The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients

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Manuscript received July 9, 2006. Accepted November 6, 2006.

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ABSTRACT

Background and Objectives

While it has long been recognized that patients with acute unprovoked deep vein thrombosis (DVT) or pulmonary embolism (PE) have a higher risk of recurrent venous thromboembolism (VTE) than that of patients with secondary thrombosis, whether other clinical parameters can help predict the development of recurrent events is controversial. The aim of this investigation was to assess the rate of recurrent VTE after withdrawal of vitamin K antagonists, and to identify clinical parameters associated with a higher likelihood of recurrence.

Design and Methods

We followed, up to a maximum of 10 years, 1626 consecutive patients who had discontinued anticoagulation after a first episode of clinically symptomatic proximal DVT and/or PE. All patients with clinically suspected recurrent VTE underwent objective tests to confirm or rule out the clinical suspicion.

Results

After a median follow-up of 50 months, 373 patients (22.9%) had had recurrent episodes of VTE. The cumulative incidence of recurrent VTE was 11.0% (95% CI, 9.5-12.5) after 1 year, 19.6% (17.5-21.7) after 3 years, 29.1% (26.3-31.9) after 5 years, and 39.9% (35.4-44.4) after 10 years. The adjusted hazard ratio for recurrent VTE was 2.30 (95% CI, 1.82-2.90) in patients whose first VTE was unprovoked, 2.02 (1.52-2.69) in those with thrombophilia, 1.44 (1.03-2.03) in those presenting with primary DVT, 1.39 (1.08-1.80) for patients who received a shorter (up to 6 months) duration of anticoagulation, and 1.14 (1.06-1.12) for every 10-year increase of age. When the analysis was confined to patients with unprovoked VTE the results did not change.

Interpretation and Conclusions

Besides unprovoked presentation, other factors independently associated with a statistically significant increased risk of recurrent VTE are thrombophilia, clinical presentation with primary DVT, shorter duration of anticoagulation, and increasing age.

Keywords: venous thrombosis, venous thromboembolism, deep vein thrombosis, pulmonary embolism, anticoagulation, thrombophilia, heparin, warfarin.

Haematologica 2007; 92:199-205

Despite adequate treatment, up to one quarter of patients with symptomatic deep vein thrombosis (DVT) and/or pulmonary embolism (PE) will experience recurrent venous thromboembolism (VTE) within the subsequent 5 years.[1-6] While it is generally accepted that patients with thromboembolic events of unknown origin have a more than two-fold higher rate of recurrent VTE in comparison to patients whose thrombosis is associated with acquired, transient risk factors,[1-6] whether other of the patients' baseline features can help to identify those subjects who might benefit from prolonged anticoagulation is unclear. For example, it is virtually unknown whether aging, an important risk factor for VTE,[4] is also associated with an increased risk of recurrence. The role of thrombophilic abnormalities, especially those that are highly prevalent in western countries (i.e., factor V Leiden and prothrombin G20210A mutation), is controversial.[5-14] Although recent data suggest that clinical presentation with primary PE[15] and male sex[16-18] increase the risk of recurrent VTE, these findings still await confirmation. Finally, whether the duration of anticoagulation following the initial thrombotic episode has any influence on the subsequent rate of recurrent VTE is uncertain.[2,19-22]

Here we report on the prospective long-term follow-up of a large series of patients with proximal DVT and/or PE. All of them received conventional anticoagulation, and were then followed-up for a maximum of 10 years after anticoagulation had been discontinued in order to document the incidence of recurrent VTE. The aim of our investigation was to assess the rate of recurrent VTE after withdrawal of vitamin K antagonists, and to identify clinical parameters associated with a higher likelihood of recurrence in both the entire cohort and, separately, in patients with VTE of unknown origin.

