Ratio (95% CI)‡
Factor V Leiden	20	30 (18-46)	1.2 (0.7-1.9)	1.3 (0.8-2.1)
Prothrombin G20210A	4	19 (5-48)	0.7 (0.3-2.0)	0.7 (0.3-2.0)
Anticoagulant deficiency§	8	45 (19-88)	1.8 (0.9-3.7)	1.8 (0.9-3.8)
High factor ¶				
VIII (>166 IU/dL)	23	29 (18-43)	1.1 (0.7-1.8)	1.3 (0.8-2.1)
IX (>129 U/dL)	13	21 (11-36)	0.9 (0.5-1.7)	1.2 (0.6-2.1)
XI (>121 U/dL)	11	16 (8-29)	0.6 (0.3-1.1)	0.6 (0.3-1.1)
Hyperfibrinogenemia	22	38 (24-58)	1.6 (1.0-2.6)	1.7 (1.1-2.8)
Hyperhomocysteinemia#	14	23 (13-39)	0.9 (0.5-1.6)	0.9 (0.5-1.6)

Abbreviation: CI, confidence interval.

*Per 1000 patient-years.

†Relative to those without the abnormality (crude ratio).

‡Relative to those without the abnormality and adjusted for age, sex, and anticoagulation as a time-dependent covariate.

§Deficiency of protein C, protein S, or antithrombin.

||Cut-off points: protein C: <0.67 (0.33) IU/mL; protein S: <0.67 (0.33) IU/mL; antithrombin: <0.80 U/mL; fibrinogen: >4.1 g/L.

¶Cut-off points are in parentheses.

#Cut-off points: homocysteine: >16.7 µmol/L (Leiden); 19.8 µmol/L (Amsterdam); 20.3 µmol/L (Rotterdam).

Table 5. Recurrence Rates by Sex and Type of First Thrombotic Event

	Men		Women	
	Provoked*	Idiopathic	Provoked*	Idiopathic
No. of patients	39	163	176	96
No. of recurrences	8	49	21	12
Incidence rate (95% CI)†	29 (13-58)	44 (32-58)	15 (10-24)	17 (9-29)
Hazard ratio (95% CI)‡	Referent	1.6 (0.8-3.4)	Referent	1.9 (0.8-4.4)
Hazard ratio (95% CI)‡		2.7 (1.4-5.1)		Referent
Hazard ratio (95% CI)‡	2.8 (1.2-6.6)		Referent	

Abbreviation: CI, confidence interval.

*Defined as pregnancy, puerperium or use of oral contraceptives within 30 days, or trauma, surgery, immobilization, or use of plaster casts within 3 months before the event.

†Per 1000 patient-years.

‡Corrected for 10-year age categories, duration of anticoagulation during follow-up as a time-dependent covariate, and thrombophilia.

up.^{12,13} An important difference of these studies was their inclusion of elderly and cancer patients—groups likely to have recurrent thrombotic events. Therefore, our results apply to patients who are younger than 70 years at their first thrombotic event, who do not have malignancy, but who are otherwise unselected.

We found a few clinical factors that affected the risk of recurrence (ie, male sex, an idiopathic first thrombotic event, and oral contraceptive use). Sex and the type of event were related: idiopathic first thrombotic events were more common in men, while provoked first thrombotic events were seen almost 5 times more frequently in women because of oral contraceptive use. Men had a 2.5-fold higher risk of thrombotic event recurrence than women. This effect of sex was the same in patients with a first idiopathic thrombotic event as in those with a first provoked thrombotic event. Similarly, the risk of thrombotic event recurrence in both men and women was higher in those who had had an idiopathic event. Although sex and type of first thrombotic event were strongly related, their effects on recurrence were not connected. The effect of prothrombotic abnormalities was small both in men and women and could therefore not explain the difference between the sexes. These findings confirm recent results from a British and an Austrian study.³⁷⁻³⁹

Use of oral contraception increased the risk of thrombotic event recur-

rence. Advice to refrain from further oral contraceptive use would be a simple and effective way to reduce the risk of a second thrombotic event in women. We did not see a major effect of postthrombotic damage on the risk of recurrence. We found similar rates of thrombotic event recurrence in the ipsilateral and contralateral leg. This makes it tempting to hypothesize that a systemic effect is as likely to contribute to the overall recurrence risk as persisting remnants of the initial clot.⁴⁰

Sixty-seven percent of the patients had at least 1 prothrombotic abnormality. In these patients the recurrence risk was only slightly increased (1.4-fold) compared with those without such abnormalities. In patients with more than 1 abnormality, the recurrence rate was higher than in those with only 1 abnormality (1.6-fold vs 1.2-fold). The effect of the prothrombotic risk factors separately varied somewhat but on the whole, they seemed to be a weak determinant of recurrences. We found no evidence of an increased risk of recurrence for carriers of factor V Leiden or the prothrombin G20210A mutation. Similarly, we could not find an excess recurrence risk for individuals with high levels of factors VIII, IX, or XI. Hyperhomocysteinemia did not show any effect on recurrence risk either. It should be noted that in the Netherlands vitamin supplementation is not currently advised to patients with hyperhomocysteinemia. Therefore, these results represent the natural course of

this condition. A mildly increased risk (1.8-fold) was observed in those with the strongest risk factors for first thrombotic events, deficiencies of protein C, protein S, and antithrombin. High fibrinogen levels also conferred a slightly increased risk of recurrence (1.7-fold). These results are at variance with some other studies in which increased recurrence risks were found for protein C, protein S, and antithrombin,¹³ for hyperhomocysteinemia,^{29,30} for increased levels of factor VIII and factor IX,^{27,28} and for factor V Leiden and prothrombin G20210A.^{21,22,24,25} These studies differed considerably with respect to design and study population, methods, sample size, and duration of follow-up, which could explain the discrepancies.^{31,32} In a prospective cohort study of unselected patients with a similar design as our study, no effect of thrombophilia was found either.³⁷ In summary, we saw no major effect for any of these factors, which is internally consistent because it is difficult to understand why some prothrombotic abnormalities would increase the risk of recurrence and others would not.

