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Do patients with a family or personal history of venous thromboembolism have an increased risk of recurrence?

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ABSTRACT

Background: A family (FH) and personal history (PH) of venous thromboembolism (VTE) are commonly evaluated risk factors for recurrence. We examined the association between FH/PH of VTE and the risk of recurrence and whether a stronger history status (i.e., both FH/PH vs. no FH/PH) carries an increased recurrence risk.

Methods: We prospectively followed 813 patients aged ≥65 years with acute VTE from 9 Swiss hospitals. We classified patients into 4 groups: no FH/PH, FH only, PH only, and both FH/PH. The primary outcome was recurrent VTE during the full observation period. We examined the association between FH/PH status and the time to VTE recurrence using competing risk regression, adjusting for confounders and periods of anticoagulation.

Results: Of 813 patients with VTE, 59% had no FH/PH, 11% a FH only, 24% a PH only, and 7% had both a FH and PH of VTE. Overall, 105 patients had recurrent VTE during the full observation period. After adjustment, patients with a FH only (sub-hazard ratio [SHR] 0.8, 95%CI 0.4-1.7), PH only (SHR 1.5, 95%CI 0.9-2.5), and both FH/PH (SHR 1.4, 95%CI 0.6-3.1) did not have an increased risk of recurrent VTE compared to those without FH/PH. When we considered the period after the completion of initial anticoagulation only, the results were similar.

Conclusion: Our findings indicate that in patients with acute VTE, a FH and/or PH of VTE does not convey an increased risk of recurrent VTE. In particular, we did not find a “dose-effect” relationship between FH/PH status and VTE recurrence.

KEYWORDS

Family history, personal history, venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) is a chronic condition with a cumulative recurrence rate of 12-29% within five years after anticoagulation is discontinued.[1, 2] Thus, identifying patients at high risk of recurrent VTE who may benefit from extended anticoagulation, is important. Several risk factors for recurrence are established, including unprovoked VTE as the index event, male sex, and cancer.[1, 3, 4] Further, to estimate the recurrence after acute VTE, the patient's family history (FH) and personal history (PH) of VTE are often evaluated, the former indicating the presence of a genetic, the latter a genetic or other permanent/recurrent non-genetic risk factor.[5,6]

While a FH of VTE in first-degree relatives is a strong risk factor for a first VTE episode,[7] several cohort studies have also shown an independent association between FH and recurrent VTE,[8-10] but others did not.[11-13] These studies focused on patients with a first [8-13] or unprovoked VTE,[8, 11, 13] or excluded older patients.[10, 12] Thus, whether a FH of VTE conveys a significant risk of recurrent VTE is still debated, at least in elderly patients and those who present with provoked or prior VTE. In contrast to FH, a PH of VTE is an accepted risk factor for recurrence,[14, 15] especially after a previous VTE episode without the presence of a major/reversible risk factor and in at-risk situations, such as surgery,[16] medical hospitalization,[17] cancer,[18] pregnancy,[19] and clinically suspected VTE.[20, 21]

Our aim was to examine the association between the FH/PH status of VTE and the long-term risk of recurrence and death in a prospective multicenter cohort of older patients with VTE. We hypothesized that there is a "dose-effect" relationship between FH/PH status and recurrence risk and that patients with both FH and PH would have a higher risk of recurrent VTE than those with neither FH nor PH.

METHODS

Study design, setting, and participants

This analysis was part of the SWIss venous Thromboembolism COhort study 65+ (SWITCO65+), a prospective multicenter cohort study that assessed the short- and long-term medical outcomes in patients with acute symptomatic VTE.[22] The study enrolled and followed consecutive in- and outpatients aged ≥65 years with objectively confirmed, acute symptomatic pulmonary embolism (PE) or lower limb deep vein thrombosis (DVT) between 09/2009 and 12/2013 from all five university and four high-volume non-university hospitals in Switzerland. The detailed study methods were previously published.[22] The study was approved by the institutional review board at each participating site. All enrolled participants provided written informed consent. This study was registered at www.clinicaltrials.gov as #NCT00973596.

Symptomatic PE was defined as a positive spiral computed tomography or pulmonary angiography, a high probability ventilation-perfusion scan, or proximal DVT confirmed by compression ultrasonography or contrast venography in patients with acute chest pain, new or worsening dyspnea or cough, hemoptysis, or syncope.[23, 24] Symptomatic DVT was defined as an acute onset of leg pain or swelling plus incomplete compressibility of a venous segment on ultrasonography or an intraluminal filling defect on contrast venography.[25] For iliac and caval DVT, additional diagnostic criteria included abnormal duplex flow patterns compatible with thrombosis, or an intraluminal filling defect on spiral computed tomography or magnetic resonance imaging venography.[26-28] Patients with isolated distal DVT were eligible only if the incompressible distal vein transverse diameter was at least 5 mm, given the lower sensitivity and specificity of compression ultrasonography for distal DVT.[29, 30] Exclusion criteria were unwillingness or inability to provide informed consent (i.e.,

severe dementia), impossibility of follow-up (i.e., terminal illness, place of living too far away from the study center), insufficient German- or French-speaking ability, thrombosis at a site other than lower limb or lung, catheter-related thrombosis, or previous enrollment in the cohort. For the purpose of this analysis, we also excluded patients with active cancer at time of enrolment, as cancer by itself represents a strong risk factor for recurrent VTE and death.[31, 32]