Design and Methods

Patients

All consecutive outpatients referred by their family physicians between May 1991 and April 2003 to the emergency department of each of three participating centers (the Department of Medical and Surgical Sciences of the University of Padua, the Division of Internal Medicine of the Hospital of Reggio Emilia, and the Department of Cardiothoracic and Vascular Sciences of the University of Padua, all in Italy) with clinically symptomatic DVT and/or PE were potentially eligible for the study, provided that less than 3 weeks had elapsed since the beginning of their symptoms. The accepted methods for diagnosing DVT were venography and compression-ultrasonography, while those for PE were spiral computed tomography (CT), ventilation-perfusion lung scan, pulmonary angiography, or a suggestive clinical picture in patients with proven DVT. No routine testing for PE was done in patients with clinically symptomatic DVT and no clinical symptoms of PE.

All patients were hospitalized and treated with full-dose unfractionated or low-molecular-weight heparin, preceded in those with massive PE and hemodynamic instability by thrombolytic drugs or embolectomy. Oral anticoagulants were started during the first week and continued on average for 3 months in patients with thrombosis triggered by transient risk factors, and for longer periods (6 months or more, on the discretion of the treating physicians) in patients with thrombosis of unknown origin.

Patients were ineligible for the study if they had a history of previous episodes of symptomatic VTE, had active cancer, had indications for indefinite anticoagulation (such as atrial fibrillation, chronic medical illnesses or other permanent risk factors for VTE), could not be followed-up, or had a life-expectancy of less than 6 months. Patients who completed the scheduled period of anticoagulation without experiencing recurrent thrombotic episodes, and were willing to participate, were enrolled in the study. The enrollment took place on the day of warfarin discontinuation.

Demographic and clinical characteristics were recorded using a standardized questionnaire, with information being centralized on a regular basis at the Department of Medical and Surgical Sciences of the University of Padua. Patients were classified as having secondary VTE if they were pregnant, had given birth within the previous 3 months, or took estrogens; if they had had a recent (less than 3 months) leg trauma, fracture, or surgical intervention; or if they had been bedridden for more than 1 week because of a chronic medical illness. All other patients were regarded as having an unprovoked episode of VTE.

The search for thrombophilia (antithrombin, protein C or S deficiency, factor V Leiden, prothrombin G20210A mutation, and lupus-like anticoagulants) was left to the discretion of the treating physicians, and was performed either before implementing anticoagulation or later on, at least 3 weeks after completing oral anticoagulant therapy, according to previously described methods.[23] The determination of thrombophilia was performed at each of the participating centers. Carriers of thrombophilia were classified as having unprovoked or secondary thrombosis according to their clinical presentation. The Institutional Review Board of each participating center approved the study protocol.

Follow-up and recurrent VTE

All eligible patients willing to participate in the study were enrolled on the day their anticoagulant treatment was discontinued. They were subsequently examined or telephoned at least once every 6 months and prospectively followed-up for a maximum of 10 years, to document the incidence of symptomatic recurrent DVT or

PE. For this purpose, patients were instructed about the main signs and symptoms of VTE, and received a card with the telephone numbers of the thrombosis clinic. They were asked to return to the study center if clinical manifestations potentially suggestive of recurrent DVT in either leg (i.e., edema, redness, tenderness, pain, swelling) or PE (i.e., dyspnea, chest pain, tachycardia) occurred.

Recurrent DVT was diagnosed by ascending phlebography until the mid 1990s, and then by compression ultrasound, followed by venography in the case of indeterminate findings. The only accepted venographic criterion for recurrent DVT was the presence of a (new) intraluminal filling defect visible in two different projections. Ultrasound criteria for recurrent ipsilateral DVT were incompressibility of a proximal vein segment previously free from thrombi, or the finding of a more than 4 mm increase of the vein diameter as compared with the last available measurement; if the vein diameter was increased by less than 4 mm, a confirmatory phlebography was required.[24] If recurrent proximal DVT was suspected in a previously unaffected leg, the sole diagnostic criterion was the incompressibility of a proximal vein. In the case of a high clinical probability and negative ultrasound findings, venography was performed to rule out an isolated iliac or calf vein thrombosis. Patients with suspected (recurrent) PE underwent a ventilation/perfusion lung scan or spiral CT, followed by pulmonary angiography in the case of indeterminate scintigraphic findings or of normal CT results and a high clinical probability.[25]

The date and cause of death were documented for all patients who died during the follow-up; in the case of a sudden and otherwise inexplicable death, a fatal PE was adjudicated by default.

