Predicting the risk of recurrent venous thrombosis: Impact and therapeutic consequences of inherited thrombophilia

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Abstract

Rationale, aims and objectives :Over the past decades, thrombophilia testing in patients with venous thrombo-embolism (VTE) has increased tremendously. However, the role of inherited thrombophilia (IT) in prediction the risk of recurrence remains controversial. Consequently, it is still unclear whether thrombophilia testing influences decisions regarding duration of anti-coagulation in clinical practices. The aim of this study was to evaluate the impact if IT on VTE treatment decisions and on predicting the risk of recurrence. Methods : A retrospective longitudinal study (January 2011-Decembre 2016) including 190 patients with confirmed VTE referred from internal medicine department for inherited thrombophilia screening was carried out. Results : The mean age patients was 40.2 years and the sex ratio (M/F) was 0.78. IT was confirmed in 27.5% of patients. A long term anticoagulation was decided in 51.6% of patients with IT. There was no significant difference in the duration of anticoagulation between patients with or without IT. VTE recurrence was recorded in 26 (13.7 %) patients. The 24 years cumulative incidence of recurrence was 9% in patients with IT and 14% in those without. IT was not associated with increased risk of recurrence after treatment withdrawal (Hazard ratio=1.31 IC(0.47-3.63); p=0.6). Conclusion : In clinical practice, IT did not influence anticoagulation duration and was not associated with a higher VTE risk of recurrence. It seems to be less relevant for decision making than presumed.

Background

Venous thrombo-embolic disease (VTE) is a common condition with an estimated annual incidence of 1-2 / 1000 persons [1]. Its incidence has remained stable during the last decade [1]. VTE is related to a mortality rate estimated between 20 and 25% at 5 years and is considered as a chronic multifactorial pathology [2]. Indeed, it involves many risk factors which can be classified as constitutional or acquired, transitory or persistent. Consensually, inherited thrombophilia (IT) screening includes testing for both natural inhibitor (antithrombin (AT), protein C (PC) and protein S (PS)) deficiencies and polymorphisms of factor V Leiden and prothrombin G20210A mutation. It is currently admitted that IT increases the risk of a first thrombotic event. Indeed it is found in 50% of patients with VTE [3]. So far, it has provided an explanation for VTE and justified indefinite anticoagulation to prevent recurrences after treatment withdrawal [4]. However, according to more recent data, impact of thrombophlia on the risk of recurrence is unclear [5]. Recent guidelines did not consider thrombophilia in therapeutic management of VTE. Consequently, guidelines from the American college of chest physicians (ACCP) [6] do not include thrombophilia in the treatment duration. For others such as the European society of Cardiology (ESC) [7] and the national Institute for Health and Care Excellence (NICE) [8], the assessment of thrombophilia can modulate the treatment duration in selected situations. In the absence of a clear consensus in clinical practice, this study aimed to evaluate the impact of IT on therapeutic decisions and on predicting the risk of VTE recurrence.

Methods

Study design and patients: This was a single center retrospective longitudinal study of patients with a confirmed VTE and undergoing IT testing between January 2011 and December 2016. An initial database of all patients who have been referred to the hematology laboratory from the internal medicine department during this period for constitutional thrombophilia testing has been established. Clinical data were obtained from medical records using a standardized form and included the following: demographic characteristics, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidimia, obesity, smoking), bleeding risk factors (renal or liver impairment, antiplatelet drugs), history of cardiovascular or venous thrombotic event, adverse pregnancy outcome, details of *index* VTE defined as the thrombotic event which had indicated thrombophilia screening (localization, provoked/unprovoked VTE [9]), indication and timing of testing, anticoagulation duration), details of recurrent VTE, other complications (bleeding events or postphlebitic syndrome). Patients from other departments were not included. Those with missing clinical data were excluded.

Thrombophilia screening: Laboratory investigation focused on screening for AT, PC, PS protein C deficiencies and activated protein C resistance (aPCR). Unfortunately, results from factor V Leiden and prothrombin gene mutation were not available. Laboratory tests were performed on automate type STA Compact Max using reagents from STAGO (STACHROM AT, STACLOT PC, STACLOT PS and STACLOT-APCR). The presence of IT was considered only if repeated tests showed persistently abnormal results (AT<80%, PC<70%, PS<55% or APCR<120 seconds) and/or if the abnormal defect was also shown in family investigation.

