Risk of recurrent venous thromboembolism related to prior risk situations: re-evaluation of a cohort study with a longer follow-up

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Risk of recurrent venous thromboembolism related to prior risk situations: re-evaluation of a cohort study with a longer follow-up

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Venous thromboembolism (VTE) is a chronic disease. Strategies to assess groups at a high risk of recurrence are needed. We reported that patients without prior risk situation for VTE had an incidence rate ratio (IRR) three times higher when compared with those with this history. The aim of this study was to re-evaluate the cohort, with a longer follow-up and evaluated the association between the absence of a prior risk situation for VTE with an increased risk for recurrence. A total of 289 patients with a previous VTE were followed for 116 months. Patients were advised to attend the outpatients' clinic in case of suspected VTE recurrence. Incidence rates of recurrent thrombotic events were calculated as the number of events over the accumulated observation time. Recurrent VTE occurred in 52 (18%) patients. Patients with a provoked first event and positive prior risk situations for VTE had an incidence rate for recurrence of 1.2 [95% confidence interval (95% CI), 0.7–1.9] per 100 patient-years. The IRR of this subgroup compared with patients with a provoked event without prior risk situations for VTE was 0.9 (95% CI 0.4–2.4). IRR was 2.5 (95% CI, 1.3–4.9) in patients with an unprovoked event and positive prior risk situations and 5.9 (95% CI, 32.8–12.5) in patients with an unprovoked event and no prior risk situations compared with patients with a provoked event without other prior risk situations for VTE. Exposure to prior risk situations for VTE was a protective factor among those patients whose first VTE event was unprovoked. *Blood Coagul Fibrinolysis* 31:434–439 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism, occurs in approximately one to two per 1000 persons per year [1]. Despite adequate treatment, VTE is regarded as a chronic disease and approximately 25% of patients with a first symptomatic VTE experience recurrence within 5 years [2].

The importance of distinguishing between provoked and unprovoked VTE has long been recognized as a predictor of VTE recurrence. Patients who develop VTE as a result of a transient risk factor have a low risk for recurrence compared with patients with either VTE provoked by a persistent risk factor or unprovoked VTE [3]. Therefore, a relatively short period of anticoagulant treatment is advised for those with VTE related to a provoking risk factor [4]. As a large number of recurrent events occur without a clear provoking risk factor, many patients may need indefinite anticoagulant treatment after a first VTE event. However, anticoagulant therapy may lead to serious side effects such as major bleeding [5]. Whereas algorithms have been developed and validated for the diagnosis of a first VTE, no well defined prediction strategy exists in the case of recurrence. The challenge is therefore to identify patient groups with a low risk for recurrence who do not require lifelong anticoagulation.

The thrombosis potential model represents the sum of risk factors in the course of time (years) in an individual [6]. According to this model, VTE will only occur when the combination of risk factors for thrombosis reaches a certain potential (by crossing the thrombosis threshold). Considering this, we hypothesized that patients at risk for recurrent VTE, who had experienced transient provoked risk factors previously and did not develop a thrombotic event at that time, would have a lower risk of recurrence than those whose first (provoked or unprovoked) event was not preceded by provoked risk factors [7,8]. In the previous evaluation of this cohort, we found an association between the absence of a prior risk situation for VTE with an increased risk for recurrence [7,8]. However, at

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that time, the median follow-up of the cohort was 43 months. The present manuscript reports the re-evaluation of the same cohort with a longer follow-up (median116 months), which incremented the robustness of our findings. We also studied the effects of sex, recanalization status and family history on the recurrence risk.

Materials and methods

Participants

Participants were patients with one prior VTE event who visited the University Hospital of Universidade Federal de Minas Gerais, Belo Horizonte, Brazil from April 2000 to September 2010. Detailed information of the baseline study has been described previously [7,8]. Briefly, a total of 378 patients were attended at the outpatients' clinic by the same clinician (DDR). Patients' data were collected by using standardized forms at the first and each subsequent visit. Patients were followed at least once a year either by phone or through clinic visits until January 2016. Patients were not systematically screened with ultrasonography. All patients were advised to attend the outpatients' clinic in case of suspected DVT or pulmonary embolism. All eligible patients for this study provided written informed consent, and the study was approved by the local ethics committees.

