

Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study

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Summary

Background Stratification for risk of recurrence after a first episode of venous thromboembolism (VTE) would affect the duration of anticoagulant therapy. We aimed to determine the incidence of recurrence of VTE in relation to clinical risk factors and standard laboratory testing for heritable thrombophilic defects.

Methods We established a database to prospectively follow-up a cohort of unselected patients who had had a first episode of objectively proven VTE. We excluded patients with malignant disease and antiphospholipid syndrome. All patients were offered testing for heritable thrombophilia.

Findings At 2 years, the cumulative recurrence rate in 570 patients was 11%. Incidence was lowest after surgery-related VTE (0%) and highest after unprecipitated VTE (19.4%) ($p < 0.001$). 85% of patients were tested for heritable thrombophilic defects. Recurrence rates were not related to presence or absence of laboratory evidence of heritable thrombophilia (hazard ratio 1.50 [95% CI 0.82–2.77]; $p = 0.187$). In patients with a first event that was unprecipitated or was associated with a non-surgical trigger, recurrence rates did not differ in patients with or without thrombophilia (1.34 [0.73–2.46]; $p = 0.351$).

Interpretation In unselected patients who have had a first episode of VTE, testing for heritable thrombophilia does not allow prediction of recurrent VTE in the first 2 years after anticoagulant therapy is stopped. However, assessment of clinical risk factors associated with the first episode of VTE does predict risk of recurrence. Patients with postoperative VTE have a very low rate of recurrence.

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Introduction

After a first episode of venous thromboembolism (VTE), patients are usually treated with oral anticoagulation for between 6 weeks and 6 months.¹ When treatment is stopped, the frequency of recurrence is 12–18% after 2 years.^{2,3} The risk of recurrence is highest soon after the acute episode and it declines with time. Continued treatment with oral anticoagulant therapy will prevent most episodes of recurrence but there is a substantial risk of major bleeding associated with prolonged treatment.^{4,5} In theory, anticoagulant treatment should be continued until the risk outweighs the benefit. However, the optimum duration of treatment is uncertain because the risk of bleeding associated with anticoagulation and the risk of recurrent VTE after stopping treatment are not easily predicted on an individual basis. Acquired risk factors are often identified in patients presenting with VTE, and heritable thrombophilic defects are identified in at least a third of patients with acute VTE.⁶ In this prospective cohort study, we aimed to determine the risk of recurrence in relation to clinical risk factors and standard laboratory testing for thrombophilic defects after a first episode of VTE.

Methods

Patients

Since August, 1997, all patients referred for oral anticoagulant therapy at Addenbrooke's Hospital, Cambridge, UK, after a first episode of objectively confirmed VTE have been registered on a clinical outcome audit database. The database was registered with the hospital Clinical Audit and Effectiveness Unit. Thrombophilia testing was offered to all patients and 85% gave informed consent to have this test.

We excluded patients with antiphospholipid activity and those with malignant disease from analyses, although they were given appropriate treatment. We also excluded patients with mesenteric vein thrombosis or cerebral vein thrombosis because the natural history might be different to limb deep vein thrombosis (DVT), and because in many patients, lifelong anticoagulant treatment is considered to be justified in view of potential risks associated with recurrent events.

At the time of registration, we recorded clinical risk factors and categorised patients into four groups: those who had had surgery in the previous 6 weeks (group A); women with pregnancy-associated VTE, including postpartum events up to 2 months after delivery (group B); patients with unprecipitated venous thromboembolism in whom there was no identifiable clinical risk factor (group C); and patients with non-surgical risk factors for VTE (group D). Some patients in group D had absolute risk factors such as a fracture or application of a plaster cast, oestrogen-containing oral contraceptive use, while others had unquantifiable risk factors such as immobilisation, a non-specific transient illness, or a history of travel.