An independent, expert committee unaware of the patients' baseline clinical details reviewed all study outcomes.

Statistical analysis

Kaplan-Meier estimates and their 95% confidence intervals (CI) were calculated to assess the time-dependent risk of recurrent VTE. The evaluated time interval spanned from the day following withdrawal of oral anticoagulants to the last available day of follow-up.

Parameters that were significantly associated with the risk of recurrent VTE on univariate analysis were entered in a multivariate Cox proportional hazard model to identify features independently associated with recurrence, both in the whole cohort and in the subset of patients with unprovoked VTE. We specifically sought to estimate the strength of any association (expressed as a hazard ratio [HR], with 95% CI) between recurrent VTE and the following parameters: presence of risk factors for venous thrombosis (unprovoked versus secondary VTE); modality of clinical presentation (DVT alone or associated with clinically symptomatic PE – primary DVT – versus PE alone – primary PE –); thrombophilia, age (calculated using 10-year periods), sex, and duration of anticoagulant therapy (≤6 months versus > 6 months). The analysis was repeated considering only those patients with VTE of unknown origin. As thrombophilia testing was performed only in 953 (59%) subjects of the cohort, the single unconditional mean imputation method was used to handle missing data.

Patients were censored if they had a completely uneventful follow-up, if they developed cancer or clinical conditions requiring anticoagulation, or if they died. The relative risk (RR) of recurrent VTE in carriers of multiple as compared to single thrombophilic abnormalities, and in patients who developed cancer as compared to those who did not, was calculated according to standard methods; similarly, the RR of recurrent PE was estimated in patients presenting with PE in comparison to those who presented with DVT alone. The RR was considered to be statistically significant when the lower limit of the 95% CI was ≥1.0.

The χ^2 test was used to compare proportions. All calculations were performed using SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients

Of 3338 consecutive patients referred to the study centers with an episode of objectively confirmed proximal DVT and/or PE, 1610 patients were excluded because of active cancer (n= 545), a history of previous symptomatic VTE (n= 409), medical diseases requiring permanent anticoagulation (n=385), follow-up not possible (n= 170), or life-expectancy of less than 6 months (n= 101). Another 62 patients died or had a recurrence of VTE during the period of anticoagulation. Of the remaining 1666 patients, 40 declined to participate in the study. Therefore, 1626 consenting patients who completed the initial period of anticoagulation without experiencing a recurrent thrombotic episode were enrolled for this investigation (Figure 1). The main baseline characteristics of the recruited patients are listed in Table 1.

Of the 1626 patients, 153 (9.4%) died of the following causes: PE (n=43), cancer (n=27), heart failure (n=22), stroke (n=20), myocardial infarction (n=14), and other causes (n=27).

Ninety-seven patients (5.9%) developed a manifest malignancy during their follow-up, and 32 (2.0%) were either lost to follow-up or resumed anticoagulation for reasons other than VTE. These 129 patients were censored at the time of cancer development or at that of their last available visit, respectively.