Definitions

The duration of anticoagulation for provoked and unprovoked VTE was 3–6 months and 6–12 months, respectively. Some patients were treated for longer or shorter time periods mainly because of individual patient preferences. The first episode of VTE was considered established when DVT was confirmed by compression ultrasound, and pulmonary embolism by ventilation/perfusion lung scanning or spiral computer tomography scanning. Recurrence was considered established when VTE was demonstrated by objective techniques at a site other than the one where the first event occurred, or at the same site when previously repeated tests had shown no residual thrombosis. When the recurrence of DVT was at the same site and we had not previously repeated tests to analyse for residual thrombosis, we only considered recurrence when the ultrasound/duplex showed new thrombus formation associated with clinical symptoms that were absent previously. Only the objectively demonstrated pulmonary embolism was considered a recurrence. When these criteria were not fulfilled, anticoagulant treatment was withheld, and the event was not classified as a recurrence.

VTE was defined as provoked when it had occurred at or within 3 months after exposure to exogenous risk factors including surgery (with more than 30 min of duration), trauma leading to hospitalization, immobilization for more than 3 days (hospitalization for clinical reasons), limb immobilization in a plaster cast for more than 7 days, pregnancy, postdelivery period (2 months), the use of oral contraceptives or hormonal replacement therapy (at the time of thrombosis), presence of autoimmune diseases or active malignancy. In the absence of these risk factors, VTE was classified as unprovoked.

Patients were asked about risk situations for VTE prior to the diagnosis of the first VTE at any time in their life. The questions were related to known risk factor for VTE (trigger factors). If the answer was positive for any of these risk situations that occurred at least 3 months or more before the event occurred, they were considered as positive for prior risk situations.

Ultrasound/duplex or ventilation/perfusion lung scanning or spiral computer tomography scanning were performed by the end of anticoagulation and patients were separated in two groups: those with complete recanalization and those with incomplete or absent recanalization. A family history was considered positive when the patient had one or more first degree relatives with documented VTE or with history of vitamin K antagonist use due to VTE.

Statistical analysis

For categorical variables, the number of events and their respective percentages were calculated. For continuous variables, we calculated median and interquartile range (IQR) or means and standard deviations (SDs) in case the presentation was nonparametric or parametric, respectively.

Observation time started after vitamin K antagonists were withdrawn and ended at time of recurrence or 1 January 2016. When patients could not be contacted at or after 1 January 2016, the last consultation was considered the end of follow-up. Incidence rates of recurrent thrombotic events were calculated as the number of events over the accumulated observation time. Incidences and 95% confidence intervals (95% CI) were calculated under the Poisson distribution assumption. Stratified analyses were used to assess the risk of thrombotic events recurrence by sex, idiopathic or provoked classification of first thrombotic event, status of image test around the end of anticoagulation (recanalization), presence or absence of family history for VTE and presence or absence of past risk situations for VTE. The presence of a triggering factor was evaluated together with past risk situations status and sex.

Statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 289 out of 378 (76.4%) patients were included (Table 1). Most (79%) were women and 195 (68%) had a provoked VTE. The median age at time of the first event was 35 years (IQR, 28.9–48.3 years). Most patients ($n = 120$; 42%) had proximal DVT, 87 (30%) had distal DVT and 55 (19%) had pulmonary embolism. Patients with DVT and pulmonary embolism ($n = 26$; 9%) were