Data collection

Trained study nurses at each site collected patient baseline characteristics, including demographics (age, sex), body mass index (BMI), type (provoked vs. unprovoked) and location (PE±DVT vs. DVT alone) of the index VTE, that led to study inclusion, comorbidities (inflammatory bowel disease, diabetes mellitus, chronic heart failure), physical activity level, systolic blood pressure, and hemoglobin from all enrolled patients using standardized data collection forms. Unprovoked VTE was defined as any VTE occurring in the absence of major surgery requiring general or spinal anesthesia, immobilization (fracture or cast of the lower extremity, bed rest >72 hours, or voyage in sitting position for >6 hours), or estrogen therapy during the last 3 months.

We also assessed the presence of five commonly measured thrombophilic factors. DNA was extracted from frozen EDTA whole blood collected at the time of the index VTE and used for polymerase chain reaction assays of the Factor V Leiden (QIAamp DNA Blood Mini QIAcube kit, Qiagen AG, Hombrechtikon, Switzerland) and prothrombin G20210A mutation (Roche Diagnostics AG, Rotkreuz, Switzerland) in a core laboratory.[33] In patients who were not under anticoagulation anymore at 12 months after the index VTE, we also measured antithrombin activity as heparin

cofactor using Coamatic® LR Antithrombin (Chromogenix®, Instrumentation Laboratory, Bedford, USA) on a BCS-XP coagulometer, protein C anticoagulant activity using STA®-Staclot® protein C reagent (Stago®, France) and a BCS-XP coagulometer, and free protein S antigen using Innovance® Free PS Ag reagent on a CS5100 coagulometer (Siemens®, Germany) in citrated platelet poor plasma from a second blood sample.[34] Antithrombin, protein C, and free protein S were expressed as a percentage of international standard normal plasmas calibrated by the manufacturers. The international standard normal plasma contained 100% of the respective factor. Antithrombin deficiency was predefined as an activity of <80% in women and <83% in men, protein C deficiency as an activity of <70% in both women and men, and protein S deficiency as a free antigen of <55% in women and <60% in men. Patients were considered to have thrombophilia if any of the five thrombophilic factors was present.

Assessment of family and personal history of VTE

Study nurses ascertained patients' FH and PH status of VTE at the time of study enrolment using patient interviews and hospital chart review. FH of VTE was considered positive if patients had at least one first-degree relative (parents, siblings, children) with a history of VTE, as done in prior studies.[9, 11-13] A positive PH of VTE was defined as the presence of any prior episode of PE or leg DVT. Assuming that a false positive history would be less likely than a false negative history, we considered a FH/PH of VTE to be present if either the patient indicated a FH/PH during the interview or if such a history was documented in the patient chart.

Study outcomes

The primary outcome was the recurrence of symptomatic, objectively confirmed VTE during the full observation period. VTE recurrence was defined as new fatal or non-fatal PE or new DVT (proximal or distal) based on previously published criteria.[35] The secondary outcome was all-cause mortality during follow-up.

Study nurses followed the participants by 1 telephone interview and 2 surveillance face-to-face evaluations during the first year of study participation and then semiannual contacts, alternating between telephone calls and face-to-face evaluations (clinic visits or home visits in house-bound patients), as well as periodic reviews of patient's hospital chart. During each follow-up contact, study nurses obtained information about VTE recurrence and death. In case of VTE recurrence or death, study nurses complemented the information by reviewing medical charts, hospital discharge letters, autopsy reports if available, and interviewing the patients' primary-care physicians and family members. A committee of 3 independent blinded clinical experts adjudicated all outcomes and classified all causes of death as definitely due to PE, possibly due to PE, or due to another cause. Death was judged a definite fatal PE if it was confirmed by autopsy or if it followed a clinically severe PE. Death in a patient who died suddenly without obvious cause was classified as possible fatal PE. Final classification was based on the full consensus of this committee.

Statistical analyses

We classified the study sample into 4 groups according to their FH/PH status for VTE: no FH/PH, FH only, PH only, and both FH/PH. We compared baseline characteristics across these groups using the Chi-square or the non-parametric Kruskal–Wallis test as appropriate. We calculated incidence rates of a first VTE

recurrence during the entire observation period after the index VTE and for the period after stop of the initial anticoagulation by FH/PH status. We also compared the 36-month cumulative incidence of VTE recurrence by FH/PH status using Kaplan-Meier analysis and the log-rank test.