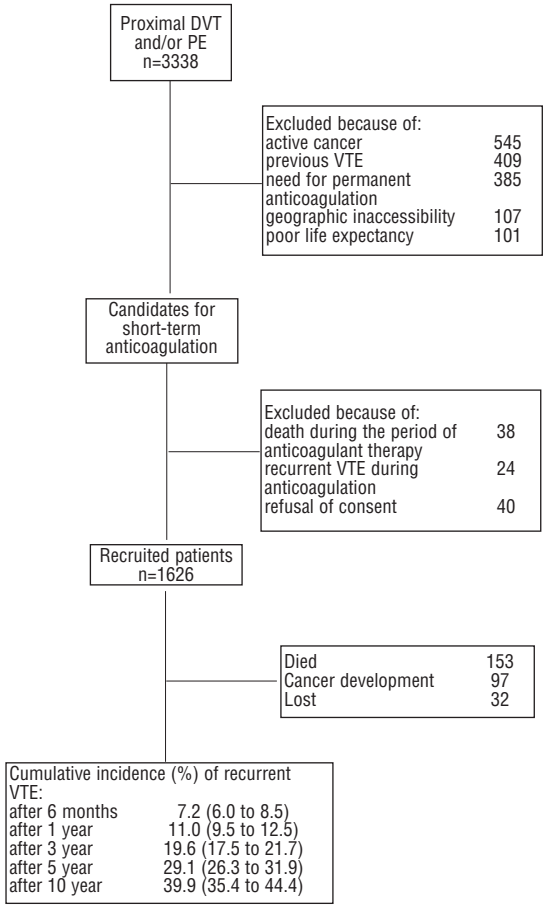


Figure 1. Flow diagram of the study.

Table 1. Characteristics of the study population.

Patients (number)	1626
Age (median, range)	66 (16,96)
Gender (n., % males)	735 (45.2)
Obesity (BMI ≥30 Kg/m^2)	244 (15.0)
Diabetes mellitus	135 (8.3)
Modality of clinical presentation	
DVT alone	1073 (66.0)
DVT + PE	292 (18.0)
PE alone	261 (16.0)
Categories of VTE	
Unprovoked	864 (53.1)
Secondary to acquired risk factors	762 (46.9)
recent trauma or surgery	581
hormonal treatment, pregnancy or puerperium	100
medical diseases	81
Thrombophilic abnormalities	229/953 (24.0)
Factor V Leiden	111
Prothrombin G20210A mutation	45
AT deficiency	7
Protein C deficiency	16
Protein S deficiency	14
Lupus-like anticoagulants	23
Combinations of two or more defects	13
Initial treatment	
Unfractionated heparin	1056 (64.9)
Low-molecular-weight heparin	514 (31.6)
Others	56 (3.4)
Duration of oral anticoagulation	
Three months or less	540 (33.2)
Between 3 and 6 months	811 (49.9)
Between 6 and 12 months	196 (12.0)
Between 1 and 2 years	67 (4.1)
Between 2 and 3 years	12 (0.7)
Duration of follow-up, months (median, range)	50 (2-120)

Numbers in parentheses are percentages, unless otherwise indicated.

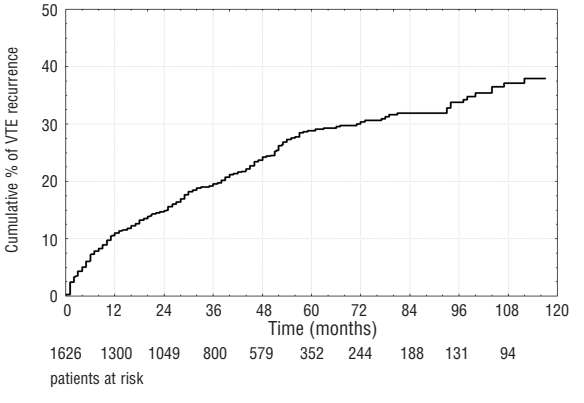


Figure 2. Cumulative incidence of recurrent thromboembolism in the study patients.