Table 1 Characteristics of the study population

Patients	*N* (%)			
Sex	Female	Male	Total	
	229 (79)	60 (21)	289 (100)	
Risk factors	Yes	No		
	195 (67.9)	92 (32.1)		
VT place	Proximal DVT	Distal DVT	PE/DVT	
	120 (41.7)	87 (30.2)	81 (28.1)	
Diagnostic method	Ultrasound/duplex	V/P Lung Scan	Angio CT	Both
	211 (73)	24 (8.3)	31 (10.7)	23 (7.9)
	Mean (years)	Median (years)		
Age first event	39.5	35.5		
Age at recurrence	48.2	46.8		
	Mean (months)	Median (months)		
Anticoagulation Period	12.6	8.0		
Time between the end of VKA and recurrence	62.7	51.8		
Time between VTs	74.6	61.0		
Follow-up	124	116		
	Yes	No		
Family history of VT	80 (28.2)	204 (71.8)		
Recurrence	52 (18)	237 (82)		
Risk factors for recurrence	12 (23.5)	39 (76.5)		
Recurrence place	Proximal DVT	Distal DVT	PE	Both
	30 (57.7)	11 (21.2)	10 (19.2)	1 (1.9)
Relapse confirmation test	Ultrasound/duplex	V/P Lung Scan	Angio CT	Other
	41 (78.8)	6 (11.5)	3 (5.8)	2 (2.8)
Recanalization	Absent/Incomplete	Complete		
	145 (58.9)	101 (41.1)		
Past history of risk situations	Yes	No		
	199 (68.9)	90 (31.1)		

CT, computer tomography; DVT, deep venous thrombosis; PE, pulmonary embolism; V/P, ventilation/perfusion; VKA denotes, vitamin K antagonist; VT, venous thrombosis.

analysed in the pulmonary embolism group. Ultrasound/duplex was the most frequently used diagnostic image method (211 patients, 73%), ventilation/perfusion lung scan was performed in 24 (8.3%) patients and spiral computer tomography scanning in 31 (10.7%) patients. A positive family history for VTE was present in 80 (28%) patients and prior risk situations were present in 199 (69%) patients. The median time of anticoagulation was 8 months, median time between the end of anticoagulation and recurrence was 52 months, median interval between VTE was 61 months and median of follow-up was 116 months. Recurrent VTE occurred in 52 (18%) patients with an incidence ratio of 1.49 (95% CI, 1.11–1.95) per 100 patient-years. The median age at recurrence was 46.7 years (IQR, 33.3–61.1 years). A total of 89 patients were lost to follow-up.

Patients with a provoked first event and positive past risk situations had an incidence rate of recurrence of 1.22 (95% CI, 0.75–1.98) per 100 patient-years (Table 2). The incidence rate ratio (IRR) of patients with a provoked event without prior risk situations for VTE compared with patients with a provoked first event and prior risk situations was 0.95 (95% CI, 0.4–2.4). The IRR between patients with an unprovoked event with prior risk situations and patients with a provoked first event with positive past risk situations was 2.54 (95% CI, 1.3–4.9) and 5.93 (95% CI, 2.8–12.5) between patients with an unprovoked event without prior risk situations and patients with a provoked first event prior risk situations. Comparing patients with unprovoked events only, the IRR between patients with an unprovoked event without prior risk situations and patients with an unprovoked first event with positive past risk situations was 2.33 (95% CI, 1.1–4.9).

Male sex was associated with an increased risk for recurrence (IRR 3.5; 95% CI, 2.0–6.0), as was unprovoked first VTE (IRR, 3.4; 95% CI, 2.0–5.8) (Table 3). Patients with a positive family history for VTE had an IRR for recurrence of 1.9 (95% CI, 1.1–3.3) compared with patients with a negative family history of VTE. Patients with residual vein

Table 2 Risk of recurrent venous thrombosis

First event type	Past risk factors situations	Observational years	Median age at first event	Number of events	IR per 100 PY (95% CI)	IRRatio (95% CI)
Provoked	Present (*N* = 132)	1308	34.6	16	1.2 (0.7–1.9)	Reference
Provoked	Absent (*N* = 56)	517.2	28.4	6	1.2 (0.5–2.5)	0.9 (0.4–2.4)
Unprovoked	Present (*N* = 64)	580	46.8	18	3.1 (1.9–4.8)	2.5 (1.3–4.9)
Unprovoked	Absent (*N* = 24)	151.7	38.9	11	7.2 (4.1–12.5)	5.9 (2.8–12.5)

CI, confidence interval; IR, incidence rate; PY, patient-years.