We examined the association between FH/PH status and the time to a first VTE recurrence during follow-up using competing risk regression according to the method of Fine and Gray,[36] accounting for non-VTE–related death as a competing event. The method yields sub-hazard ratios (SHRs) with corresponding 95% confidence intervals (CIs). We adjusted for risk factors that have been previously shown to be associated with recurrent VTE, including age, sex, BMI, type of index VTE (provoked, unprovoked), inflammatory bowel disease,[1, 3, 31, 37] and periods of anticoagulation as a time-varying covariate. As the effect of FH/PH status on recurrent VTE may vary by clinical characteristics,[8, 9] we explored the association between FH/PH status and VTE recurrence across pre-specified patient strata: age 65-75 vs. >75 years, men vs. women, provoked vs. unprovoked index VTE, and presence vs. absence of thrombophilia.

To examine the association between FH/PH status and all-cause mortality, we used Cox proportional hazards analysis, adjusting for previously reported predictors of mortality in patients with VTE, i.e., age, sex, major surgery during the last 3 months prior to the index VTE, PE as index VTE, diabetes mellitus, chronic heart failure, low physical activity, systolic blood pressure <100 mm Hg, anemia (hemoglobin <13 g/dL for men or <12 g/dL for women),[32, 38-41] and periods of anticoagulation as a time-varying covariate.

In the primary analysis, we included the full observation period, regardless of whether patients were under anticoagulants or not. In a sensitivity analysis, we

considered only the observation period after completion of the initial anticoagulant treatment. We imputed missing values using chained equations. Imputation models were based on all other co-variates as well as an indicator variable for VTE recurrence, death, and hospital site. In total, fifty imputed data sets were generated, which were analyzed as described above using Rubin's rules to combine results across data sets.[42] We did all analyses using Stata 16 (Stata Corporation, College Station, Texas).

RESULTS

Study sample

Of 1863 patients with acute symptomatic VTE, 860 patients had at least one exclusion criterion (**Figure 1**). We further excluded 190 patients, who either had active cancer, denied use of data, or withdrew consent, leaving a final study sample of 813 patients with VTE. Analyzed patients had a median age of 75 years (interquartile range [IQR] 69-81 years), 51% were men, 74% had unprovoked VTE as the index VTE, and 20% had at least one thrombophilic factor confirmed by laboratory testing. Overall, 478 patients (59%) had no FH/PH of VTE, 89 (11%) had a FH only, 193 (24%) had a PH only, and 53 patients (7%) had both a FH and PH. Patient characteristics by FH/PH status are shown in **Table 1**. Compared to patients without FH or PH of VTE, patients with both FH and PH were more likely to be aged 65-75 years (64% vs. 51%) and to have unprovoked VTE (81% vs. 70%) and thrombophilia (36% vs. 17%). The median duration of the initial anticoagulant treatment and the median full observation period were 9 months (IQR 5-26 months) and 30 months (IQR 24-41 months), respectively.

Recurrent VTE

During the full observation period, 105 patients had a VTE recurrence. Of these, 70 (67%) were PEs ±DVTs (18 were fatal), while 35 (33%) were isolated DVTs. The overall incidence rate of recurrent VTE was 5.5 events (95% CI 4.5-6.7) per 100 patient-years, varying from 4.5 events (95% CI 2.3-8.6) for patients with a FH of VTE to 5.9 events (95% CI 4.6-7.6) per 100 patient-years for patients with no FH/PH (**Table 2**). When we considered only the observation period after completion of the initial anticoagulant treatment, the overall incidence of recurrent VTE was 10.2 events (95% CI 8.2-12.7) per 100 patient-years, with the highest incidence rate among patients with

both a FH and PH for VTE (17.0 events [95% CI 7.1-40.7] per 100 patient-years). The 36-month cumulative incidence of recurrent VTE over the entire observation period was 14.6% (95% CI 12.0-17.6%) and did not differ by FH/PH status (**Figure 2**).

After adjustment for age, sex, BMI, type of index VTE, inflammatory bowel disease, and periods of anticoagulation, FH/PH status was not statistically significantly associated with recurrent VTE, although patients with a PH of VTE tended to have a somewhat greater risk of VTE recurrence (**Table 3**). When we considered only the observation period after completion of the initial anticoagulant treatment in a sensitivity analysis, the results did not change markedly (**Table 3**). Similarly, when we stratified our analyses by age, sex, type of index VTE, and presence of thrombophilia, we did not find an association between FH/PH status and recurrent VTE (**Figure 3**), except for an increased risk of recurrence in patients with a PH of VTE who were aged 65-75 years (SHR 2.1, 95% CI 1.1-4.1) or had thrombophilia (SHR 3.7, 95% CI 1.1-12.6).

