



Impact du phénotype de la maladie veineuse thrombo-embolique (MVTE) sur le phénotype de la MVTE chez les membres de famille

Elize Campillo

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UNIVERSITE DE BREST - BRETAGNE OCCIDENTALE
Faculté de Médecine & des Sciences de la Santé

Année 2017

N°

THESE DE DOCTORAT EN MEDECINE
DIPLOME D'ETAT

Par

Madame Elize CAMPILLO

Née le 19 août 1988 à Aire-Sur-L'Adour (40)

Présentée et soutenue publiquement le 20 avril 2017

**IMPACT DU PHENOTYPE DE LA MALADIE VEINEUSE
THROMBO-EMBOLIQUE (MVTE) SUR LE PHENOTYPE DE LA
MVTE CHEZ LES MEMBRES DE FAMILLE**

Président : Monsieur le Professeur C. LEROYER

Membres du jury : Monsieur le Professeur F. COUTURAUD
Monsieur le Professeur L. BRESSOLLETTE
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RIOU Morgan	Anglais

Septembre 2016

SERMENT D'HIPPOCRATE

Au moment d'être admise à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

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LIST OF ABBREVIATIONS

APC : Activated protein C

AT : Antithrombin

DVT : Deep venous thrombosis

FDR : First-degree relatives

FIT : Familial idiopathic thrombophilia

FVL : Factor V Leiden mutation

ICC : Intraclass correlation coefficient

PE: Pulmonary embolism

PS : protein S

PTm : Prothrombin 20210A mutation

TAFI : Thrombin activatable fibrinolysis inhibitor

TF : Tissue factor

TFPI : Tissue factor pathway inhibitor

VTE : Venous thromboembolism

RATIONAL

Venous thromboembolism (VTE) and incidence

Venous thromboembolism (VTE) is a frequent and common disease. Annual incidence rates are estimated by several Western Europe, North America and Australia studies from 0.75 to 2.69 per 1000 individuals in the population (1). Delluc *et al.* reported that incidence of VTE in France was 1.57 per 1000 individuals per year, 0.76 and 0.81 per 1000 individuals per year for deep venous thrombosis (DVT) and pulmonary embolism (PE) respectively (2). A recent study of the French national insurance database over two years highlighted an annual incidence of VTE of 184.0 per 100 000 subjects. In addition, annual incidences of DVT and PE were respectively 119.8 and 64.2 per 100 000 subjects (3).

The burden of VTE

VTE is a major public health concern and its cost is substantial. An estimation of VTE related deaths was conducted in six European countries (France, Germany, Italy, Spain, Sweden and the UK). Cohen *et al.* found an estimated number of 370,012 deaths per year in 2004. They also estimated 543,454 VTE-related deaths per year in all member states of European Union (4). In the United States of America (USA), medical costs of treating VTE and its complications were estimated by Grosse *et al.* at \$6.7 to \$9.8 billion (5). A recent review emphasises a cost of \$15,123 per VTE event in the USA. In Canada and European countries, costs were lower because of global lower health care costs. In Belgium, a PE hospitalization costs €3,394 and a VTE hospitalization costs €1,349 in Italy (6). It is important to notice that complications of VTE including recurrences, post-thrombotic syndrome after DVT, chronic thromboembolic pulmonary hypertension after PE and anticoagulation-related adverse drug events, participate to this considerable cost.

VTE: a multifactorial disease

VTE is a multifactorial disease with potential interactions caused by genetic and acquired risk factors.

Acquired risk factors

One of the major acquired risk factor is age with an incidence of VTE in different studies between 2 and 7 per 1000 individuals aged ≥ 70 years and between 3 and 12 per 1000 individuals aged ≥ 80 years (1). Recent major surgery particularly orthopaedic surgery, trauma and neurosurgery, neoplasia and chemotherapy, hospitalisation and acute diseases as myocardial infarction, acute respiratory failure or stroke, immobilization, institutionalization, inflammatory bowel diseases, are well known risk factors. Hormonal risk factors include

pregnancy, postpartum, combined oral contraceptive use and hormone replacement therapy, especially oral administration. Acquired thrombophilia include antiphospholipid syndrome defined by clinical and biological criteria, paroxysmal nocturnal hemoglobinuria, myeloproliferative disorders as essential thrombocythaemia or polycythemia vera. (7,8).

Genetic risk factors

Confirmed genetic risk factors are protein C, protein S and antithrombin deficiencies, factor V Leiden mutation (FVL), prothrombin 20210A mutation (PTm), non O-blood group, high levels of factor VIII, dysfibrinogenaemia and hyperhomocysteinaemia (9).

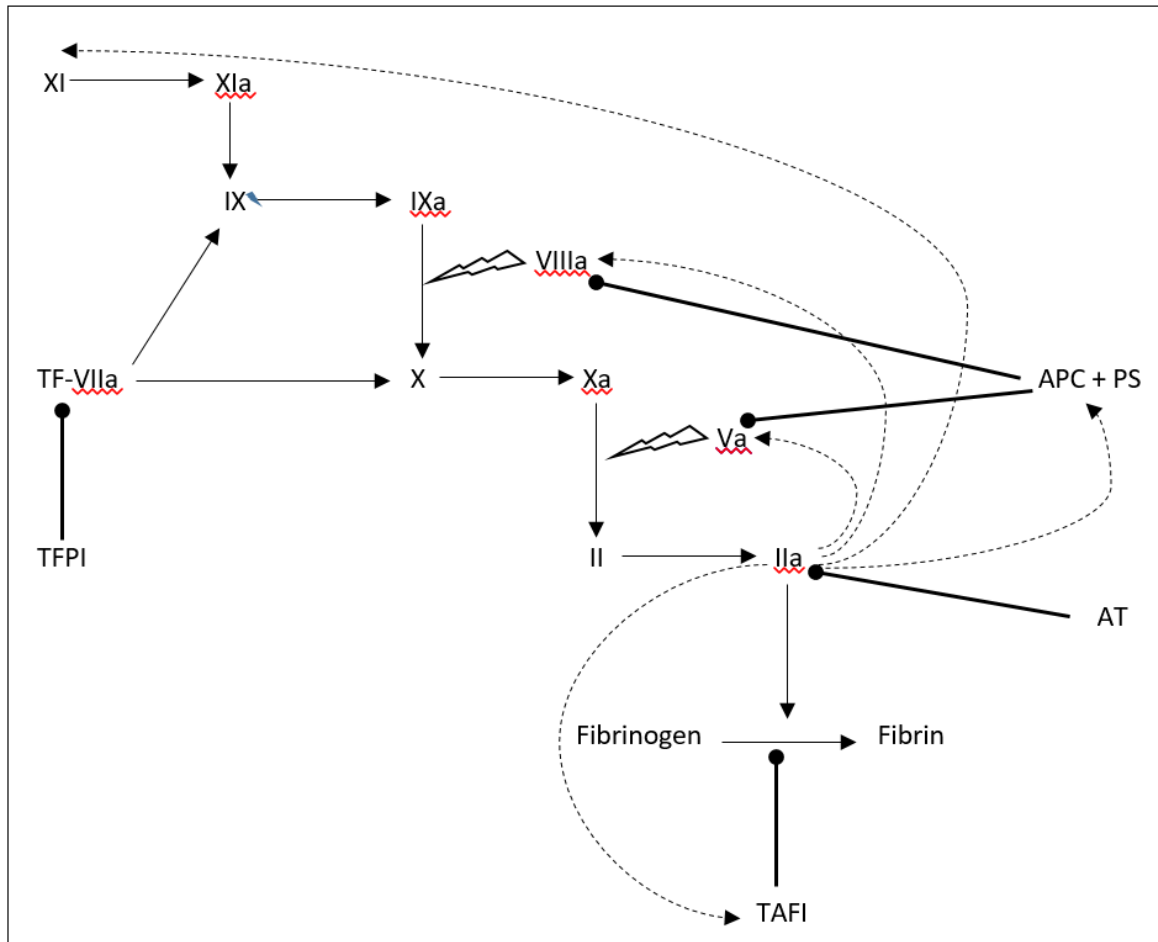
In order to understand precisely how these genetic factors can influence the risk of VTE, physiology of blood coagulation is shown in the figure below (10,11). Firstly, after a vascular damage, Tissue Factor (TF)-factor VIIa complex activates factor IX or factor X. Factor IXa can activate factor X thanks to cofactor VIIIa. Then, factor Xa activates factor II thanks to cofactor Va, leading to factor IIa also called enzyme thrombin. Finally, factor IIa converts fibrinogen into fibrin.