	Factor V Leiden (95% CI)	F2G20210A (95% CI)	AT deficiency (95% CI)	PC deficiency (95% CI)	PS deficiency (95% CI)
Group					
A	6/73 (8%) (3.1–17.0)	0/71	1/73 (1%) (0–7.4)	0/68	4/67 (6%) (1.7–14.6)
B	3/11 (27%) (6.0–61.0)	0/11	0/11	0/9	0/9
C	26/157 (17%) (11.1–23.3)	8/154 (5%) (2.3–10.0)	6/156 (4%) (1.4–8.2)	1/142 (<1%) (0–3.9)	10/142 (7%) (3.4–12.6)
D	42/246 (17%) (12.4–21.8)	12/240 (5%) (2.6–8.6)	1/245 (<1%) (0–2.3)	4/212 (2%) (0.5–4.8)	13/210 (6%) (3.3–10.4)
Total cohort	77/487 (16%) (12.6–19.1)	20/476 (4%) (2.6–6.4)	8/485 (2%) (0.7–3.2)	5/431 (1%) (0.4–2.7)	27/428 (6%) (4.2–9.1)

AT=antithrombin. PC=protein C. PS=protein S. Data are number (%) (95% CI)

Table 1: Thrombophilic defects identified by laboratory testing

Procedures

Deep vein thrombosis was diagnosed by compression ultrasonography or contrast venography. Pulmonary embolus was diagnosed by ventilation-perfusion lung scanning, CT, or pulmonary angiography. Patients were treated with tinzaparin, European grade 1 or 2 compression stockings, and warfarin. All patients had a target International Normalised Ratio (INR) of 2.5.¹

After treatment was completed, patients were counselled and offered thrombophilia testing. We told patients that the test results might help to explain why they had suffered venous thrombosis, but that results might not affect their treatment after their one episode of thrombosis. Anticoagulant treatment was not restarted in any patient on the basis of evidence of heritable thrombophilia. All patients were told their results and advised of acquired risks for VTE and the need for short-term antithrombotic therapy at times of high risk—eg, after surgery. We advised women who were taking combined oral contraceptive pills at the time of thrombosis not to use oestrogen-containing contraceptive pills after stopping treatment with warfarin.

Patients were followed up at 6 months, 1 year, and 2 years and we recorded all objectively diagnosed episodes of recurrent venous thromboembolism after stopping anticoagulant treatment. In all patients, the radiological evidence for recurrence was reviewed by one investigator (TB) who was unaware of the results of the thrombophilia tests. Only patients with a new or extended clot, which resulted in reintroduction of anticoagulant therapy, were recorded as having recurrent VTE.

We measured concentrations of natural anticoagulants and lupus anticoagulant activity using methods and normal local ranges that are described elsewhere.⁷ Antithrombin and protein C activity were measured by chromogenic assays (Quadrach, Epsom, UK). Free protein S was measured by ELISA (Quadrach). The lower limits of normal were 78% for antithrombin, 73% for protein C, and 71% for free protein S in men and 54% for free protein S in women. Deficiency of a natural anticoagulant had to be confirmed on a repeat sample.

Factor V Leiden and F2G20210A polymorphisms were detected by conventional DNA amplification and

restriction enzyme analysis. Lupus anticoagulant activity was measured by the dilute Russell viper venom time⁸ and the silica clotting time.⁹ We measured Anti-cardiolipin titres by ELISA using bovine cardiolipin antigen (Sigma, St Louis, MD, USA) for antibody capture. Conjugated anti-human IgG and IgM antibodies were used to detect cardiolipin-bound antibody with a standard curve derived from a positive plasma calibrated against reference standard 90/656. Normal concentrations were less than 20 GPLU/mL for IgG and less than 20 MPLU/mL for IgM.

The quality of laboratory results was monitored throughout the study through participation in the United Kingdom National External Quality Assurance Scheme (NEQAS).

Statistical analysis

We used SPSS (version 10) for statistical analysis. Time-to-event analysis was done with Kaplan-Meier estimates and Cox proportional hazards modelling. Hazard ratios (HR) were not calculated when no events were recorded. Based on a 30% frequency of thrombophilic defects in unselected patients presenting with a first episode of VTE, we calculated that 500 patients would be needed to allow detection of a 10% increased VTE rate in patients with thrombophilia at $\alpha=0.05$ (one-tailed) and 90% power when the event rate in patients without thrombophilia was 10% (HR 2.3) and 80% power when it was 15% (1.9).