Ethical considerations: All patient data were anonymized prior to analysis. This study was approved by the local ethics committee.

End points: Decision to pursuit or discontinue anticoagulation and occurence of recurrent thrombotic events

Statistical analysis: Qualitative variables were expressed as percentages and frequencies. Quantitative variables were expressed as means. Comparisons of qualitative variables were tested by $\chi 2$ or Fisher test, as appropriate. Comparisons of quantitative variables were performed with T Student test. The recurrence-free survival analysis was done by Kaplan Meier method: The log-Rank test was used to compare two curves of survival without recurrence. The Hazard recurrence ratios were carried out using a COX model. The time scale used in the two statistical survival tests (the Kaplan Meier method and the COX model) was the time between the *index* VTE (model A) or the anticoagulation withdrawal (model B) and the recurrent event/the end of the follow up or the end of the study. A p value <0.05 was considered as statistically significant. All statistical analysis were performed using SPSS 20.0 Software.

Results

Populations characteristics: During the study period, 300 patients were referred to the hematology department from the internal medicine department for IT screening. after exclusion of patients with missing clinical data, 190 patients were included (Figure 1). Demographic and clinical characteristics of patients are summarized in table 1.

Index venous thrombotic event: Thrombosis sites were proximal deep venous thrombosis of lower limbs (52.5%), pulmonary embolism (12.6%), both proximal deep venous thrombosis of lower limbs and pulmonary embolism (7.9%), distal deep venous thrombosis of lower limbs (19%), superficial venous of lower limbs (7.4%), unusual sites (14.9%). the thrombotic event was secondary to a persistent risk factor (6%), transient major risk factor (5%), transient minor risk factor (28%) and mostly idiopathic (61%). Indefinite treatment duration was decided in 34 (23.4%) patients for the following reasons: thrombophilic abnormalities (n=21), previous thrombosis (n=10), Behçet disease (n=1), myeloproliferative disorder (1), immobilization (n=1). In patients who stopped treatment, the mean duration of anticoagulation was 13.9±15.5 [1-96] months. The treatment duration was statistically more prolonged in patients with pulmonary embolism or proximal deep veins than distal localizations (29.9, 13.9 vs 8.1 moonths; p=0.02 and p=0.005 respectively). However, the durations of treatment in patients with thrombosis of unusual site and in those with thrombosis of

other localizations were comparable (p=0.36). Curiously, duration of anticoagulation was not significantly associated to neither a history of thrombosis (22 vs 12 months; p=0.08) nor circumstances of thrombosis: provoked by a transient factor (15.1 months), persistent factor (10.1 months) and idiopathic (13.4 months); p=0.6.

Inherited Thrombophilia screening: Laboratory investigations were indicated in the following situations: age inferior to 50 years old (57%), previous thrombosis (15%), family history of thrombosis (14%), unusual localization (10.4%), idiopathic episode (3.1%). Among the 190 included patients, 131 were screened for the four parameters. The prevalence of IT was 27.5% (n=36). As expected, the most frequent abnormality was aPCR (27.5%). Deficiencies in AT, PC, and PS were found in 2, 5 and 3 patients respectively. IT was not statistically associated to the following factors: personal previous venous thrombotic/cardiovascular events, family history of thrombosis, adverse pregnancy outcome, idiopathic thrombosis.

Follow up: Among 190 included patients, 66 were lost to follow up (Fig 1). For the other 124 patients, the mean duration of follow up was 34±37.2 months since the Index VTE and 22.3 ±24.7 months since anticoagulation withdrawal.

Impact of thrombophilia on treatment duration

Among the 36 patients with IT abnormalities, we could evaluate the decisions regarding therapeutic management in only 31 patients. Sixteen (51.6 %) patients pursuit anticoagulation (1 AT deficiency, 2 PC deficiency, 1 protein S deficiency and 11 patients with aPCR). Neither thrombophilia nor clinical characteristics were associated to the decision to pursuit or to stop anticoagulation. Besides, treatment duration was not longer in patients with IT than in those without (12.3 vs 13.3 months; p=0.76). Moreover patients with both idiopathic index VTE and IT were anticoagulated during a period longer than those with both provoked thrombosis and IT (14.6 vs 6 months; p=0.04). Among 5 patients with IT and VTE at unusual site, 3 patients received a prolonged anticoagulation.