Thrombin is at the center of coagulation control: it activates factor V and factor VIII as well as factor XI which activates factor IX. Thrombin also downregulates fibrinolysis and activates protein C: activated protein C and protein S inactivates cofactors Va and VIIIa. Thrombin also activates Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) which prevents formation of fibrin. Lastly, Tissue Factor-Pathway Inhibitor (TFPI) inhibits TF.

This can explain why antithrombin, protein C and protein S deficiencies lead to a procoagulant state. Factor V Leiden is resistant to degradation by activated protein C and prothrombin 20210A mutation (PTm) leads to high levels of thrombin. Prevalence of antithrombin, protein C and protein S deficiencies are respectively estimated between 0.02 and 0.2%, 0.2 and 0.4%, 0.03 and 0.1% in the general population and are respectively estimated at 1%, 3% and 2% in patients with VTE. In the general population, heterozygous FVL and PTm are estimated at 5% and 2% respectively whereas in patients with VTE, they are estimated at 20% and 6%. (12).

Among other genetic risk factors, non-O blood group is associated with a two-fold increased risk of VTE, probably because of high factor VIII and von Willebrand factor levels in this group (13,14). High levels of homocysteine are also associated with at least a two-fold increased risk of VTE in different studies. Then, it had been demonstrated that high factor VIII or fibrinogen levels are risk factors for VTE (9).

Figure : Simplified physiology of blood coagulation



(APC: Activated Protein C, AT: Antithrombin, PS: Protein S, TAFI: Thrombin Activatable Fibrinolysis Inhibitor, TF: Tissue Factor, TFPI: Tissue Factor Pathway Inhibitor)

Thrombophilia and risk of VTE

Nonetheless, all genetic thrombophilias do not confer the same risk of VTE. Lijfering *et al.* proposed to classify antithrombin, protein C and protein S deficiencies into strong risk factors for VTE and heterozygous FVL, PTm and high FVIII levels into mild risk factors (15). In relatives with strong risk factors from probands with genetic thrombophilia who had VTE, the annual risk of first VTE was 1.77% to 1.90% whereas with mild risk factors, it was 0.34% to 0.49% (15). VTE risk is approximately increased three- to seven-fold in carriers of factor V Leiden compared with non-carriers (16–18). PTm is associated with a 3.8-fold increased risk of VTE (17). Both heterozygous FVL and heterozygous PTm increase 20-fold the risk of venous thrombosis (17).

Recurrence of VTE

All patients combined, the risk of recurrence is 20 to 25% after 5 years. When patients experienced firstly an unprovoked venous thrombosis, it is higher than 25% (19). A retrospective analysis of data from a French health insurance called CNAMTS (Caisse Nationale d'Assurance Maladie des Travailleurs Salariés) which covers 77% of the population showed a recurrence of VTE in 5.5% patients over 1-year of follow-up (3).

Kyrle *et al.* conducted an interesting review about risk assessment for recurrent venous thrombosis (19).

Clinical features

Clinical features are summarized in the table below. It is now well-known that patients with an idiopathic VTE (termed “unprovoked VTE”) have a higher risk of recurrence compared to those with a provoked event. Patients with PE or proximal DVT also have an increased risk of recurrence compared to those with distal vein thrombosis (19). Compared to women, men have a four-fold risk of recurrence. Multiple episodes of VTE as well as its complications (post-thrombotic syndrome or residual vein obstruction) and treatment by vena cava filters increase risk of recurrence (19).

Results are controversial regarding to age, some studies found an association between increased age and increased risk of recurrence, whereas others did not reveal it (19).

Results are controversial about family history. In their study, Kyrle *et al.* did not find an association between family history and risk of recurrence. A more recent Swedish prospective study showed a two-fold increased risk of recurrence in patients with an unprovoked first VTE and a family history of VTE compared to those without a family history of VTE (20).

Patients with neoplasia are more at risk of recurrence than those without neoplasia, even if they have a well-conducted anticoagulation treatment. Overweight and dyslipidaemia also increase independently the risk of recurrence.

Kearon *et al.* found that PE or DVT have similar risk of recurrence; however, in patients with PE, the clinical presentation of recurrence is PE in 80% of cases whereas patients with DVT will be more likely to have recurrence as DVT (in 80% of cases)(21). In the PADIS PE trial (Couturaud JAMA 2015), we found similar observations (22). In addition, a study of the French national insurance database showed that when patients had PE or DVT and experienced recurrence, they respectively had PE in 80.9% of cases, and DVT in 85.7% (3). Therefore, these results may indicate a genetic susceptibility for PE or DVT.

Table: Clinical risk factors for VTE recurrence

Type of VTE	Unprovoked
Localisation	PE and proximal DVT
Sexe	Male
Medical history	Multiple episodes of VTE Family history Neoplasia Antiphospholipid syndrome Overweight Dyslipidaemia
Complications of VTE	Post-thrombotic syndrome Residual vein obstruction
Treatment	Vena cava filters

DVT: Deep Venous Thrombosis, VTE: Venous ThromboEmbolism

Laboratory markers

Interestingly, heterozygous FVL and PTm which are the most common mutations, do not increase substantially the risk of recurrence as compared to patients without genetic thrombophilia (19,23,24). However, homozygous FVL or double heterozygous FVL and PTm increases the risk of recurrence (16,17,19,25). An interesting finding is the FVL paradox: in patients with FVL, the risk of PE seems to be lower than that of DVT (26).

More studies are necessary to prove a higher risk of recurrence for partial deficiency of antithrombin, protein C, protein S or Tissue Factor Pathway Inhibitor; for high levels of fibrinogen, factor VIII, factor IX or homocysteine (19).

About D-dimer, several studies showed an increased risk of recurrence, more than 2-fold in patients with first unprovoked VTE and high D-dimer levels after discontinuation of anticoagulation therapy compared with those with normal D-dimer levels (19,27,28).

In patients with a first unprovoked VTE, non OO-blood type increased risk of recurrence (29).

Thus, clinical risk factors are more important than biological markers to predict risk of recurrence.

Family history and risk of VTE in relatives

Family history of VTE is an important risk factor for first VTE in relatives. First-degree relatives of patients with VTE have an increased risk of 2.2- to 3.0-fold (30). Zöller *et al.* also found an increased risk in second and third-degree relatives (31).

Age of index cases

Age at diagnosis of VTE influences risk in relatives. In two studies, Couturaud *et al.* demonstrated a higher risk of VTE in first-degree relatives if the index case was younger (OR, 0.97 per year older; 95% CI 0.96-0.99) and a 3.27-fold increased risk of VTE in first-degree relatives of index cases with unprovoked VTE < 45 years compared with index cases with unprovoked VTE > 71 years (32,33). Sorensen *et al.* also reported a standardized incidence ratio that decreased with increased age of index case (34). In addition, other studies from Bezemer *et al.* and Zöller *et al.* support this association (35,36).

Number of affected family members

Furthermore, the number of affected probands influences risk in relatives. Bezemer *et al.* found a four-fold risk in first-degree relatives when ≥ 2 relatives were affected (OR, 3.9; 95% CI, 2.7-5.7) (35) whereas Couturaud *et al.* showed a 2.47-, 3.54- and 5.17-fold risk when respectively 2, 3 and 4 relatives were affected (32).

Provoked and unprovoked VTE

Distinction between provoked and unprovoked VTE in family history is important. Couturaud *et al.* reported a higher risk of VTE in first-degree relatives of patients with an unprovoked VTE compared with patients with a provoked VTE (OR, 2.38; 95% CI, 1.43-3.85) (32).