Table 3 Venous thrombosis in different subgroups

	Observational years	Median age at first event	Number of events	IR per 100 PY (95% CI)	IRRatio (95% CI)
Sex					
Female ($N=229$)	2227.3	33.8	30	1.3 (0.9–1.9)	Reference
Male ($N=60$)	470.6	43.5	22	4.7 (3.1–7.0)	3.5 (2.0–6.0)
Risk factors					
Provoked ($N=195$)	1905.8	31.9	22	1.1 (0.8–1.7)	Reference
Unprovoked ($N=92$)	772.1	45.9	30	3.9 (2.7–5.5)	3.4 (2.0–5.8)
Recanalization[a]					
Complete ($N=101$)	917.1	35.5	11	1.2 (0.7–2.1)	Reference
Incomplete ($N=145$)	1342.9	34.5	32	2.4 (1.7–3.3)	1.9 (1.0–3.9)
Family history[a]					
Absent ($N=204$)	1906.7	34.5	29	1.5 (1.1–2.2)	Reference
Present ($N=80$)	748.1	36.9	22	2.9 (1.9–4.4)	1.9 (1.1–3.3)

CI, confidence interval, IR, incidence rate; PY, patient-years. [a] Data were missing for some patients in these subgroups.

thrombosis had an IRR of 1.9 (95% CI, 1.0–3.9) compared with patients with complete recanalization.

Because the risk of recurrence in men compared with women may partly be explained by provoking hormonal factors [9], we performed a subgroup analysis wherein the first event type (unprovoked or provoked) was taken into account (Table 4). Women experienced a provoked first event at a median age of 31.4 years (IQR, 26.8–38.7 years); their incidence rate of recurrence was 1.14 (95% CI, 0.74–1.76) per 100 patient-years. Women with an unprovoked first event had a median age of 46.4 years (IQR, 36.5–61.2 years); their relative risk of recurrence was 1.9 (95% CI, 0.9–4.0) when compared with women who had a first provoked event. Men with a provoked first event had a median age of 39.6 years (IQR, 32.3–61.9 years) and presented a 1.1 (95% CI, 0.3–4.9)-fold relative risk compared with women with a first provoked VTE, while men with an unprovoked first event had a median age of 44.4 years (IQR, 35.8–59.8 years) and a 5.5 (95% CI, 3.0–10.2)-fold increased risk of recurrence. In first unprovoked event, men had 2.9 (95% CI, 1.4–6.0)-fold increased risk compared with women.

Discussion

We have studied a cohort of 289 patients with a first VTE event who were followed up for 116 months. Recurrent VTE occurred in 52 (18%) patients. Exposure to prior risk situations for VTE was a protective factor among those patients whose first VTE event was unprovoked.

This study aimed at re-evaluating a Brazilian cohort of patients with a first VTE event with a longer follow-up. In the first analysis of this cohort, there were 25 recurrences in 378 (7%) patients who were followed for a median of 30 months. We found that the risk for recurrence was related with the nature of a first provoked or unprovoked event and only slightly with the presence of other prior risk situations for VTE [7]. In the second analysis, with a median follow-up of 43 months, there were 35 recurrences in 378 patients, and we found an increased risk for VTE recurrence in patients whose first event was unprovoked and no history of prior risk situation [8]. Therefore, a longer follow-up of this cohort would be needed to confirm our initial findings. In the present study, we showed that 69% of patients had been exposed to risky situations for VTE in the past, which did not result in thrombotic event at the time. The high rate of positive answers to this question (i.e. 69%) formed a large group of patients that, according to our hypothesis, could also be at lower risk for recurrence than those who experienced their first event without ever having had a risky situation for VTE. We found an association for this variable only when unprovoked events were taken into account. The risk of VTE among patients who had not been exposed to a risky situation for VTE and presented an unprovoked event compared with patients who had a provoked event was increased almost six-fold (5.93; 95% CI, 2.8–12.5). When we analysed the group of patients with an unprovoked event, we found that patients who were not exposed to past risky situations for VTE had 2.3-fold higher risk for recurrence than patients whose first event was unprovoked and were exposed to risk situations.