Results

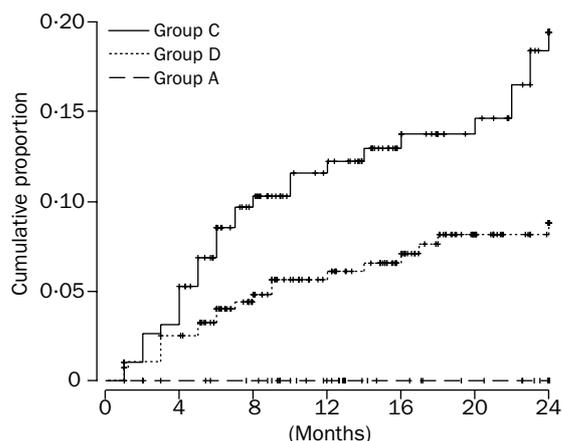
We included 781 patients who registered at Addenbrooke's Hospital, Cambridge, between August, 1997, and January, 2002. 211 patients were excluded from further analysis either because of malignant disease at registration or follow-up (118), antiphospholipid syndrome (47), cerebral vein thrombosis (six), continued anticoagulant therapy (22), death (14), or proven recurrent symptomatic VTE before completing anticoagulant therapy (four). Thus, there were 570 patients in the final analyses—86 in group A, 12 in group B, 193 in group C, and 279 in group D.

Median age in this cohort was 67 years (range 19–100 years) and 251 (44%) were men. The distribution of the initial thrombotic events in the cohort of 570 patients was symptomatic pulmonary embolus 165 (29%), proximal leg vein 323 (57%), calf vein

Patient (group)	Age at first event (years)	First event	Time on therapy after first VTE (weeks)	Time to recurrence (months)*	Second event	Thrombophilia
1 (C)	83	Calf DVT	13	20	Proximal DVT	AT
2 (C)	47	Calf DVT	13	10	Proximal DVT	AT
3 (D)	91	Proximal DVT	26	14	Proximal DVT	PC/FVLeiden
4 (C)	75	Proximal DVT	26	2	Proximal DVT	PS/FVLeiden
5 (D)	64	Proximal DVT	13	17	Proximal DVT	PS
6† (D)	23	PE	26	8	PE	PS
7 (C)	83	PE	26	6	PE	PS

DVT=deep vein thrombosis. PE=pulmonary embolus. AT=antithrombin deficiency. PC=protein C deficiency. PS=protein S deficiency. FV Leiden=factor V Leiden. Patients did not have a family history of thromboembolism unless otherwise stated. *After completion of anticoagulant therapy. †Patient had a family history of thromboembolism.

Table 2: Characteristics of seven patients with deficiency of a natural anticoagulant and recurrent venous thromboembolism



Number at risk							
Group C	193	184	153	133	110	98	81
Group D	279	269	235	209	185	155	139
Group A	86	82	79	71	61	58	53

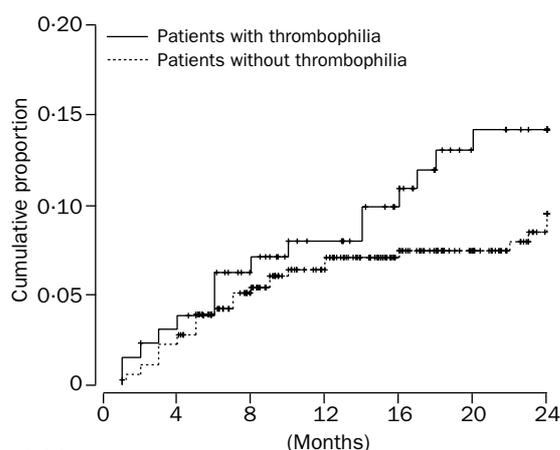
Figure 1: Cumulative proportions of recurrent thrombosis after cessation of anticoagulant therapy

Data for group B are not included because it was a small group with no recurrences.