Clinical presentation of VTE (PE/DVT)

Couturaud *et al.* did not find an association between the clinical presentation of VTE (DVT or PE) in index cases and risk of VTE in relatives (32). Nevertheless, Zöller *et al.* highlighted an association between the type of VTE in parents or siblings and the type of VTE in offsprings (37).

Gender

According to Zöller *et al.* there were no significant differences between males and females in the overall familial standardized incidence ratio even if incidence rates were higher for younger females and older males in both familial and non-familial cases (36). Nevertheless, it was noticed in a study by Sorensen *et al.* that male siblings of male index cases had the highest risk (SIR, 3.99; 95%CI, 3.39-4.17) compared with female siblings of male index cases (SIR, 2.59; 95% CI, 2.13-3.15), with female siblings of female index cases (SIR, 2.97; 95% CI, 2.47-3.57), and with male siblings of female index cases (SIR, 2.97; 95%CI, 2.17-3.17) (34).

FVL and PTm

If a patient have FVL or PTm and experienced VTE, his/her relatives who have the same mutation will have a higher risk of VTE compared with relatives without this mutation. However, relatives without the same mutation have a higher risk compared with the general

population (32,38). In index cases with unprovoked VTE, the presence of FVL or PTm in index cases is a weak independent risk factor of VTE in relatives (OR, 1.48; 95% CI, 0.94-2.33, $p < 0.09$) (33). Noboa *et al.* showed that a family history of VTE is associated with an increased risk of first VTE in relatives, independently of carrying or not FVL or PTm and independently of the presence or absence of major acquired risk factors in relatives (OR, 2.7; 95% CI, 1.8-3.8) (39). Bucciarelli *et al.* demonstrated a four-fold higher risk of VTE in relatives of heterozygous patients (FVL or PTm) with VTE compared with relatives of homozygous patients without VTE. When probands were heterozygous and did not have VTE, the risk was not statistically significant (40).

Thus, clinical features in family history are more important than biological markers.

Hypothesis

Firstly, FVL and PTm are frequent thrombophilias and associated with a 3 to 4-fold risk of VTE (12,16–18). However they do not increase substantially the risk of recurrence after unprovoked first event (19,23,24). Indeed, clinical features are more important to determine risk of recurrence: patients with an unprovoked VTE have a higher risk of recurrence compared to patients with provoked VTE (19).

Secondly, in first-degree relatives of index cases with VTE, risk of VTE is not influenced by presence or absence of detectable thrombophilia in index cases. FIT-1 study found that first-degree relatives of index cases with an unprovoked VTE and FVL or PTm had a high but similar risk of VTE than first-degree relatives of index cases with an unprovoked VTE without thrombophilia (33). It suggests an unknown underlying thrombophilia. Furthermore, FIT-2 study highlighted a higher risk of VTE in first-degree relatives of index cases with an unprovoked VTE compared with a provoked VTE. Risk of VTE was also increased in first-degree relatives of index cases < 45 years of age at VTE (32,33).

These findings identify important characteristics which have an impact on the risk of VTE in first-degree relatives: age, unprovoked or provoked VTE whereas detectable thrombophilia do not have a strong impact.

VTE have different clinical manifestations and severity from hence the importance of counselling relatives of patients who experienced VTE.

We hypothesized that presentation of VTE in probands may influence presentation of VTE in their first-degree relatives. We aimed to determine impact of the phenotype of VTE in probands on the phenotype of VTE in their first-degree relatives according to the following characteristics:

- the impact of age of VTE in index cases on the age of VTE in first-degree relatives: such correlation is plausible as most of young patients are likely to have an underlying inherited thrombophilia that has yet to be discovered;

- the impact of clinical presentation as PE (rather than DVT) on the clinical presentation or severity of VTE in first-degree relatives: such correlation might be plausible as, for example, it has been suggested that patients with FVL might be more likely to have DVT rather than PE; consequently, it is plausible that some inherited thrombophilia might more often predispose to PE rather than DVT;
- the impact of the absence of provoking risk factors for VTE in index cases on the clinical circumstances of VTE in first-degree relatives: as unprovoked VTE is more often associated with underlying thrombophilia, we could expect that VTE might occur more often in the absence of clinical risk factors;
- lastly, as VTE might be associated with hormonal mechanisms in women, it is plausible that VTE occurring under hormonal exposure in women index cases might be associated with more often hormonal exposure-associated VTE in women first-degree relatives.

MANUSCRIPT

Title: Factors that predict the phenotype of venous thrombosis in first-degree relatives of patients with venous thromboembolism

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Abstract (<300 words)

Introduction- Aims of the study were to determine if age of venous thromboembolism (VTE) in index cases have an impact on age of VTE in their first-degree relatives and if the phenotype of VTE in index cases was associated with the phenotype of VTE in first-degree relatives.

Methods- It was a post-hoc analysis from two prospective studies FIT-1 and FIT-2 (Familial Idiopathic Thrombophilia) which included index cases with respectively, a first episode of unprovoked or provoked VTE and their first-degree relatives.

Results- 123 index cases and their 123 first-degree relatives with previous VTE were included. Correlation between age of index cases and age of their first-degree relatives at diagnosis of VTE was highlighted (Intraclass Correlation Coefficient (ICC) = 0.37, $p = 0.045$) and was high when index cases were < 47 years (ICC = 0.39, $p = 0.007$). There was no concordance between the clinical presentation of VTE as pulmonary embolism or deep venous thrombosis in index cases and in their first-degree relatives (kappa coefficient = 0.055, $p = 0.532$) as well as between index cases' gender and their first-degree relatives' gender (kappa coefficient = 0.057, $p = 0.51$). Conversely, there was a significant concordance between the unprovoked or provoked character of VTE in index cases and their first-degree relatives (kappa coefficient = 0.157, $p = 0.023$).

Conclusion- VTE occurring at a young age in index cases is more likely to occur at a young age in their first-degree relatives whether an inherited thrombophilia is detected or not. A weak association between the clinical circumstances of VTE in index cases and that in their first-degree relatives was observed. In contrast, this study shows that the phenotype of VTE in index cases in terms of clinical presentation as PE or DVT, and gender, is not associated with a similar phenotype of VTE in their corresponding first-degree relatives.

Introduction

Venous thromboembolism (VTE) is a frequent and potential severe disease caused by acquired clinical risk factors and/or inherited risk factors (thrombophilia) (41). As a hereditary prothrombotic state is detected in about 20% of patients with VTE, physicians often screen patients for such abnormality in order to identify first-degree relatives who will carry on the same abnormality and to provide some prevention's counselling (42,43). However, there is now evidence that the presence or the absence of inherited thrombophilia in patients with VTE does not discriminate between those with a high and those with a low familial risk of VTE (33).

In a previous study performed in 2830 first-degree relatives of 507 patients with a first episode of VTE (index cases), we found that in first-degree relatives of patients with an acute episode of VTE (index cases), the risk of VTE was 3 to 4-fold higher when VTE in index cases occurred before 47 years, or was unprovoked or when 2 or more relatives had previous VTE whether a detectable inherited thrombophilia was identified or not (32). In addition, the presence of a detectable inherited thrombophilia in index cases was not significantly associated with an increased risk of VTE in first-degree relatives. These observations, consistent with others, reinforce the hypothesis that patients with VTE at young age or with unprovoked VTE are likely to have an underlying inherited prothrombotic state that has yet to be discovered. If the risk intensity might therefore be more accurately estimated for family members of patients with VTE, however, a little is known about the impact of the clinical presentation of VTE in patients with VTE on the clinical presentation of VTE in their first-degree relatives (e.g.; age of VTE occurrence, presentation as PE or DVT, the clinical circumstances as provoked or unprovoked). Such more qualitative issue is important to resolve in order to provide a more complete information to the patients and their relatives and to better answer to their concerns.

In this post-hoc analysis, we first aimed to determine if age of VTE in index cases was correlated with age in their first-degree relatives. Second aims were to determine if VTE in first-degree relatives occurred more often as PE if the index case had PE, as unprovoked VTE if index case had an unprovoked VTE and more often VTE in women relatives if the index case was a woman.

Methods

Study design

We used databases from two studies: FIT-1 and FIT-2 (Familial Idiopathic Thrombophilia). FIT-1 included index cases with a first episode of unprovoked VTE and their relatives, whereas FIT-2 included index cases with a first episode of provoked VTE and their relatives (31,32).