Outcomes and recurrences: Among 124 patients followed up, recurrent thrombotic events were reported in 26 patients (21%) (fig 1a). The mean time between Index VTE and the first recurrence was 38.5 months (2.5-144). The mean time between treatment withdrawal and recurrence was 11.7 months (±16.9). Recurrences were reported in 8 patients while on indefinite treatment duration. Analysis of predictors of recurrent VTE showed that recurrences were significantly associated to male gender, smoking, history of previous VTE or cardiovascular events, proximal localization, presence of a persistent risk factor, idiopathic thrombosis and post phlebitic syndrome (Table 2).

Association of thrombophilia with the risk of recurrence: Among patients who were followed up, 29 had IT and 16 developed recurrent events (figure 1b). A recurrent thrombotic event was reported in 6 patients (20.7%) with IT (fig 1b). Three patients with IT and recurrent VTE were on indefinite treatment duration. The cumulative incidence of recurrence associated to IT was 4% and 12% at both 12 and 24 months of follow up; p=0.48. The hazard ratio of recurrent event was 1.45 IC (0.51-4.07) after index VTE and 1.31 IC (0.47-3.63) after treatment withdrawal (table 3). When adjusting for gender, smoking, history of previous thrombotic or cardiovascular events, proximal localization, persistent risk factor/idiopathic thrombosis and post phlebitic syndrome, thrombophilia did not increase the risk of recurrence. Similarly, neither the presence of aPCR nor the deficiencies of natural inhibitors had significantly increased the risk of recurrence compared to patients with a normal IT testing results.

Discussion:

This study showed the following results: firstly, IT did not influence the decision to pursuit or to stop anticoagulation. In patients who stopped anticoagulation, IT was not associated with longer treatment duration. However patients with idiopathic VTE and IT received anticoagulation for a period of time longer than those with provoked VTE and IT. Secondly IT did not increase the risk of VTE recurrence. In univariate analysis, male gender, smoking, history of previous VTE or cardiovascular events, proximal localization, persistent risk factor, idiopathic thrombosis and post phlebitic syndrome significantly increased the risk of

recurrence. This retrospective study provided a real life vision of clinical decisions regarding VTE treatment duration in response to a tedious laboratory workup results. However it had some limitations, mainly the monocentric and retrospective character of the study as well as the small cohort. Thus, results could not be generalized. We mentioned also as a limitation the non availability of factor V Leiden and prothrombin gene mutation results that are included in the IT workup as well as the absence of a control group of patients with VTE who were not tested for IT.

Therapeutic implications of IT: This study showed that anticoagulation was pursued in half the patients with IT. Patients with both IT and idiopathic VTE received a longer course of anticoagulation comparing to patient with IT and provoked VTE. So far, there is no prospective study assessing the benefice of prolonged anticoagulation versus routine duration in patients testing positive for IT [10]. In the MEGA study [11], which is the largest case controlled study, the authors have evaluated the influence of treatment decisions taken after obtaining IT screening results. Testing was performed in 35% of patients who had had recurrence versus 30% of patients without recurrence. Testing for IT did not reduce the risk of recurrence. Similarly, data from literature stipulate that IT seems to have a minor role in determining the duration of anticoagulant treatment after a VTE [12]. The evaluation of real professional practices showed that IT testing was frequently realized after an episode of VTE but rarely considered in deciding treatment duration [5,13].

Regarding the available recommendations [6,8,14,15], there is no clear consensus concerning patients' management according to the results of IT testing which led to heterogeneity in therapeutic attitude among clinicians. Nevertheless, it is obvious that IT screening is no longer a determinant factor in treatment decisions. Deconstructing the actual recommendations, IT screening still has a minor therapeutic implication in specific situations essentially after an unprovoked first proximal VTE in patients without a high hemorrhagic risk and desiring to interrupt anticoagulation [8,16]. In addition, some experts tend to restrict more the indication of a prolonged anticoagulation and reserve it to patients with proximal first VTE and deficiency of AT or deficiencies of PC and PS less than 30% [17]. On the topic of VTE at unusual site, the optimal duration of anticoagulation is still unknown due to the lack of solid evidence [18]. According to recent recommendations [18,19], the duration of treatment depends essentially on the site of thrombosis and the presence of an eventual underlying condition. Nevertheless, some authors enhance a prolonged anticoagulation in patients with cerebral venous thrombosis, portal vein or supra hepatic thrombosis and major thrombophilia [18,19].