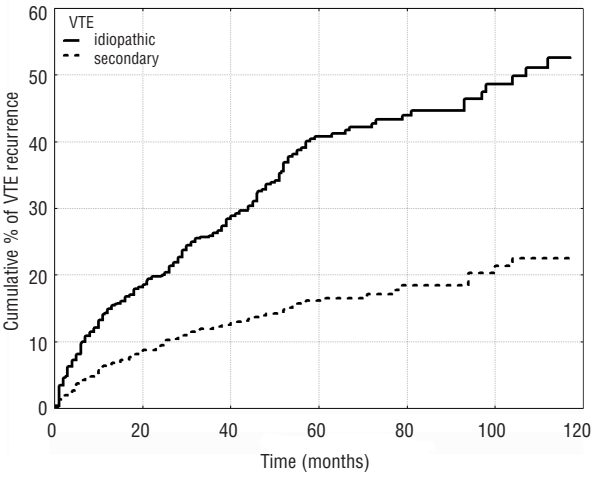
Recurrent thromboembolism

During the study period, 373 patients (22.9%) experienced recurrent VTE, which was fatal in 43 (11.5%). Of the 43 patients who died, 32 had a sudden death. Of the recurrent events, 117 occurred within 6 months (cumulative incidence, 7.2%; 95% CI, 6.0 to 8.5); 56 within 1 year (cumulative incidence, 11.0%; 95% CI, 9.5 to 12.5); 108 within 3 years (cumulative incidence,19.6%; 95% CI, 17.5 to 21.7); 70 within 5 years (cumulative incidence, 29.1%; 95% CI, 26.3 to 31.9); 15 within 8 years (cumulative incidence, 34.3%; 95% CI, 30.6 to 38.0); and 7 within 10 years (cumulative incidence, 39.9%; 95% CI, 35.4 to 44.4) (Figure 2).

Figure 3 reports the cumulative incidence of recurrent events, separately in patients with unprovoked and secondary VTE.

Predictors of recurrent thromboembolism

In the Cox's model evaluating the whole cohort, recurrence was significantly associated with unprovoked thrombotic episodes (adjusted HR, 2.30; 95% CI, 1.82 to 2.90); thrombophilia (adjusted HR, 2.02; 1.52 to 2.69); presentation with primary DVT (adjusted HR, 1.44; 1.03 to 2.03); shorter (up to 6 months) duration of anticoagulation (adjusted HR, 1.39; 1.08 to 1.80); and aging (adjusted HR, 1.14; 1.06 to 1.22), but not with male sex (adjusted HR, 1.16; 0.94 to 1.43). Conditions independently associated with recurrence in the 864 patients with unprovoked VTE were thrombophilia



	Idiopathic VTE				Secondary VTE		
months	*N. of VTE*	*Cum Incid (%)*	*95% CI*	*N. of VTE*	*Cum Incid (%)*	*95% CI*
6	85	10.0	8.0-12.0	32	4.2	2.8-8.7
12	39	15.0	12.6-17.4	17	6.6	4.8-8.4
36	74	26.3	23.0-29.6	34	12.3	9.8-14.8
60	56	40.8	36.5-45.1	14	16.1	13.0-19.2
96	9	46.4	41.1-51.8	6	20.3	15.8-24.8
120	5	52.6	45.6-59.5	2	22.5	17.2-27.8

Figure 3. Cumulative incidence of recurrent thromboembolism separately in patients with idiopathic (unprovoked) and secondary VTE.

(adjusted HR,1.91; 95% CI, 1.35 to 2.69); presentation with DVT (adjusted HR, 1.50; 1.00 to 2.27); shorter duration of anticoagulation (adjusted HR, 1.46; 1.09 to 1.96); and aging (adjusted HR, 1.09; 1.00 to 1.20), while male sex was not (adjusted HR, 1.21; 0.95 to 1.55).