All-cause mortality

One hundred and eleven patients (13.7%) died during the full observation period. Of these, 23 (21%) died from PE (3 from the initial event and 20 from recurrence), 9 (8%) from bleeding, and 79 (71%) from other causes. The proportion of patients who died from PE was 20% (14/70) for those with no FH/PH, 14% (1/7) for FH only, 26% (8/31) for PH only, and 0% (0/3) for those with both FH/PH.

After adjustment, patients with a PH of VTE had the highest risk of all-cause mortality (hazard ratio [HR] 1.6, 95% CI 1.0-2.5) (**Table 4**). When we limited observation to the period after completion of initial anticoagulant treatment, the strength of the association between PH and all-cause mortality increased further (HR 2.4, 95% CI 1.3-4.4).

DISCUSSION

In this multicenter prospective cohort, patients with a FH or a PH of VTE did not have a statistically significantly increased risk of recurrent VTE. However, we observed a trend suggesting that patients with both a FH and PH of VTE may have a higher recurrence risk, especially, after the completion of the initial anticoagulation period. A larger study may have been able to detect a significant difference.

Overall, a FH for VTE was not associated with recurrent VTE. In the subgroup of patients with a PH and no FH, a younger age and the presence of thrombophilia were associated with recurrence. Compared to patients without FH/PH, those with PH only had also a higher risk of overall mortality, especially after discontinuing initial anticoagulation.

Overall, 17-31% of patients with a first VTE have a positive FH of VTE,[8-13] which is considered a marker for known or unknown thrombophilia.[13] Most prior studies examining the association between a FH of VTE and recurrence focused on patients with a first [8-13] or unprovoked VTE,[8, 11, 13] and included predominantly younger patients (mean/median age 34.5-62.7 years). While several studies supported a weak association (HR around 1.5) between a FH among first-degree relatives and VTE recurrence,[8-10] those that excluded patients with major thrombophilia did not.[11-13] A study found an interaction between age and FH, with a FH having a stronger effect on VTE risk in younger patients.[8] In our study of elderly patients, in which 30% of participants had a PH of VTE and 20% thrombophilia, a FH for VTE was not a useful predictor of recurrent VTE.

A PH of VTE is a known risk factor for recurrence, although it is controversial whether a PH of VTE conveys a weak, moderate, or strong risk for recurrent VTE.[14, 15, 43] Among unselected patients with VTE, several cohort and case-control studies

found a 1.7 to 15-fold increased risk of recurrent VTE in patients with a prior VTE.[4, 44-46] In our study of elderly patients, in which the patient age was substantially higher than in the above mentioned studies (median 75 vs. mean 58-66 years[4, 45, 46]), we did not observe a significant association between PH of VTE and recurrence (SHR 1.5), except in the "younger elderly" aged 65-75 years (SHR 2.1) and those with thrombophilia (SHR 3.7).

Elderly patients do not only have a higher prevalence of "classical" risk factors for VTE, (e.g., immobility and co-morbid conditions), but also present age-specific risk factors for VTE, such as reduced muscle strength, endothelial risk factors (e.g. muscle fibers atrophy, wall remodeling), and frailty.[47] Thus, it is conceivable that the effect of an individual risk factor, such as a prior VTE, may be different in elderly compared to younger patients.[47] Indeed, younger patients with a PH of VTE had a higher recurrence risk in our study. Our results challenge recommendations to initiate anticoagulant treatment (e.g., for isolated subsegmental PE or distal DVT)[48] or to extend anticoagulation beyond 3 months based on a positive PH status of VTE,[15] at least in elderly patients.

Although patients with both FH/PH of VTE tended to have a slightly higher risk of recurrent VTE, we did not find a clear "dose-effect" relationship between FH/PH status and recurrence, refuting the hypothesis that the presence of both FH and PH of VTE might confer a stronger genetic recurrence risk. Our results are consistent with previous findings that genetic risk factors are weak predictors for recurrent VTE.[2, 49]

In our study, patients with a PH of VTE only had a 2.4-fold increase in all-cause mortality compared to those without FH/PH after stopping anticoagulation. This finding could at least partially be explained by the higher proportion of PE-related death among patients with PH only compared to those without FH/PH (26% vs. 20%).

Despite adjustment for prognostic factors, we cannot exclude the possibility that the higher mortality risk in patients with PH is attributable to residual confounding.