Risk of VTE recurrence: In this study, the recurrence rate after treatment withdrawal was 21%. This rate varies from one study to another (7.75-23.9%) [20,21]. This variation is essentially due to differences in inclusion criteria of patients and duration of follow up. In Satpanish et al [22] study including 198 patients with either first or recurrent VTE from 2004 to 2014 followed up during a mean period of 52 months, the recurrence rate was 11%.

In the present study, male sex, smoking, personal history of venous thrombosis or cardiovascular events, persistent trigger, unprovoked VTE and post phelebitic syndrome were predictors of recurrence in the univariate study. Compared to distal VTE, proximal VTE were not associated with a high risk of recurrence. This observation may be explained, at least partially, by the duration of anticoagulation which was significantly longer in proximal VTE than in distal thrombosis. Nevertheless, and comparing to other localizations, proximal deep venous thrombosis was a risk factor of recurrence. Predictors of the risk of recurrence are not formally established. This is due to the multifactorial character of the VTE, the complexity of interactions between the risk factors and the differences in study methodologies. Nevertheless, available data from literature showed that the following factors were predictive, regularly or not, of a high risk of recurrence: young age [23], male sex [24], obesity [25], dyslipidemia [26], family history of thrombosis [27], personal history of thrombosis [20], proximal VTE [28], unprovoked VTE [29], persistent risk factor [30] and post phlebitic syndrome [31]. In fact, it is proved that the main clinical characteristic considered as determinant in estimating the risk of recurrence is the idiopathic type of VTE [6,8,14,15].

Regarding the impact of IT on the risk of recurrence, it did not affect the risk of recurrence in the present study. In the absence of a methodologically powerful study, it is still controversial whether IT confers a greater risk of recurrence. Such study would have as intervention thrombophilia testing and as result the occurrence

of a recurrent thrombotic event [32]. A study following this model was initiated but was early interrupted because of a low inclusion rate [32]. Nevertheless, several studies with heterogeneous methodologies have assessed the role of IT on the risk of recurrences. Some investigators did not find an increased risk of recurrence associated with the presence of IT regardless of the idiopathic or provoked type of VTE [13,24,33]. On the other hand, several retrospective and prospective studies have shown that IT significantly impacted the risk of recurrence after anticoagulation withdrawal [21,22,34]. Concerning the deficiencies of natural inhibitors, the study of their impact on the risk of recurrence is difficult due to their low prevalence and the lack of prospective studies [35]. Available data demonstrated that the risk of recurrence conferred by these deficiencies was at best moderately elevated and seemed to be highest in patients with AT deficiency [33,36]. Three systematic reviews have demonstrated that the risk of recurrence in carriers of an heterozygous factor V Leiden mutation was modesty increased with a relative risk varying from 1.36 to 1.56 [37-39]. Concerning the heterozygous prothrombin gene mutation, data diverged between the absence of an increased risk to a modest significant increase. Uncertainty remains also with homozygous mutations and compound heterozygosity for both mutations [11].

Conclusion: Despite the small cohort and the non exhaustivity of thrombophilia testing, we could draw some conclusions: Practically, the value of screening in patients with VTE is limited. Results did not alter initial management in real practice. Decisions usually depend on clinician judgment and sometimes the patient preferences. IT testing should be performed only in the case the result influences patient management. Prospective studies determining the situations where changing management in response to thrombophilia testing results is of clear clinical benefit are warranted.

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Figure 1 legend: During the study period, 300 patients were referred to the hematology department from the internal medicine department for IT screening. After exclusion of patients with missing clinical data, 190 patients were included in the evaluation of the impact of demographic and clinical characteristics on the risk of recurrence. Among these 190 patients, 94 patients with complete thrombophilia screening were appropriately followed up and were included in the study of the impact of IT screening on the risk of recurrence.

Table 1 : Demographic and clinical characteristics of patients

Characteristics
Age at *index* VTE, n (%)
Gender, n(%) Males Females
Cardiovascular risk factors, n(%) Body mass index >30 Hypertention Diabetes Dyslipidemia Smoking
Bleeding risk factors, n(%) Renal failure Antiplatelet treatment
History of cardiovascular events, n (%)
History of venous thrombotic events; n (%) >2 events Median time[Last VTE-VTE index], months Proximal localiza
History of adverse pregnancy outcome, n(%) Early fetal loss Preeclampsia Late fetal loss
Family history of thrombosis, n(%) First degree relatives