Additional observations

The rate of recurrent VTE did not differ between patients in whom investigations for thrombophilia were conducted (21.9%; 95% CI, 19.4 to 24.7) and those in whom they were not (21.5%; 95% CI, 18.8 to 24.6). Recurrences developed in 38/111 (34.2%; 95% CI, 26.1 to 43.5) carriers of FVL; in 11/45 (24.4%; 95% CI, 14.2 to 38.7) carriers of the prothrombin mutation; 2/7 (28.6%; 95% CI, 8.2 to 64.1) carriers of antithrombin deficiency; in 7/16 (43.8%; 95% CI, 23.1 to 66.8) carriers of protein C deficiency; in 4/14 (28.6%; 95% CI, 11.7 to 54.6) carriers of protein S deficiency; and in 9/23 (39.1%; 95% CI, 22.2 to 59.2) carriers of lupus-like anticoagulants (χ^2=1.64, p=0.744). Recurrences developed in 6/13 (46.2%; 95% CI, 19.2 to 74.9) carriers of multiple abnormalities, and in 71/216 (32.9%; 95% CI, 26.6 to 39.1) carriers of single defects.

Patients with clinically manifested PE were more likely to develop a recurrent PE than patients with DVT alone (69/122 versus 61/250, respectively; RR, 2.32; 95% CI, 1.77 to 3.03). Among patients with secondary VTE, those with medical diseases were more likely to develop recurrent thromboembolism (18/81; cumulative incidence, 31.8%; 95% CI, 18.2 to 45.3) than those with recent trauma or surgery (75/581; cumulative incidence, 11.4%; 95% CI, 4.7 to 18.0) and those in whom the VTE was associated with hormonal therapy, pregnancy or puerperium (12/100; cumulative incidence, 20.3%; 95% CI, 8.9 to 31.7).

Discussion

The results of our study clearly show that after discontinuing anticoagulation the rate of recurrent VTE increases steadily over time, approaching 40% among all patients after 10 years. Of interest, more than 10% of all recurrences were either documented fatal PE or sudden and otherwise inexplicable deaths, in which PE could not be ruled out. The rate of recurrent VTE was not lower than that previously reported by our group,[1] although the duration of oral anticoagulation was on average longer (6 versus 3 months), patients with active cancer and other permanent risk factors for recurrent VTE were excluded, and only those recurrences that occurred after discontinuing anticoagulation were computed. Thus, improving the long-term prognosis of patients with acute VTE still remains a challenging task.

Our results fully confirm that patients who present with thrombotic episodes of unknown origin have a more than two-fold higher risk of recurrences than that observed in patients with temporary risk factors.[1-7] Of interest, in the latter category of patients, those with associated medical diseases had the highest risk, while those with VTE triggered by recent trauma or surgery the lowest, and this is consistent with previous reports.[5] In addition, our findings shed some light on the role of other potential risk factors for recurrent thromboembolic events, thus helping to identify those patients who might benefit from a longer duration of anticoagulation.

Whether thrombophilia is to be regarded a risk factor for recurrent VTE is controversial, as there are as many reports in favor[7,8,13,14] as against this association.[5,6,9-12] In our study, thrombophilia was found to be an independent risk factor for recurrent VTE both in the entire cohort and in the subgroup of patients with unprovoked VTE. However, screening for thrombophilia was performed in less than 60% of the patients, and was performed in retrospect in a substantial proportion of patients; thrombophilia tests were not centralized, and the indication for testing was left to the discretion of the treating physicians. Therefore, our findings should be interpreted with caution. We think that further prospective studies addressing the role of thrombophilia in determining the risk of recurrent VTE are indicated, as are randomized studies addressing the benefit-to-risk ratio of prolonging anticoagulation in carriers of thrombophilic abnormalities.

The risk of recurrence increased with age, both in the entire cohort and in the subgroup of patients with unpro-

voked VTE. However, the effect of age was modest when compared to that of other variables, especially in the subgroup of patients with unprovoked VTE. In disagreement with recent observations,[16-18] we found a similar risk of recurrence in both sexes; and the picture did not change when the analysis was confined to patients with unprovoked VTE. In contrast with findings from a recent study,[15] patients with primary DVT had a 50% higher risk of recurrence than patients with primary PE. However, it should be noted that in patients presenting with primary PE the recurrent event was a new episode of PE more than twice as frequently as in patients presenting with DVT alone, and this is consistent with previous observations.[15]