The aim of FIT-1 was to demonstrate that the risk of VTE in first-degree relatives increases when index cases have a first episode of unprovoked VTE at a young age (32). The aim of FIT-2 was to show that the risk of VTE in the first-degree relatives of patients with unprovoked VTE is higher than the risk of VTE in the first-degree relatives of patients with provoked VTE (31).

In these cross-sectional studies, index cases and their first-degree relatives were enrolled in 5 Canadian and one French university hospitals for FIT-I (Henderson, Montréal, McMaster, St Joseph, Ottawa and Brest) and in one university hospital for FIT-II (Brest).

In our study, in order to answer the question, we firstly studied correlation between age of index cases and age of their first-degree relatives. We included 123 index cases from FIT-1 and FIT-2 and their first-degree relatives who experienced VTE and were classified as “have had VTE”. We could not extend to patients classified as “uncertain for previous VTE” because we did not know age of first-degree relatives when they potentially had previous VTE. Correlation between age of index cases and age of their first-degree relatives was tested for all ages and also according to 4 age groups: 16-46, 47-61, 62-72 and > 72 years of age. Then, we tested if correlation between ages persisted when we consider one other clinical and biological feature of the index cases: provoked, unprovoked, DVT, PE, men, women, presence or absence of thrombophilia. Finally, we also tested correlation between ages according to two characteristics of the index case.

As there were some missing data in the 123 first-degree relatives who experienced VTE, we completed type of VTE (DVT or PE) and risk factors. We established global characteristics of the 123 index cases and their first-degree relatives.

Then, we studied correlation between clinical presentation of VTE as PE or DVT in index cases and in their first-degree relatives. We tested if this correlation changed with one clinical or biological feature of the index cases. The same analysis was conducted for provoked or unprovoked VTE as well as gender.

Inclusion criteria

Index cases had to satisfy all the following criteria:

- Objectively confirmed proximal DVT or PE
- Willingness to provide blood for testing FVL and PTm
- To have at least one first-degree relative who could be evaluated for previous VTE
- To provide written informed consent to participate to the study
- To allow at least one first-degree relative to be approached for the study

First-degree relatives were eligible if they satisfy all following criteria:

- They were a biological child, full sibling or biological parent of the index case
- They had at least 16 years of age
- They provided written informed consent to participate to the study.

Dead first-degree relatives could be included if the index case agreed and information about previous VTE was available.

Exclusion criteria

- No information about previous VTE was available in first-degree relatives. For example, the first-degree relative cannot be contacted and other family members cannot give any information
- Index cases and first-degree relatives who were under 16 years of age
- Index cases and first-degree relatives who were not members of a health care insurance

Definitions

DVT/PE

VTE included proximal DVT (popliteal vein or more proximal) and/or PE. In index cases, DVT was diagnosed by ultrasonography (lack of full compression on compression) or venography (intraluminal filling defect). PE was diagnosed by ventilation-perfusion lung scan (high probability), or CT pulmonary angiography (intraluminal filling defect in a segmental or more proximal pulmonary artery) or pulmonary angiography (intraluminal filling defect) or diagnostic criteria for DVT in patients with suspected PE who had a non-high probability lung scan.

Provoked/Unprovoked

VTE was provoked when there was surgery (with general anaesthesia more than 30 minutes), trauma (leg fracture and/or cast), immobilization (at least 3 days) in the last 3 months, or active neoplasia in the last 2 years. VTE was unprovoked when it did not satisfy these criteria.

Procedure

- Index cases were included after a first VTE
- Index cases gave their consent to approach their first-degree relatives. They informed them about the aim of the FIT-1 or FIT-2 study
- First-degree relatives were contacted firstly by post, then by a member of the thrombosis research team by phone. The aim of the study was explained, and they were asked to come to the hospital a half-day. If they could not, after written consent, a questionnaire by post or by telephone determined if they could be classified as “have had VTE” or “have not had VTE”, and blood samples could be taken at home or at medical analysis laboratory and were sent to the hospital.
- First-degree relatives who were firstly classified as “uncertain for previous VTE” had an ultrasonography and answered to a questionnaire in order to look for a postthrombotic syndrome
- Results were explained and advice was given

Diagnosis of previous VTE in first-degree relatives

First-degree relatives of index cases were classified as “have had VTE”, “have not had VTE” or “uncertain for previous VTE” according to criteria from Frezzato *et al.* and Vivalta *et al.*

Subjects were classified “have had VTE” if one of the three criteria was satisfied:

- Available results of testing that proved previous DVT or PE: ultrasonography, venography, ventilation-perfusion lung scan, CT pulmonary angiography, pulmonary angiography, autopsy results or a medical history of vena cava filter
- All criteria had to be satisfied
 - o At least one of these criteria:
 - Patient or the first-degree relative thinks she/he had a deep venous thrombosis, a phlebitis, a venous blood clot, a pulmonary embolism or a pulmonary clot
 - Patient has an unexplained leg swelling or pain or has an ankle or calf discoloration
 - Patient had an unexplained leg swelling or pain at least 2 weeks for which they consulted a doctor
 - Patient had an unexplained acute dyspnea or chest pain at least 2 weeks for which she/he consulted a doctor
 - o Patient was treated at least 2 months or until a bleeding event occurred by anticoagulant therapy for no other reason than a pulmonary or a lower-limb problem
 - o Anticoagulant therapy was initiated after 1985 for thrombosis, or after further examinations for VTE (venography, or plethysmography, or ventilation-perfusion lung scan, CT pulmonary angiography or pulmonary angiography)
- Patient only had one of the two criteria about anticoagulant therapy and was available for further investigation. If ultrasonography of the lower-limbs confirmed VTE (lack of full compression of popliteal or femoral vein, or popliteal venous reflux on the symptomatic side), patient was classified as “have had VTE”

Subjects were classified “have not had VTE” if at least one of the three criteria was satisfied

- Available results of investigations excluded VTE and there was no medical history of vena cava filter
- Anamnesis excluded VTE
- Patient only had one of the two criteria about anticoagulant therapy but was not available for further investigations and had a post-thrombotic syndrome scale < 5.

Subjects were classified “uncertain for previous VTE” if they did not satisfy “have had VTE” or “have not had VTE” criteria. These patients had an ultrasound examination and were classified “have had VTE” if it showed a not fully compressible proximal deep veins, or a reflux in popliteal vein on the symptomatic side. Patients who could not realise the examination were definitely classified “uncertain for previous VTE”. If ultrasonography was

normal, the post-thrombotic syndrome, defined as a score of 5 or higher on the Villalta scale, was searched for. If it was 5 or higher, patients were definitely classified as “have had VTE”, otherwise, they were definitely classified as “have not had VTE”.

Risk factors in first-degree relatives

VTE circumstances of first-degree relatives was specified: surgery in the last 3 months, leg trauma on the symptomatic side in the last 3 months, immobilisation in the last 3 months, long travel >4 hours in the last 3 months, treatment of neoplasia or neoplasia in the last 2 years, good health, number of episodes of VTE, age at VTE, and for women, VTE during pregnancy, post-partum, oral contraceptives or hormone replacement therapy. Definitions of provoked and unprovoked VTE were the same in index cases and in their first-degree relatives.

Laboratory studies

All included index cases provided blood samples. After written consent, relatives' blood samples were taken. All samplings of blood were labelled with an inclusion number and taken between 08:00 to 10:00 A.M., with an empty stomach, in a sitting position, in the anterior cubital region, after tourniquet application, with a Vacutainer brand pump body. Samples were collected and kept in a freezer.

Ethical framework

First-degree relatives were contacted only with agreement of index cases.

Index cases and their first-degree relatives gave informed and written consent and could withdraw at any time.

None clinical and biological investigations was done before written consent.

Index cases and their first-degree relatives were informed about results during a specific personalized consultation.

All collected data were anonymized.

Ethics Committee of Brest Hospital Center (France) and Henderson General Hospital, McMaster University (Hamilton, ON, Canada) approved the study.