Our study has several potential limitations. First, our study sample of VTE comprised patients aged 65 years or older only. As the effect of risk factors on the risk of VTE recurrence may vary between younger and older patients,[8, 47] our results are not necessarily generalizable to the younger population with VTE. However, patients aged ≥65 years not only represent the majority of patients with VTE,[40] older patients are underrepresented in most previous studies examining the association between FH/PH status and recurrence. [8-13, 45, 50, 51] Second, we used a mix of patient interviews and hospital chart review to establish FH/PH status. Patient interviews may be subject to recall bias and potentially under- or overestimate the true prevalence of FH/PH. However, the prevalence of FH and PH of VTE in our study was 17% and 30%, respectively, and comparable to other studies.[8, 13] Third, we did not collect information on how many first-degree relatives had suffered a VTE, as a higher number of affected family members could be associated with a greater genetic risk.[8] Fourth, given the relatively small sample size of the subgroups of patients with FH only and those with both FH/PH, our study may not have sufficient power to detect relevant associations with recurrent VTE in these subgroups. Fifth, although our analyses stratified by age, sex, type of VTE, and presence of thrombophilia were preplanned, subgroup analyses are prone to both false positive and negative conclusions and therefore must be interpreted with caution. Finally, we did not have any information about the type and number of prior VTE episodes. Unprovoked VTE, i.e. VTE that is not related to a major transient or reversible risk factor, carries a higher risk of recurrence.[52] Evidence also suggests that patients with ≥2 prior VTEs may have a higher risk of recurrence than those with only 1 previous VTE episode.[53]

In conclusion, our findings indicate that the presence of a FH or PH of VTE are no clinically relevant predictors for long-term VTE recurrence in most elderly patients with VTE. Although patients with both FH/PH of VTE tended to have a slightly higher risk of recurrent VTE than those with FH/PH, there was no significant “dose-effect” relationship between FH/PH status and recurrence. Thus, the presence of FH and/or PH for VTE may not be useful in determining the duration of anticoagulation in older patients with VTE. Our findings should be confirmed in a large prospective study.

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Conflict-of-interest disclosure

Conflict of Interest: none declared.

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FIGURE CAPTIONS

Figure 1. Flowchart of study cohort

Multiple exclusion criteria were possible.

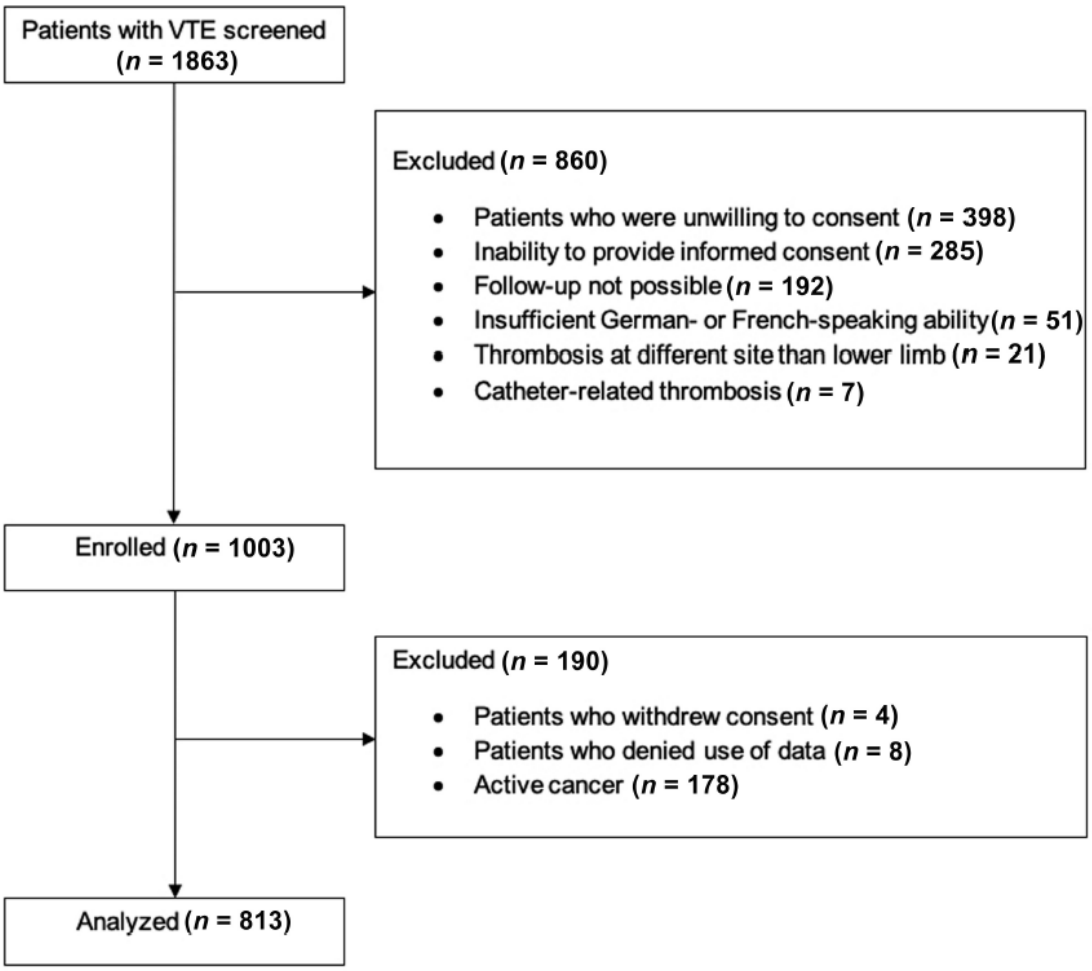
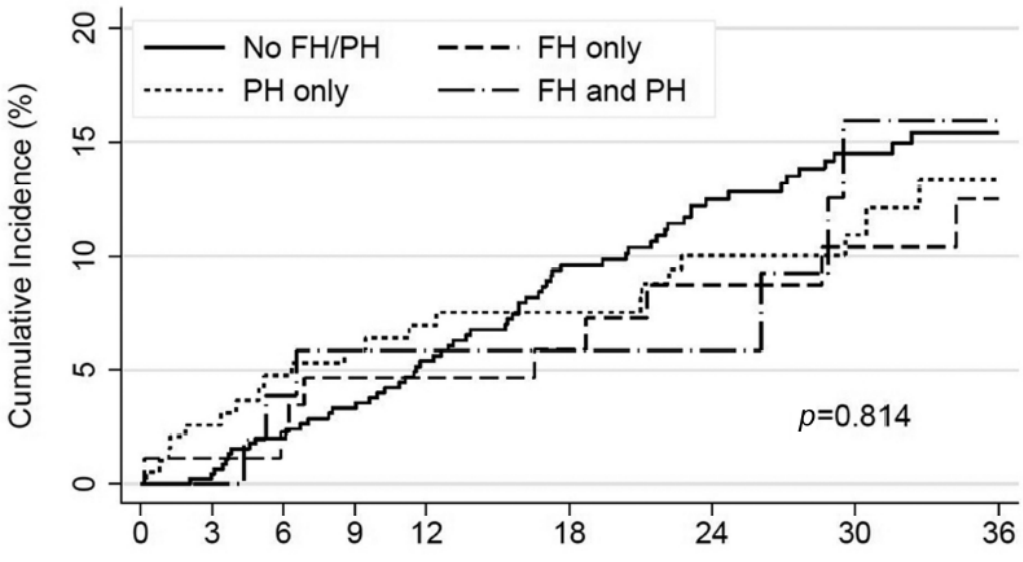