Both in the entire cohort and in the subgroup of patients with unprovoked VTE a shorter (up to 6 months) course of vitamin K inhibitors was associated with a significantly higher rate of recurrence than were longer periods of anticoagulation. This finding should be interpreted with extreme caution, as decisions on the duration of secondary prevention were taken on an individual basis by the attending physicians. However, as a course of anticoagulation longer than 6 months was reserved to those patients with unprovoked VTE who were reputed to be at a particularly high risk of recurrent events, the potential for bias is likely to point in the right direction. Although our results contrast with those of several randomized clinical trials, which suggest that, at least in patients with unprovoked VTE, prolonging anticoagulation beyond 3 months does not confer an additional advantage over shorter anticoagulation periods,[20-22] they are in line with those obtained by others,[2,26] and with the results of two recent meta-analyses.[27,28] Our findings should encourage further studies to explore the potential advantage of longer courses of anticoagulation, at least in subgroups of patients with VTE.

We believe that our observations reflect the true clinical course of patients with symptomatic VTE after discontinuing anticoagulation. The diagnosis of VTE was based on widely accepted methods, and the demographic and clinical characteristics of the study patients were collected using a standard questionnaire. All candidates for indefinite anticoagulation were excluded, as were patients who developed a recurrent event while on anticoagulants. Patients with advanced cancer were also excluded, because they are usually kept on anticoagulants indefinitely and have a short life-expectancy. Patients were treated according to standard practice. Follow-up started in all patients from the time of warfarin discontinuation, was performed prospectively at each of the participating study centers, and only a few patients were lost to long-term follow-up. Finally, predefined criteria were strictly applied to diagnose recurrent VTE.

A potential study limitation is the failure to have assessed thrombophilia in all recruited patients. Although operators were instructed to obtain this information as often as possible, this was often precluded by a variety of problems including the need for prompt administration of anticoagulation in the nighttime and during the weekends, unavailability of dedicated physicians or laboratory technicians, lack of easily accessible veins, and cost considerations. However, our goal was not to assess the prevalence of thrombophilia in our population. We aimed to evaluate the risk of recurrent VTE in carriers as compared to non-carriers of thrombophilia, and were able to assess this risk in almost 1000 consecutive patients without any selection bias. This is confirmed by the fact that the rate of recurrent VTE did not differ between patients in whom thrombophilic status was assessed and those in whom it was not. Another limitation was the failure to perform autopsies in the 32 patients who died unexpectedly. As sudden death can be caused by conditions other than PE, our conservative approach may have increased, although to a limited extent, the calculated rate of recurrences, and may have increased the case fatality rate of VTE episodes.[29] However, the proportion of patients who were classified as having died of PE in this cohort (11.5%) did not differ at all from that (11.5%) observed in our previous cohort, in which the autopsy rate was much higher and the analysis was confined to only those patients in whom the diagnosis of PE could be made.[1]

What do our findings imply for the management of patients with VTE? Twenty years of intensive research have not improved the prognosis of patients with acute VTE. While our findings confirm the strong predictive role of unprovoked presentation, they challenge several current views, as they suggest that: (i) thrombophilia is an independent risk factor for recurrent VTE; (ii) the risk of recurrent VTE is higher in patients with primary DVT than in those with primary PE; (iii) the risk is similarly high in males and females; (iv) the longer the duration of anticoagulation the lower the risk of subsequent recurrent events. The still persistently high incidence of recurrent VTE after withdrawal of vitamin K inhibitors suggests that a prolonged course of anticoagulation should be considered in more patients than is currently the case.

Authors' Contributions

PP, FN and EB designed the investigation and wrote the manuscript; AG, VP, RP, MI and DT recruited the study patients and followed them over time; FN and EB performed the statistical analyses; PS and AP reviewed the manuscript for important intellectual content. All the authors read the final version of the manuscript and approved it.

Conflicts of Interest

The authors reported no potential conflicts of interest.