Statistical analysis

Continuous variables were expressed as mean (\pm standard deviation (SD)) and median (interquartile range (IQR)); categorical variables were expressed as numbers and percentages. Paired Student t test was used to compare means between groups in case of normal distribution and Paired Wilcoxon test in case of non normal distribution. McNemar test or exact Fisher test was used to compare proportions as appropriate. In order to estimate

correlation between index cases and their corresponding first-degree relative, intra-class correlation (ICC) was computed. A p-value <0.05 was considered statistically significant. All tests were two-sided. Statistical analyses were performed using SAS version 9.4 software. Ethics Committee of Brest University Hospital approved the protocol.

Results

Between October 2002 and December 2006, 197 patients with a provoked VTE were assessed in FIT-1 study, of whom 59 were excluded (Figure 1). The remaining 138 index cases with provoked VTE had 915 enrolled first-degree relatives among whom 21 had previous VTE. Between March 2008 and March 2012, 530 patients with an unprovoked VTE were assessed in FIT-2 study, of whom 152 were excluded. The remaining 378 index cases had 1,916 first-degree relatives among whom 102 had previous VTE. A total of 123 index cases and their 123 first-degree relatives with previous VTE were included in the present study. Their characteristics are described in Table 1 and Table 2.

Correlation between age of index cases and age of their first-degree relatives at the time of VTE diagnosis (Tables 3, 4 and 5)

We found a statistically significant correlation between age of index cases and age of their first-degree relatives at diagnosis of VTE (ICC = 0.32, $p < 0.001$); this correlation was particularly high when index cases were < 47 years of age (ICC = 0.39, $p = 0.007$) whereas beyond this age, no correlation was found (Table 3).

In strata analyses, we observed similar findings: a significant correlation was observed between age of VTE in index cases and age in first-degree relatives whether index cases had a PE or a DVT, an unprovoked or a provoked VTE, a VTE with or without thrombophilia, or were men or women (Table 4). In addition, in all the strata, correlation was statistically significant when index cases were younger than 47 years but not when index cases were older than 47 years.

Interestingly, correlation between age of young index cases and age of their first-degree relatives at diagnosis of VTE appeared to be strongest when index cases were women (ICC = 0.62, $p = 0.002$), had an unprovoked VTE (ICC = 0.43, $p = 0.005$) or had a PE (ICC = 0.49, $p = 0.015$) (Table 4).

When 2 or more characteristics of the index case were considered, we observed the followings: (i) if index cases were women <47 years with either an unprovoked VTE or a PE, correlation between age of index cases and age of their first-degree relatives at VTE was strong (Table 5); (ii) a correlation between age of men index cases with unprovoked VTE and age of their first-degree relatives at VTE was found (ICC = 0.36, $p = 0.002$).

Association between clinical presentation of VTE in index cases in their first-degree relatives (Table 6)

The distribution between the clinical presentation of VTE as PE or DVT in the index cases and the clinical presentation of VTE in their first-degree relatives was statistically different and there was no concordance (kappa coefficient = 0.055, $p = 0.532$). These results were not affected by age, gender, presence or absence of thrombophilia and in subgroup of index cases with unprovoked VTE (Table 6). We only found a weak concordance between the clinical presentation of VTE in index cases and that in first-degree relatives when index cases had provoked VTE (kappa coefficient = 0.42, $p = 0.049$) (Table 6).

Furthermore, among index cases with FVL, 10 had DVT and 12 had PE (Table 7). Their first-degree relatives had 18 DVT and 5 PE.

Association between clinical circumstances of VTE as unprovoked or provoked in index cases and in their first-degree relatives (Table 8)

The distribution between the presence or the absence of provoking risk factors of VTE in index cases and that in their first-degree relatives was statistically different and there was a weak concordance (Kappa coefficient = 0.157, $p = 0.023$). These results were observed also when index cases were younger than 47 years, were men or had PE: however, although statistically significant, the Kappa coefficient remained less than 0.2. In other subgroups, concordance test was not significant (Table 8).

Association between gender in index cases and in their first-degree relatives (Table 9)

The distribution between index cases' gender and their first-degree relatives' gender was statistically different and there was no significant concordance (Kappa coefficient = 0.057, $p = 0.51$), even if index cases had thrombophilia or not, DVT or PE, provoked or unprovoked VTE, or were <47 or >47 years of age (Table 9).

Discussion

In this post-hoc analysis of patients with VTE and their symptomatic first-degree relatives issued from a large cross-sectional study on the familial risk factor of VTE, we found that age of VTE occurrence in index cases was significantly correlated with age of VTE occurrence in first-degree relatives. Conversely, the phenotype of VTE in terms of clinical presentation as PE or DVT, circumstances of VTE as provoked or not and gender were not associated with a similar phenotype in their corresponding first-degree relatives. Our results suggest that VTE phenotype in index cases is associated with the intensity of the relative risk of VTE in first-degree relatives but not with the severity or the type of VTE.

A young age in index cases predisposes to develop thrombosis at a young age in first-degree relatives whereas when index cases have VTE after 47 years, it does not predict a young or an old first-degree relatives' age at thrombosis. It has been previously demonstrated that incidence of VTE in first-degree relatives of young index cases < 47 years was almost 5 times higher than in first-degree relatives of old index cases > 72 years (32). This observation suggests a not yet detectable underlying thrombophilia in index cases possibly shared by first-degree relatives. Correlation between index cases' age and first-degree relatives' age is higher when index cases are young women, probably because of hormonal background. Indeed, compared with men of the same age, *Silverstein et al.* showed higher incidence of VTE among younger women, as well as *Zöller et al.* (36,44). Moreover, risk of VTE in female relatives of patients with hormonally related VTE was increased compared to female relatives of patients without hormonally related VTE (45). When index cases have unprovoked VTE, correlation with ages is stronger because of a transmissible undetectable thrombophilia. First-degree relatives of patients with unprovoked VTE without a detectable thrombophilia have a similar risk of VTE compared to first-degree relatives of patients with unprovoked VTE with a detectable thrombophilia (33). Correlation between age of index cases and age of their first-degree relatives is high when index cases are young and have PE but correlation also exists in index cases with DVT even if it does not reached significance because of a small sample.

We did not observed a correlation between the clinical presentation as PE or DVT of VTE index cases and the clinical presentation of VTE in their first-degree relatives. In other words, our results suggest that VTE occurring as PE (the most severe presentation of VTE) in index cases is not associated with a higher probability to develop PE rather than DVT in their first-degree relatives. If index cases have PE or DVT, first-degree relatives have an increased risk of VTE but will have PE in one chance in three and DVT in two chances in three as described in general population (46). In new ways, this result goes against FVL paradox. Van Stralen *et al.* found a lower risk of PE as compared to DVT in patients with APC resistance (26). In our study, index cases with FVL do not have less PE than DVT even if sample is small. No correlation was found between type of VTE in index cases with FVL or PTm and type of VTE in first-degree relatives. *Zöller et al.* found an association between type of VTE in parents and offspring and between type of VTE in siblings (37). However, statistical analysis did not take into account matching between index cases and their relatives which affected the findings. Correlation found between the clinical presentation of VTE in index cases with a provoked event and the clinical presentation of VTE in first-degree relatives is not really significant because of a small sample.

Provoked or unprovoked character of VTE does not appear to be transmitted to family members: the paired McNemar test was statistically significant which means distributions were different and the concordance Kappa test, although significant, yielded a low Kappa coefficient of less than 0.2 in the overall population as well as in subgroups. Interestingly, the Kappa coefficient was also significant (although of low value) when index cases had unprovoked VTE, which means that their first-degree relatives tended to have a higher risk to develop VTE as unprovoked rather than provoked. Such observation is consistent with that of patients with underlying thrombophilia are more likely to develop VTE at young age and in

the absence of provoking risk factors (30). Such concordance was also observed in men but not in women but as no information was available in women index cases about hormonal exposure, no conclusion could be drawn. Lastly, a significant concordance was also observed when index cases had PE, however, no underlying hypothesis supports this observation. Finally, kappa coefficient was less than 0.2 despite p-value less than 0.05, our results do not demonstrate a significant association between risk factors of VTE in index cases and their corresponding first-degree relatives. In other words, index cases can transmit a likelihood of risk of VTE but not a provoked or unprovoked character of VTE. Unprovoked VTE ranges from 25 to 40%, which cannot be in agreement with our study because of distinction between FIT-1 and FIT-2 patients enrolment (47).