68 (12%), arm vein 14 (3%). 26 patients died during follow-up without recurrence of VTE, and data were censored at the time of death. Specific causes of death were not recorded, only whether or not death was attributable to pulmonary embolus. We did not record autopsy rates and findings, other than pulmonary embolus.

487 (85%) patients were genotyped for factor V Leiden and 476 (83%) of these were also genotyped for F2G20210A. 485 (85%) had concentrations of antithrombin measured, 431 (76%) protein C, and 428 (75%) free protein S. 126 (22%) patients had an abnormal result that was confirmed on separate samples in cases of low concentrations of a natural anticoagulant. Table 1 shows the distribution of heritable thrombophilic defects identified by laboratory testing in each clinical group.

The mean duration of anticoagulation following the first episode of VTE was 24 weeks in group A, 27 weeks in group B, 26 weeks in group C, and 24 weeks in group D. After completion of anticoagulant therapy, the cumulative recurrence rate at 2 years was 11% (95% CI 7.9–13.7%),



Number at risk							
Patients with thrombophilia	130	125	111	100	90	76	71
Patients without thrombophilia	359	350	308	272	230	201	174

Figure 2: Cumulative proportions of recurrent thrombosis in patients with and without laboratory evidence of a heritable thrombophilic defect

by Kaplan Meier analysis. There was no VTE recurrence in group A or group B. 32 (17%) of patients in group C had VTE recurrence, as did 21 (8%) in group D. The cumulative 2-year recurrence rate for group C was 19.4% (95% CI 13–26%) and 8.8% (5.1–12.5%) for group D.

Figure 1 shows rates of VTE recurrence after cessation of anticoagulant therapy by clinical group. The recurrence rate for group A was significantly lower than that for groups C (logrank $\chi^2=15.32$; $p<0.0001$) and D (logrank $\chi^2=6.8$; $p=0.009$). The recurrence rate for group C was higher than for group D (logrank $\chi^2=8.11$; HR 2.20 [95% CI 1.26–3.84]; $p=0.004$). The number of patients in group B was too small for a meaningful analysis.

Figure 2 shows the rate of recurrent VTE in the total cohort in relation to presence or absence of laboratory evidence of a heritable thrombophilic defect. There was no evidence of a difference between patients with or without thrombophilia (logrank $\chi^2=1.74$; HR 1.50 [95% CI 0.82–2.77]; $p=0.187$). When we did an analysis for the presence or absence of the factor V Leiden mutation, there was no evidence of a significant difference (logrank $\chi^2=0.66$; HR 1.35 [0.65–2.80]; $p=0.417$). Likewise, when analysis was done to test for the presence or absence of the F2G20210A mutation, we noted no evidence of a difference (logrank $\chi^2=0.87$; HR 1.74 [0.54–5.62]; $p=0.3508$).

Because there was a low incidence of recurrence in groups A and B, we assessed the effect of thrombophilia after exclusion of these patients. However, even after this exclusion, we noted no evidence of a difference in recurrence rates between patients with or without thrombophilia in the 472 patients in groups C and D (logrank $\chi^2=0.87$; HR 1.34 [0.73–2.46]; $p=0.351$).

Two of eight patients with low antithrombin had a recurrence (relative risk [RR] 2.59, [95% CI 0.8–8.8]); two had combined defects, one with factor V Leiden heterozygosity and one with a low concentration of protein S—neither of these patients suffered a recurrence during the follow-up period.

One of five patients with low protein C had a recurrence (RR 1.84, [0.3–10.8]), and this person had a combined defect with heterozygosity for factor V Leiden.

Three of 27 patients with low protein S had a recurrence, including one with a combined defect with heterozygosity for factor V Leiden (RR 1.00, [0.3–3.01]). Five patients without recurrence had combined defects. Table 2 shows details of the seven patients who had low concentrations of natural anticoagulant and a recurrent VTE.