Several authors have previously reported that a first unprovoked VTE is a risk factor for recurrence [10,11]. Our study corroborates this finding, as patients with a first unprovoked event had almost four times higher risk for a

Table 4 Risk of recurrence venous thrombosis stratified by first event type and sex

First event type	Sex	Obsevational years	Median age at first event	Number of events	IR per 100 (95% CI)	IRRatio (95% CI)
Provoked	Female ($N=177$)	1752.6	31.4	20	1.1 (0.7–1.8)	Reference
Unprovoked	Female ($N=50$)	454.7	46.4	10	2.2 (1.2–4.0)	1.9 (0.9–4.0)
Provoked	Male ($N=18$)	153.2	39.6	2	1.3 (0.4–4.6)	1.1 (0.3–4.9)
Unprovoked	Male ($N=42$)	317.3	44.4	20	6.3 (4.1–9.5)	5.5 (3.0–10.2)

CI, confidence interval; IR, incidence rate; PY, patient-years.

recurrence when compared with those with provoked events. Our previous publications on this cohort had already reported a similar finding [7,8].

The risk of recurrence is also known to be influenced by sex. Men have approximately three to four-fold higher risk for recurrence than women [9,12–14]. Some studies proposed that the difference in recurrence risk could be explained partly by exposure to hormonal factors in women, which contributed to the first event, but the role of this exposure in the recurrence of VTE is not well established [9,14]. Nevertheless, in the present study, when we compared women and men who had a first unprovoked event, men still held an increased risk for VTE recurrence of 2.9 (95% CI, 1.4–6.0) fold, similar to what has been reported in other studies [12–14].

Previous studies suggest that the presence of residual vein obstruction at the end of the regular period of anticoagulation treatment might increase the risk of VTE recurrence [15,16]. Indeed, a meta-analysis of 14 studies showed that residual vein thrombosis is a mild risk factor for recurrent VTE (hazard ratio, 1.5; 95% CI, 1.1–2.0) [17]. Our study supports this finding with an IRR of 1.9 (95% CI, 1.0–3.9) for patients who had residual thrombosis.

Not many studies reported on positive family history as a risk factor for recurrence, but the few that did report no influence on recurrence risk [18,19]. In our study, we found an increased risk of VTE recurrence (IRR 1.9; 95% CI, 1.1–3.3) in patients with a positive family history of VTE when compared with patients with a negative history.

The main strength of this study is the long follow-up of the cohort. Some limitations warrant further comments. First, the young age of patients enrolled in our investigation (median age, 35.5 years) suggests that the cohort does not represent a normal distribution of patients with first VTE in the community wherein most of the events happen in the sixth decade. To test the influence of these data in our relative risk estimates, we performed subgroups analyses that showed similar findings with other population studies [2,3]. Second, patients with distal DVT were included in our analysis, although they seem to have a lower probability of VTE recurrence [20,21]. They represented 30% of the cohort. This might partially explain the lower recurrence rate found in this study when compared with others. Third, 89 (23.6%) patients were lost to follow-up. Therefore, recurrence events could have been underestimated. Fourth, due to the small number of events and the absence of information about some well known risk factor for VTE, such as obesity and severe thrombophilias, we could not adjust for these possible confounders. Finally, as far as we know, this cohort is the only study thus far that hypothesized that past risk situations for VTE can be associated with recurrence. As replication is essential, confirmation of our results in different cohorts is warranted before clinical conclusions can be drawn from our study.

In conclusion, after a follow-up of about 10 years, we showed that the absence of past risk situations for VTE was associated with recurrence, while the first event was unprovoked. Therefore, asking a patient about past exposure of VTE risk factors that were present long before the occurrence of a first VTE may help to classify patients at lower risk for recurrence if the first event was unprovoked. This should be analysed in conjunction with other individual risk factors. We also confirm that male, a first unprovoked event, the presence of family history of VTE and incomplete recanalization increased the risk of recurrence.

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Conflicts of interest

All authors have nothing to declare as to a conflict of interest.

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