Female or male index cases can transmit risk of VTE both in female or male first-degree relatives. In other words, female index cases do not transmit more specifically a risk of VTE in female first-degree relatives. Indeed, risk of VTE in first-degree relatives of female patients is comparable to the risk of VTE in first-degree relatives of male patients (45).

We are not aware of previous studies that explored correlation between phenotype of VTE in index cases and phenotype of VTE in their first-degree relatives. We found that index cases do not transmit a phenotype of VTE in their first-degree relatives apart from age. Being young when index cases have VTE predispose their first-degree relatives to have VTE at a young age. Our findings are important because patients do not transmit a type of VTE (PE or DVT) thus a severity or the unprovoked or provoked character. Moreover, a male or female patient can transmit risk of VTE both in their male or female first-degree relatives.

Counselling which arises from these results is important for families. For example, if a patient have a pulmonary embolism and dies, his/her children can ask about their own risk of VTE. Actually, it is well-known that first-degree relatives of patient with VTE have a higher risk of VTE compared with patient without a familial history of VTE. But they do not have higher risk of PE than general population. Similarly, if a female patient have thrombosis, she will transmit a risk of VTE both in her female and male children.

Strengths of our study are the followings: enrolment of index cases with an unprovoked or a provoked VTE was prospective and unselected and diagnosis of previous VTE in first-degree relatives was assessed using predefined, validated and standardized criteria. Statistical analysis include matching between index cases and their first-degree relatives. Our study have a number of limitations. First, the sample size is low which lowered the strengths of our findings. Second, index cases and their first-degree relatives were only evaluated for FVL mutation and prothrombin 20210A gene variant status. The other hereditary thrombophilia, such as protein C, protein S and antithrombin deficiencies, were not tested. Third, as hormonal exposure (estrogen-containing pill, pregnancy and hormone replacement therapy) was not systematically collected in index cases, unprovoked VTE in index cases and their first-degree relatives include hormonally-related VTE, which can have an impact on results.

In conclusion, VTE occurring at young age in index cases was more likely to occur at young age in first-degree relatives, whether a detectable inherited thrombophilia was detected or not

and whether VTE in index cases was PE or DVT, provoked or unprovoked or occurred in men or in women. A trend towards an association between the clinical circumstances of VTE in index cases and that in their first-degree relatives was observed. In contrast, our results do not suggest that the phenotype of VTE in index cases (i.e.; clinical presentation as PE or DVT or gender) was associated with a similar phenotype of VTE in first-degree relatives. Larger studies are needed to confirm our findings. This study provides additional important information for counselling of the patients and their relatives.

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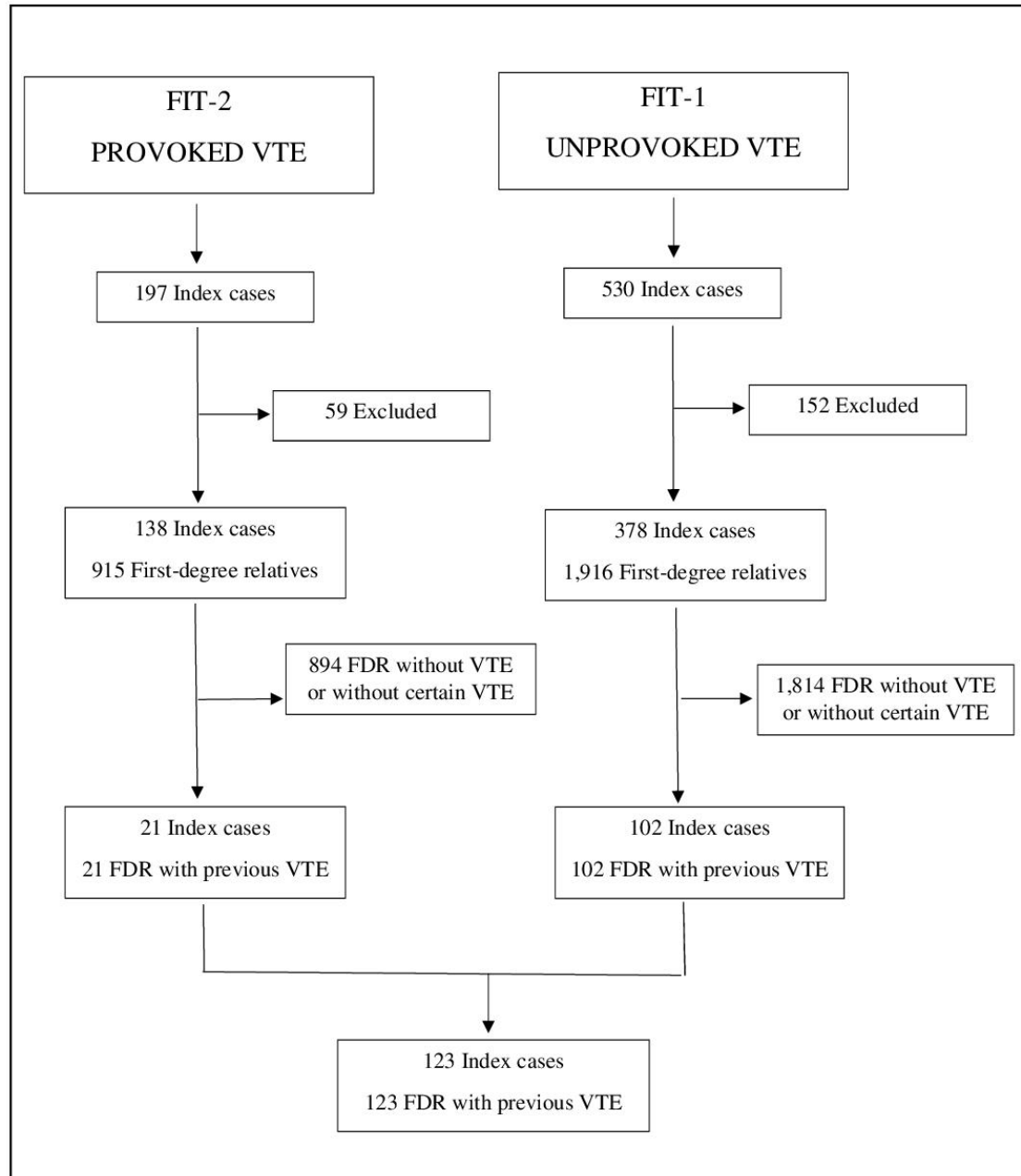
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FIGURES AND TABLES

Figure 1 - Enrolled index cases and their first-degree relatives who experienced VTE



FDR, First-Degree Relatives; FIT, Familial Idiopathic Thrombophilia; VTE, Venous ThromboEmbolism

Table 1 - Characteristics of the 123 index cases

Index cases (%)		
Mean age		56.5 (100)
Gender	Women	57 (46.3)
	Men	66 (53.7)
Type of VTE	DVT	52 (42.3)
	PE	71 (57.7)
Unprovoked VTE	Total	102 (82.9)
Provoked VTE	Total	21 (17.1)
	Surgery	8 (6.5)
	Trauma	1 (0.8)
	Immobilisation	9 (7.3)
	Cancer	3 (2.4)
Thrombophilia	Yes	42 (34.1)
	Heterozygous FVL	26 (21.1)
	Homozygous FVL	1 (0.8)
	Heterozygous PTm	12 (9.8)
	Heterozygous FVL+Heterozygous PTm	2 (1.6)
	Homozygous FVL+Heterozygous PTm	1 (0.8)

FVL, Factor V Leiden; PTm, G20210A prothrombin gene mutation; VTE, Venous thromboembolism