Table 2: predictive factors of thrombotic venous recurrence

	Model A+	**Model A+**	**Model B++**	
Variables	**Hazard ratio (IC)**	**p**	**Hazard ratio (IC)**	**p**
Age <50 ans	0.84 (0.31-2.24)	NS	0.9 (0.34-2.4)	NS
Male gender	2.2 (1.01-4.86)	0.04 *	1.95 (0.9-4.23)	NS
Cardiovascular risk factors				
Smoking	2.63 (1.18-5.89	0.02*	2.96 (1.34-6.55)	0.007**
Hypertension	0.5 (0.11-2.16)	NS	0.38 (0.05-2.88)	NS
Diabetes	0.88 (0.3-2.57)	NS	0.9 (0.25-3.24)	NS
Obesity	1.27 (0.55-3)	NS	1.14 (0.51-3.80)	NS
Dyslipidemia	0.88 (0.2-3.82)	NS	1.22(0.28-5.22)	NS
Previous venous thrombosis	2.19 (1.01-4.76)	0.04*	4,11 (1.82-9.32)	0.001**
Previous cardiovascular events	3.32 (1-11.2)	0.04*	4.23 (1.24-14.45)	0.02*
Family history of venous thrombosis	1.19 (0.44-3.19)	NS	0.87 (0.33-2.3)	NS
Thrombosis circomstunces				
Idiopathic	2,7 (1.03-7.36)	0.04*	2.24(0.82-6.07)	NS
Secondary to transient risk factor	Referent		Referent	
Persistant risk factor	4.92 (1.64-14.74)	0.004**	2.57 (0.88-7.51)	NS
Localizations				
Proximal deep venous thrombosis	0.95 (0.31-2.9)	NS	1.01 (0.32-3.14)	NS
	1.93 (0.86-4.35)§	NS	3.2 (1.36-7.54) §	0.008**
Pulmonary embolism	0.19 (0.03-1,07)	NS	0.37(0.08-1.69)	NS

	Model A+	**Model A+**	**Model B++**	
Distal deep venous thrombosis	referent		referent	
Treatment duration< 6 mois	0.6 (0.14-2.74)	NS	0.28(0.06-1.24)	NS
Indefinite treatment duration	0.97 (0.41-2.32)	NS	-	-
Post phlebitic syndrome	2.68 (1.23-5.82)	0,01*	3.45 (1.59-7.48)	0.002**
Thrombophilia	1.45 (0.51-4.07)	0,49	1.31 (0.47-3.63)	0.6

IC : interval of confidence; $^{+}$*:Model A uses as observational time the interval between the index VTE and the recurrence or the end of the study or the loss to follow up; ++: Model B uses as observational time the interval between the withdrawal of anticoagulation and recurrence or the end of the study or the loss of follow up; *: <0.05 ; **: p<0.01;*§: *Hazard ratio calculated by* comparing proximal deep venous thrombosis to other localizations

Table 3: Association between inherited thrombophilia and venous thrombosis recurrence

Authors	**Origin (years)**	**Study type**	**Population**	**Mean duration of follow-up**	**Association between IT and recurrence**
Christiansen et al [33]	Netherlands (2005)	Prospective cohort	474 patients with a firts VTE	7.3 years	HR=1.4 ; IC= 0.9-2.2 HR=1.6 IC=1-2.7^{+}
Santamaria et al [21]	Italy (2005)	Randomized mulicentric prospective study	195 patients with first proximal unprovoked VTE	46,8 months	HR=1.78, p=0.046 $^{++}$
Douketis et al [24]	Canada (2010)	Meta-analysis of 7 prospective studies	1818 patients with first unprovoked VTE	26.9 months	HR=1 ; p=1
Kudo et al [34]	Australia (2016)	Retrospective multicentric study	152 patients with an index VTE	1 year	Patients with recurrent VTE had a higher rate of positive thrombophilia results (52% vs 27% (p=0.007)
Lim et al [13]	Australia (2017)	Retrospective study	742 patients with an index VTE	27 months	HR= 1.19 ;p= 0.74
Satpanich and Rojnuckarin [22]	Thai (2018)	Retrospective cohort	198 patients with an index VTE	52 months	HR= 3.52 ; p = 0.01 $^{++}$

VTE: venous thrombo-embolism, HR=:hazard ratio, VTE :venous thrombormbolism, +:in patients with two

or more IT abnormalities ; ++:antiphospholipids antibodies are included in thrombophilia abnormalities

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