Figure 2. Kaplan-Meier estimates of a first recurrent VTE by FH/PH status

The 36-month cumulative incidence of first recurrent VTE during follow-up was 15.4% (95% confidence interval [CI] 12.1-19.5%) in patients with no FH/PH, 12.5% (95% CI 6.6-23.1%) in patients with FH only, 13.3% (95% CI 8.7-20.2%) in patients with PH only, and 15.9% (95% CI 7.2-33.0%) in patients with both FH and PH (p=0.814 by the log-rank test). Abbreviations: FH, family history; PH, personal history; VTE, venous thromboembolism.

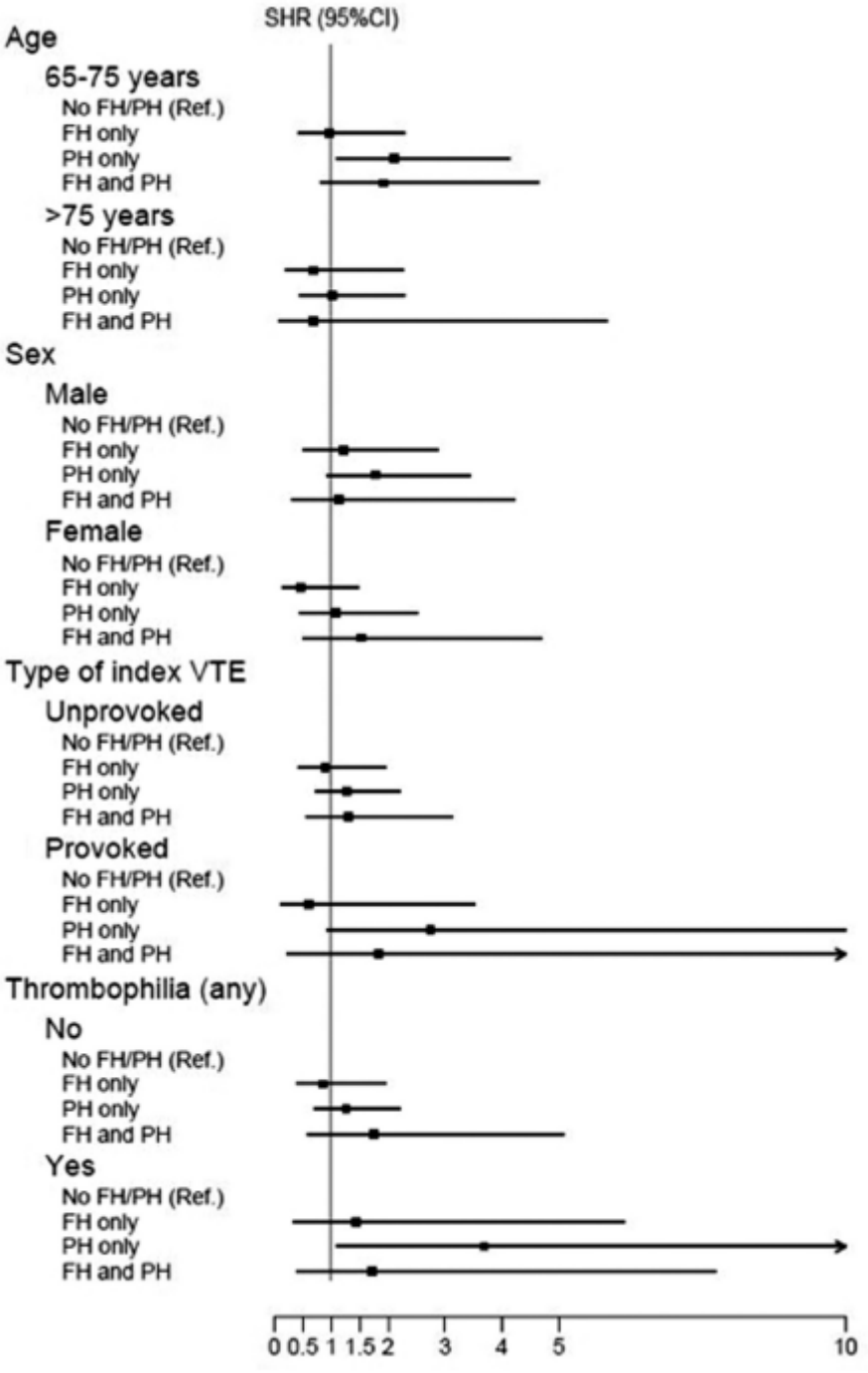


Number at risk

No FH/PH	478	456	438	427	413	365	286	202	128
FH only	89	85	83	81	79	70	57	46	26
PH only	193	187	175	171	165	152	122	79	53
FH and PH	53	52	49	48	48	42	32	22	10

Figure 3. Forest plot with adjusted sub-hazard ratios for recurrent VTE by FH/PH status stratified by age, sex, type of index VTE, and thrombophilia

Adjusted for age, sex, body mass index, type of index VTE (provoked, unprovoked), inflammatory bowel disease, and periods of anticoagulation, except the respective stratification variable. Abbreviations: FH, family history; PH, personal history; SHR, sub-hazard ratio; VTE, venous thromboembolism.



TABLES

Table 1. Patient baseline characteristics by FH/PH status[a]

Characteristic	No FH/PH (n=478)	FH only (n=89)	PH only (n=193)	FH and PH (n=53)	p-value
	No. (%) or median (IQR)				
Age, years					0.001
65-75	243 (51)	61 (69)	87 (45)	34 (64)	
>75	235 (49)	28 (31)	106 (55)	19 (36)	