Venous thrombosis is a multicausal disease.⁴ Individuals need a certain combination of risk factors, each adding to the thrombotic event potential, which exceeds the thrombosis threshold. When patients have similar thrombotic event potentials, recurrence risks may be similar, too. This explains the equal risks we found for all thrombophilic defects. In patients whose first thrombotic event

Table 6. Recurrence Rates by Oral Contraceptive Use in 215 Women Between 16 and 55 Years

	Taking Oral Contraceptive at First Event		Not Taking Oral Contraceptive at First Event	
	Used During Follow-up (n = 50)	Discontinued Use (n = 77)	Used During Follow-up (n = 8)	No Use (n = 80)
No. of recurrences	10	6	2	10
No. of patient-years	366.6	621.0	61.5	616.4
Overall incidence (95% CI)*	27.3 (14.7-50.7)	9.7 (4.3-21.5)	32.5 (8.1-130.0)	16.2 (8.7-30.2)
No. of recurrences while taking oral contraceptive	10		1	
No. of oral contraceptive use patient-years	180.7		28.5	
Incidence (95% CI) while taking oral contraceptive*	55.3 (29.8-102.9)		35.1 (4.9-249.1)	

Abbreviation: CI, confidence interval.

*Per 1000 patient-years.

was idiopathic, the recurrence rate was equal in those with and without a prothrombotic abnormality. This can be explained from the existence of a not yet identified prothrombotic abnormalities, which hold the same thrombotic event potential as the known prothrombotic abnormalities. The recurrence risk was actually only increased in those patients who had 2 or more abnormalities, or in other words, only those with a somewhat higher thrombotic event potential stood out.

Among patients with thrombophilia, those who had a provoked first thrombotic event had a recurrence risk that was still lower than patients who had an idiopathic first thrombotic event. This is remarkable because one would expect these rates to be equal after the environmental factor (surgery, puerperium) that contributed to the initial thrombotic event has been removed. This can only be explained when patients with thrombophilia and an idiopathic first thrombotic event have a higher thrombotic event potential than patients with thrombophilia and a provoked first thrombotic event—this could be an extra (a not yet identified) laboratory risk factor or a local factor such as an anatomical abnormality.

These findings have important implications for clinical strategies. Patients with an idiopathic first thrombotic event are often extensively tested for prothrombotic defects. However, a positive result of a defect does not predict the risk of thrombotic event recurrence and therefore has no clinical consequence.

Our study may be limited with respect to the generalizability of the findings because we excluded patients older than 70 years and cancer patients. Our main findings may therefore not be applicable to these groups. Also, in our study population the use of prophylactic anticoagulation for short periods was quite high. This may have affected the overall relatively low rate of recurrences. However, we do not expect that this has had an influence on the lack of effect we found for the separate prothrombotic abnormalities. In all analy-

ses, the use of anticoagulation was adjusted for and even when we excluded all risk-enhancing (surgery, oral contraception use, pregnancy, puerperium) and risk-decreasing (oral anticoagulation) situations, we did not find an effect of thrombophilia. Another issue is the diagnosis of thrombotic event recurrence because a new event is often difficult to distinguish from postthrombotic syndrome.⁴¹ An incorrect classification of a thrombotic event recurrence could have affected the total rate of recurrent events. However, the incidence rate of a contralateral second DVT was only slightly lower than that of an ipsilateral DVT. It is therefore unlikely that the low rate of recurrent events was overestimated. The distribution of the prothrombotic risk factors was also equal between ipsilateral and contralateral DVTs. Therefore, our conclusion with respect to the effect of thrombophilia would remain unchanged.

In conclusion, patients who had a first thrombotic event had a high risk of recurrence. This risk is higher in men, in patients whose first thrombotic event was idiopathic, in women who use oral contraceptives, and in patients with 2 or more prothrombotic risk factors. Solitary laboratory abnormalities appear not to predict the risk of recurrence. Therefore, extensive, if any, thrombophilic work-up after a first thrombotic event is not likely to confer a clinical benefit to the patient. Similarly, a differential treatment with regard to duration of oral anticoagulation in patients with prothrombotic abnormalities does not seem to be rational based on these data. Adequate prophylactic anticoagulation during risk situations for all patients with a history of a thrombotic event may be the most important measure to reduce the risk of a recurrent event. Women using oral contraceptives should be advised to refrain from further use. The decision on optimal duration of anticoagulation therapy after a first thrombotic event will probably need to be based on clinical factors (male sex, oral contraceptive use, and idiopathic first thrombotic event) rather than laboratory abnormalities.

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Study concept and design: Koster, Vandenbroucke, Rosendaal.

Acquisition of data: Christiansen, Koster.

Analysis and interpretation of data: Christiansen, Cannegieter, Koster, Rosendaal.

Drafting of the manuscript: Christiansen, Cannegieter, Rosendaal.

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