Table 2 - Characteristics of the 123 first-degree relatives who experienced VTE

First-degree relatives (%)		
Mean age		51.98
Gender	Women	76 (61.8)
	Men	47 (38.2)
FDR status	Mother	38 (30.9)
	Father	18 (14.6)
	Sister	31 (25.2)
	Brother	23 (18.7)
	Daughter	6 (4.9)
	Son	7 (5.7)
State	Alive	94 (76.4)
	Dead	29 (23.6)
Risk factors of VTE	Unprovoked	63 (51.2)
	Provoked	60 (48.8)
Detail of risk factors		
	No minor nor major risk factors	39 (31.7)
	<i>PROVOKED by major risk factors</i>	
	Surgery	28 (22.8)
	Trauma	10 (8.1)
	Prolonged immobilization	14 (11.4)
	Cancer	8 (6.5)
	<i>PROVOKED by minor risk factors</i>	
	Air travel	5 (4.1)
	Pregnancy	2 (1.6)
	Postpartum	9 (7.3)
	Estrogen-containing pill	4 (3.3)
	Hormone replacement therapy	4 (3.3)
Type of VTE	PE	38 (30.8)
	DVT	70 (56.9)
	Unknown	15 (12.1)
Thrombophilia	Yes	18 (14.6)
	Unknown	66 (53.7)
FVL	Negative	43 (35)
	Heterozygous	14 (11.4)
	Unknown	66 (53.7)
PTm	Negative	46 (37.4)
	Heterozygous	5 (4.1)
	Homozygous	1 (0.8)
	Unknown	71 (57.7)

FDR, First-degree relative; FVL, Factor V Leiden; PTm, G20210A prothrombin gene mutation; VTE, Venous thromboembolism

Table 3 - Correlation between age of index cases and age of their first-degree relatives (FDR) at VTE

Index cases		FDR	ICC	p
Age groups, n	Mean age (\pm SD)	Mean age (\pm SD)		
16-46 (n=38)	34.5 \pm 10.6	44.1 \pm 16.4	0.39	0.007
47-61 (n=28)	54.7 \pm 3.9	52.3 \pm 20.2	-0.07	0.64
62-72 (n=31)	66.8 \pm 3.2	57.8 \pm 18.4	-0.15	0.53
>72 (n=26)	78.4 \pm 4.7	56.2 \pm 18.3	-0.016	0.47
All (n=123)	56.5\pm18.0	52.0\pm18.9	0.32	< 0.001

FDR, First-Degree relatives; ICC, Intraclass Correlation Coefficient

Table 4 - Influence of one index case's characteristic on correlation between age of index case and age of his/her first-degree relative

Index cases variables			FDR	Student	ICC	p
Characteristics	Age group	Mean age (\pm SD)	Mean age (\pm SD)	p		
Provoked	All (n=21)	62.5 \pm 16.3	55.5 \pm 21.0	0.15	0.371	0.045
	Age < 47 (n=4)	34.8 \pm 8.8	35.5 \pm 14.0	0.94	-0.157	0.600
	Age \geq 47 (n=17)	69.0 \pm 9.0	60.2 \pm 19.8	0.12	-0.015	0.523
Unprovoked	All (n=102)	55.3 \pm 18.2	51.3 \pm 18.4	0.06	0.30	0.001
	Age < 47 (n=34)	34.4 \pm 10.9	45.1 \pm 16.5	<0.001	0.434	0.005
	Age \geq 47 (n=68)	65.7 \pm 10.5	54.3 \pm 18.7	<0.001	0.045	0.358
Thrombophilia	All (n=42)	54.7 \pm 18.1	52.5 \pm 19.1	0.52	0.28	0.033
	Age < 47 (n=12)	32.3 \pm 13.5	46.6 \pm 16.1	0.008	0.454	0.059
	Age \geq 47 (n=30)	63.7 \pm 10.0	54.9 \pm 20.0	0.03	0.093	0.309
No thrombophilia	All (n=81)	57.5 \pm 18.1	51.7 \pm 18.8	0.017	0.34	0.001
	Age < 47 (n=26)	35.5 \pm 9.0	43.0 \pm 16.7	0.017	0.381	0.025
	Age \geq 47 (n=55)	67.8 \pm 10.2	55.8 \pm 18.5	<0.001	0.012	0.465
Women	All (n=57)	56.9 \pm 20.2	52.5 \pm 19.1	0.17	0.268	0.021
	Age < 47 (n=19)	32.9 \pm 10.0	48.9 \pm 15.8	<0.001	0.617	0.002
	Age \geq 47 (n=38)	68.8 \pm 11.3	54.3 \pm 20.5	<0.001	0.138	0.201
Men	All (n=66)	56.2 \pm 16.1	51.5 \pm 18.8	0.06	0.369	0.001
	Age < 47 (n=19)	36.1 \pm 11.2	39.3 \pm 15.9	0.39	0.315	0.09
	Age \geq 47 (n=47)	64.4 \pm 9.0	56.5 \pm 17.7	0.01	-0.032	0.59
DVT	All (n=52)	53.8 \pm 19.1	51.1 \pm 19.6	0.35	0.41	0.001
	Age < 47 (n=19)	33.4 \pm 11.7	41.1 \pm 17.0	0.07	0.30	0.10
	Age \geq 47 (n=33)	65.6 \pm 10.7	56.9 \pm 18.8	0.022	0.06	0.36
PE	All (n=71)	58.5 \pm 17.1	52.6 \pm 18.4	0.028	0.24	0.024
	Age < 47 (n=19)	35.6 \pm 9.5	47.2 \pm 15.6	0.001	0.49	0.015
	Age \geq 47 (n=52)	66.9 \pm 10.1	54.6 \pm 19.1	<0.001	0.04	0.39

DVT, Deep Venous Thrombosis; FDR, First-Degree Relatives; ICC, Intraclass Coefficient; PE, Pulmonary Embolism; SD, Standard Deviation

Table 5 - Correlation between age of index cases and their first-degree relatives according to two characteristics of the index case

Index cases variables				FDR	Student	ICC	Significance, p
Characteristic 1	Characteristic 2	Age group	Mean age (m±SD)	Mean age (m±SD)	p		
Unprovoked	Women	All (n=49)	55.2±20.1	51.4±19.2	0.27	0.24	0.046
		Age <47 (n=18)	33.3±10.1	48.8±16.3	<0.001	0.63	0.002
		Age ≥47 (n=31)	68.0±11.6	52.9±20.8	0.001	0.11	0.28
Unprovoked	Men	All (n=53)	55.3±16.5	51.1±17.9	0.12	0.36	0.004
		Age <47 (n=16)	35.7±11.9	40.9±16.3	0.22	0.33	0.1
		Age ≥47 (n=37)	63.8±9.3	55.5±16.9	0.01	0.007	0.5
PE	Women	All (n=31)	58.6±20.9	50.6±19.6	0.09	0.19	0.15
		Age <47 (n=10)	33.0±10.3	50.0±17.1	0.002	0.61	0.02
		Age ≥47 (n=21)	70.8±11.3	50.8±21.0	<0.001	0.19	0.20

FDR, First-Degree Relatives; ICC, Intraclass Coefficient; PE, Pulmonary Embolism; SD, (Standard Deviation)

Table 6 - Correlation between the clinical presentation of VTE as PE or DVT in index cases and in their first-degree relatives : cross-tabulations, Mac Nemar and Kappa test results

Characteristics of index cases		Characteristics of first-degree relatives			Mac Nemar	Kappa test	
All		DVT	PE	Total	p	Coeff.Kappa	p
	DVT	32	15	47	0.003	0.055	0.532
	PE	38	23	61			
	Total	70	38	108			
<47 years		DVT	PE	Total	0.031	-0.176	0.190
	DVT	13	4	17			
	PE	14	1	15			
	Total	27	5	32			
>47 years		DVT	PE	Total	0.041	0.104	0.337
	DVT	19	11	30			
	PE	24	22	46			
	Total	43	33	76			
Unprovoked		DVT	PE	Total	<0.001	0.016	0.860
	DVT	26	11	37			
	PE	36	14	50			
	Total	62	25	87			
Provoked		DVT	PE	Total	0.688	0.42	0.049
	DVT	6	4	10			
	PE	2	9	11			
	Total	8	13	21			
Men		DVT	PE	Total	0.064	0.169	0.177
	DVT	16	7	23			
	PE	17	16	33			
	Total	33	23	56			
Women		DVT	PE	Total	0.024	-0.08	0.508
	DVT	16	8	24			
	PE	21	7	28			
	Total	37	15	52			
No thrombophilia		DVT	PE	Total	0.003	0.038	0.714
	DVT	19	9	28			
	PE	28	16	44			
	Total	47	25	72			
Thrombophilia		DVT	PE	Total	0.454	0.097	0.549
	DVT	13	6	19			
	PE	10	7	17			
	Total	23	13	36			