Male sex	237 (50)	46 (52)	108 (56)	27 (51)	0.523
Body mass index, kg/m^2	26 (24-30)	27 (24-32)	28 (24-31)	27 (25-31)	0.161
Type of index VTE					0.001
Unprovoked	336 (70)	58 (65)	161 (83)	43 (81)	
Provoked[b]	142 (30)	31 (35)	32 (17)	10 (19)	
Major surgery during last 3 months[c]	63 (13)	16 (18)	17 (9)	3 (6)	0.060
Estrogen therapy during last 3 months	14 (3)	3 (3)	1 (1)	2 (4)	0.245
Immobilization during last 3 months[d]	107 (22)	22 (25)	25 (13)	8 (15)	0.021
Location of index VTE					0.575
PE ± DVT	344 (72)	59 (66)	131 (68)	36 (68)	
Isolated DVT	134 (28)	30 (34)	62 (32)	17 (32)	
Inflammatory bowel disease[e]	14 (3)	3 (3)	10 (5)	2 (4)	0.563
Diabetes mellitus	70 (15)	17 (19)	31 (16)	9 (17)	0.737
Chronic heart failure	46 (10)	3 (3)	10 (5)	3 (6)	0.074
Low physical activity[f]	173 (36)	27 (30)	71 (37)	14 (26)	0.359
Systolic blood pressure <100 mm Hg	21 (4)	1 (1)	6 (3)	1 (2)	0.366
Anemia[g]	175 (37)	24 (27)	60 (31)	10 (19)	0.023
Thrombophilic factor					
Factor V Leiden mutation[h]	30 (6)	12 (13)	17 (9)	9 (17)	0.047
Prothrombin G20210A mutation[i]	14 (3)	6 (7)	11 (6)	7 (13)	0.004
Antithrombin deficiency[j]	31 (6)	7 (8)	10 (5)	3 (6)	0.850

Protein C deficiency[k]	4 (1)	2 (2)	0 (0)	1 (2)	0.324
Protein S deficiency[l]	3 (1)	1 (1)	1 (1)	1 (2)	0.709
Any thrombophilia[m]	80 (17)	24 (27)	37 (19)	19 (36)	0.003

Abbreviations: DVT, deep venous thrombosis; FH, family history; IQR, interquartile range; PE, pulmonary embolism; PH, personal history; VTE, venous thromboembolism.