Discussion

We have shown three important findings that could have implications for clinical practice. First, patients with postoperative VTE have a very low risk of recurrence and a low incidence of thrombophilic defects. Second, patients with unprecipitated VTE have a 20% cumulative recurrence rate at 2 years; however, despite 27% of patients having heritable thrombophilic defects, testing does not allow prediction of a high risk of recurrence. Third, patients with non-surgical triggers for a first VTE event have a significantly lower risk of recurrence (8%) compared with patients who do not have identifiable triggers (20%). Again, testing for heritable thrombophilic defects in these patients does not aid prediction of recurrence.

A low risk of recurrence in patients who have postoperative VTE has previously been reported;^{3,10–12} however, our study prospectively assessed this hypothesis as a primary outcome measure in conjunction with thrombophilia testing. This finding suggests that these patients can be reassured that after a finite period of

anticoagulation and use of compression stockings that their risk of another VTE is very low.

That patients with unprecipitated VTE have a high risk of recurrence has been reported.¹³ Debate continues about the use of testing for evidence of thrombophilia;¹⁴ however, as results of more studies are reported, the value of such testing becomes less likely.¹⁵ In our large prospective cohort, we have shown that no correlation exists between abnormal laboratory results and the incidence of VTE recurrence. Furthermore, results of several recent studies lend support to the argument against testing for thrombophilia.^{16,17} Our findings provide strong justification for not screening for thrombophilic defects in unselected patients who have had a first episode of unprecipitated VTE. However, that testing of patients from thrombosis-prone families is warranted might be argued. If such testing is done, a clinician should have a clear idea before the tests are done about how to act on the results, and he or she should use an objective assessment of what constitutes a significant family history.¹⁸

In this study, we have reported the frequency of recurrent VTE in patients from a population of about 200 000. All thrombotic events were objectively diagnosed and we noted recurrence only after independent validation by a clinician who did not know the thrombophilia status of the patient. Patients were not selected on the basis of family history of thrombosis, but rather from a cohort of unselected patients from which those with malignant disease or antiphospholipid syndrome had been excluded. This cohort is, therefore, likely to be representative of patients presenting with VTE to other hospitals for whom the optimum duration of anticoagulation is uncertain. The generalisability of our results is also lent support by the distribution of venous thromboembolic events at presentation and the overall cumulative recurrence rate of 11% at 2 years, which concurs with other reports.^{3,12,19}

The high rate of testing and the incidence of thrombophilic defects also suggests that this cohort is typical of an unselected patient group. The frequency of the factor V Leiden and F2G20210A gene mutations was 15.8% and 4.2%, respectively, which is the same as that reported for patients in a case-control study in the same geographical location (15.1% and 5.0%, respectively).²⁰ The incidence of confirmed low concentrations of antithrombin, protein C, and protein S in an unselected patient population is also as expected.²¹ The recurrence rate in patients with deficiency of a natural anticoagulant was 17.5% (7 of 40) but this result is not statistically different to the overall recurrence rate of 11%. If there is an increased risk of recurrence in these patients, the increase seems to be small and most patients do not have a recurrence.

Our results provide objective evidence that in unselected patients presenting with a first episode of venous thromboembolism, testing for heritable thrombophilia does not allow prediction of a new event during the highest risk period—that is, the first 2 years after anticoagulant therapy is stopped. This study also emphasises the predictive value of clinical risk factors. Testing might yet prove to be informative in patients from families with a strong predisposition to thrombosis; however, such testing is not useful in most patients.

Contributors

T Baglin designed the audit database, contributed to patients' care, interpretation of laboratory results, and statistical analysis. R Luddington did laboratory analysis. C Baglin helped design the database, maintained the database, and contributed to patients' care. K Brown did laboratory analysis. All investigators participated in study design, interpretation of results, and preparation of the manuscript.

Conflict of interest statement

Dr T Baglin has received honoraria for consultancy to Organon Teknika, bioMérieux and Sanofi-Synthelabo. He is secretary to the Thrombosis and Haemostasis Task Force of the British Society for Haematology and chair of the steering committee for the UK National External Quality Assurance Scheme for Coagulation.

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