DVT, Deep Venous Thrombosis; PE, Pulmonray Embolism; VTE, Venous Thrombo-Embolism

Table 7 - Correlation between index case's and first-degree relative's VTE type according to index case's thrombophilia including certain and uncertain VTE in first-degree relatives

Characteristics of index cases	Characteristics of first-degree relatives			Mac Nemar	Kappa test	
				significance p	Coeff.Kappa	significance p
FVL	DVT	PE	Total	0.021	0.141	0.364
	DVT	9	1			
	PE	9	3			
	Total	18	4			
PTm	DVT	PE	Total	1.0	0.16	0.659
	DVT	2	2			
	PE	1	2			
	Total	3	4			

DVT, Deep Venous Thrombosis; FVL, Factor V Leiden mutation; PTm, ProThrombin mutation; PE, Pulmonary Embolism

Table 8 - Correlation between provoked or unprovoked VTE in index cases and in their first-degree relatives

Characteristics of index cases		Characteristics of first-degree relatives			Mac Nemar	Kappa test	
All		UP	P	Total	p	Coeff.Kappa	p
UP		57	45	102	<0.001	0.157	0.023
P		6	15	21			
Total		63	60	123			
<47 years		UP	P	Total	<0.001	0.191	0.045
UP		18	16	34			
P		0	4	4			
Total		18	20	38			
>47 years		UP	P	Total	<0.001	0.146	0.10
UP		39	29	68			
P		6	11	17			
Total		45	40	85			
Men		UP	P	Total	<0.001	0.245	0.016
UP		32	21	53			
P		3	10	13			
Total		35	31	66			
Women		UP	P	Total	<0.001	0.064	0.49
UP		25	24	49			
P		3	5	8			
Total		28	29	57			
Thrombophilia		UP	P	Total	<0.001	0.114	0.11
UP		23	17	40			
P		0	2	2			
Total		23	19	42			
No thrombophilia		UP	P	Total	<0.001	0.166	0.076
UP		34	28	62			
P		6	13	19			
Total		40	41	81			
DVT		UP	P	Total	0.004	0.11	0.33
UP		24	18	42			
P		4	6	10			
Total		28	24	52			
PE		UP	P	Total	<0.001	0.19	0.025
UP		33	27	60			
P		2	9	11			
Total		35	36	71			

DVT, Deep Venous Thrombosis; PE, Pulmonary Embolism; P, provoked; UP, Unprovoked

Table 9 - Correlation between index cases' gender and their first-degree relatives' gender

Characteristics of index cases		Characteristics of first-degree relatives			Mac Nemar	Kappa test	
		M	W	Total	p	Kappa	p
All	M	27	39	66	0.019	0.057	0.51
	W	20	37	57			
	Total	47	76	123			
<47 years	M	6	13	19	0.26	-0.053	0.73
	W	7	12	19			
	Total	13	26	38			
>47 years	M	21	26	47	0.055	0.101	0.33
	W	13	25	38			
	Total	34	51	85			
Thrombophilia	M	8	13	21	0.26	0.048	0.75
	W	7	14	21			
	Total	15	27	42			
No thrombophilia	M	19	26	45	0.055	0.059	0.58
	W	13	23	36			
	Total	32	49	81			
DVT	M	13	13	26	1,000	0,000	1,000
	W	13	13	26			
	Total	26	26	52			
PE	M	14	26	40	0.002	0.116	0.26
	W	7	24	31			
	Total	21	50	71			
Provoked	M	6	7	13	0.55	-0.036	0.86
	W	4	4	8			
	Total	10	11	21			
Unprovoked	M	21	32	53	0.03	0.069	0.47
	W	16	33	49			
	Total	37	65	102			

DVT: Deep Venous Thrombosis, M : Men, PE : Pulmonary Embolism, W : Women

UNIVERSITE DE BREST - BRETAGNE OCCIDENTALE
Faculté de Médecine & des Sciences de la Santé

AUTORISATION D'IMPRIMER

Présentée par Madame / Monsieur le Professeur : LEROYER -----

Titre de la thèse (en MAJUSCULES) : IMPACT DU PHENOTYPE DE LA MALADIE
VEINEUSE THROMBO-EMBOLIQUE (MVTE) SUR LE PHENOTYPE DE LA MVTE
CHEZ LES MEMBRES DE FAMILLE -----

ACCORD DU PRESIDENT DU JURY DE THESE SUR L'IMPRESSION DE LA THESE

OUI : ☒

NON : ☐

En foi de quoi la présente autorisation d'imprimer sa thèse est délivrée à

Madame CAMPILLO ELIZE -----

Interne en DES de MEDECINE GENERALE -----

Fait à BREST, le

10/4/12

VISA du Doyen de la faculté

A BREST, le 10-04-12

Professeur C. BERTHOU




Le Président du Jury de Thèse,



CAMPILLO (Elize) – IMPACT DU PHENOTYPE DE LA MALADIE VEINEUSE THROMBO-EMBOLIQUE SUR LE PHENOTYPE DE LA MVTE CHEZ LES MEMBRES DE FAMILLE – 57 feuilles, 2 figures et 10 tableaux

RESUME :

Introduction : Si les facteurs de risques familiaux de maladie veineuse thrombo-embolique (MVTE) sont mieux identifiés, en revanche, l'impact du phénotype d'une MVTE chez les patients (cas index (CI)) sur le phénotype de MVTE chez leurs membres de famille (MDF) au 1^{er} degré est inconnu. L'objectif de ce travail était donc de déterminer l'impact du phénotype d'une MVTE chez des CI sur le phénotype de MVTE chez leurs MDF correspondants.

Matériels et méthodes : Cette analyse post-hoc a été réalisée à partir de 2 études prospectives FIT-1 et FIT-2 (Familial Idiopathic Thrombophilia) qui incluaient respectivement les CI avec un premier épisode de MVTE non provoquée ou provoquée et leurs MDF.

Résultats : 123 CI et 123 MDF au 1^{er} degré avec une MVTE antérieure ont été inclus. Une corrélation significative entre l'âge du CI et l'âge du MDF correspondant au diagnostic de MVTE a été mise en évidence (Coefficient de Corrélation Intra-classe (ICC)=0,37, p=0,045) ; en analyse de strate, cette corrélation était observée uniquement si l'âge du CI était inférieur à 47 ans (ICC=0,39, p=0,007). Il n'y avait pas de concordance entre la présentation clinique de la MVTE de type embolie pulmonaire (EP) ou thrombose veineuse profonde (TVP) chez les CI et chez leur MDF (coefficient kappa=0,055, p=0,53), ni entre le sexe des CI et celui de leur MDF (coefficient kappa=0,057, p=0,51). A l'inverse, il y a avait une concordance significative entre le caractère non provoqué ou provoqué de la MVTE chez les CI et leur MDF (coefficient kappa = 0,157, p = 0,023).

Conclusion : L'âge de survenue d'une MVTE chez les CI est corrélé à l'âge de survenue d'une MVTE chez leur MDF au 1^{er} degré, qu'une thrombophilie soit détectable ou non. En revanche, la présentation clinique de la MVTE (EP ou TVP) n'est pas concordante avec celle de la MVTE des MDF, tout comme le sexe n'était pas concordant entre les CI et leur MDF. Une concordance entre le caractère provoqué ou non de la MVTE chez les CI et celui de la MVTE chez les MDF est suggérée.

MOTS CLES :

MALADIE VEINEUSE THROMBO-EMBOLIQUE
PHENOTYPE
CAS INDEX
MEMBRES DE FAMILLE
AGE

JURY :

Président : Pr C. LEROYER

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