References

1. Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125:1-7.
2. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, Nicol P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. N Engl J Med 1995; 332: 1661-5.
3. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis. Incidence and risk factors. Arch Intern Med 2000; 1260:769-74.
4. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton III LJ. Predictors of recurrence after deep vein thrombosis and pulmonary embolism. A population-based cohort study. Arch Intern Med 2000;160:761-8.
5. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003; 362:523-6.
6. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 2005;293: 2352-61.
7. Palareti G, Legnani C. Cosmi B, Valdrè L, Lunghi B, Bernardi F, et al. Predictive value of D-Dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation 2003;108: 313-8.
8. Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. Circulation 1995; 92:2800-2.
9. Eichinger S, Pabinger I, Stumpflen A, Hirschl M, Bialonczyk C, Schneider B, et al. The risk of recurrent venous thromboembolism in patients with and without factor V Leiden. Thromb Haemost 1997;77:624-8.
10. Lindmarker P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of recurrent venous thromboembolism in carriers and non-carriers of the G1691A allele in the coagulation factor V gene and the G20210A allele in the prothrombin gene. Thromb Haemost 1999;81: 684-9.
11. Margaglione M, D'Andrea G, Colaizzo D, Cappucci G, Del Popolo A, Brancaccio V, et al. Coexistence of factor V Leiden and factor II A20210 mutations and recurrent venous thromboembolism. Thromb Haemost 1999;82:1583-7.
12. De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, et al. The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210 prothrombin mutation. N Engl J Med 1999;341:801-6.
13. Simioni P, Prandoni P, Lensing AWA, Manfrin D, Tormene D, Gavasso S, et al. Risk for subsequent venous thromboembolic complications in carriers of the prothrombin or the factor V gene mutation with a first episode of deep-vein thrombosis. Blood 2000;96:3329-33.
14. Miles JS, Miletich JP, Goldhaber SZ, Hennekens CH, Ridker PM. G20210A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. J Am Coll Cardiol 2001; 37:215-8.
15. Eichinger S, Weltermann A, Minar E, Stain M, Schonauer V, Schneider B, et al. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. Arch Intern Med 2004;164:92-6.
16. Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med 2004;350: 2558-63.
17. Baglin T, Luddington R, Brown K, Baglin C. High risk of recurrent venous thromboembolism in men. J Thromb Haemost 2005;2:2152-5.
18. McRae S, Tran H, Schulman S, Ginsberg J, Kearon C. Effect of patient's sex on risk of recurrent venous thromboembolism: a meta-analysis. Lancet 2006;368:371-8.
19. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999;340:901-7.
20. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. N Engl J Med 2001;345:165-9.
21. Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation 2001; 103: 2453-60.
22. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003; 139:19-25.
23. Simioni P. The molecular genetics of familial venous thrombosis. Bailliére's Best Pract Res Clin Haematol 1999; 12:479-503.
24. Prandoni P, Lensing AWA, Bernardi E, Villalta S, Bagatella P, Girolami A. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. Thromb Haemost 2002; 88:402-6.
25. Musset D, Parent F, Meyer G, Maitre S, Girard P, Leroyer C, et al. Diagnostic strategy for patients with suspected pulmonary embolism: a prospective multicentre outcome study. Lancet 2002;360:1914-20.
26. Schulman S. The effect of the duration of anticoagulation and other risk factors on the recurrence of venous thromboembolism. Wien Med Wöchenschr 1999;149:66-69.
27. Pinede L, Duhaut P, Cucherat M, Ninet J, Pasquier J, Boissel JP. Comparison of long versus short duration of anticoagulant therapy after a first episode of venous thromboembolism: a meta-analysis of randomized, controlled trials. J Int Med 2000; 247:553-62.
28. Ost D, Tepper J, Mihara H, Lander O, Heinzer R, Fein A. Duration of anticoagulation following venous thromboembolism: a meta-analysis. JAMA 2005;294:706-15.
29. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998;279:458-62.