[a] Data were missing for FH (n=7), body mass index (n=4), low physical activity (n=2), systolic blood pressure (n=15), anemia (n=61), factor V Leiden mutation (n=83), prothrombin G20210A mutation (n=83), antithrombin deficiency (n=240), protein C deficiency (n=560), and protein S deficiency (n=519).

[b] Major surgery, estrogen therapy, or immobilization during the last 3 months before index VTE.

[c] Surgery requiring general or spinal anesthesia.

[d] Fracture or cast of the lower extremity, bed rest for >72 hours, or voyage in a sitting position for more than 6 hours.

[e] Defined as a history of Crohn's disease or ulcerative colitis.

[f] Based on self-report ("I am mostly sitting or lying, do not move a lot" or "I often walk but I avoid climbing stairs or carrying light weight").

[g] Serum hemoglobin concentration <12 g/dL in women and <13 g/dL in men.

[h] Heterozygous (n=65) and homozygous (n=3).

[i] All heterozygous.

[j] Antithrombin level <80% in women and <83% in men.

[k] Protein C level <70%.

[l] Protein S level <55% in women and <60% in men.

[m] Presence of at least one thrombophilic factor.

Table 2. Incidence rates of recurrent VTE by FH/PH status

Risk factors	No. of patients	No. of events/ patient-years	Incidence rate per 100 patient-years (95% CI)
Full observation period			
No FH/PH	478	61/1029	5.9 (4.6-7.6)
FH only	89	9/202	4.5 (2.3-8.6)
PH only	193	21/422	5.0 (3.2-7.6)
FH and PH	53	6/115	5.2 (2.3-11.6)
After initial anticoagulation only			
No FH/PH	313	55/551	10.0 (7.7-13.0)
FH only	64	7/110	6.4 (3.0-13.3)
PH only	70	13/97	13.4 (7.8-23.1)
FH and PH	18	5/30	17.0 (7.1-40.7)

Abbreviations: CI, confidence interval; FH, family history; PH, personal history; VTE, venous thromboembolism.

Table 3. Association between FH/PH status of VTE and recurrence

Risk factors	No. of events/ No. of patients	Crude SHR (95% CI)	Adjusted SHR (95% CI)[a]
Full observation period			
No FH/PH	66/478	1 (Reference)	1 (Reference)
FH only	10/89	0.8 (0.4-1.6)	0.8 (0.4-1.7)
PH only	23/193	0.9 (0.5-1.4)	1.5 (0.9-2.5)
FH and PH	6/53	0.9 (0.4-2.0)	1.4 (0.6-3.1)
After initial anticoagulation only			
No FH/PH	55/313	1 (Reference)	1 (Reference)
FH only	7/64	0.6 (0.3-1.4)	0.7 (0.3-1.5)
PH only	13/70	1.2 (0.6-2.2)	1.3 (0.7-2.4)
FH and PH	5/18	1.7 (0.7-4.1)	1.7 (0.7-4.2)

Abbreviations: CI, confidence interval; FH, family history; PH, personal history; SHR, sub-hazard ratio; VTE, venous thromboembolism.

[a] Adjusted for age, sex, body mass index, type of the index VTE (provoked, unprovoked), inflammatory bowel disease, and periods of anticoagulation.

Table 4. Association between FH/PH status of VTE and all-cause mortality

Risk factors	No. of events/ No. of patients	Univariate HR (95% CI)	Multivariate HR (95%CI)[a]
Full observation period			
No FH/PH	70/478	1 (Reference)	1 (Reference)
FH only	7/89	0.5 (0.2-1.1)	0.7 (0.3-1.6)
PH only	31/193	1.1 (0.7-1.7)	1.6 (1.0-2.5)
FH and PH	3/53	0.4 (0.1-1.3)	0.6 (0.2-2.0)
After initial anticoagulation only			
No FH/PH	39/313	1 (Reference)	1 (Reference)
FH only	5/64	0.7 (0.3-1.7)	0.9 (0.4-2.4)
PH only	16/70	2.2 (1.2-3.9)	2.4 (1.3-4.4)
FH and PH	1/18	0.5 (0.1-3.3)	0.8 (0.1-5.6)

Abbreviations: CI, confidence interval; FH, family history; HR, hazard ratio; PH, personal history; VTE, venous thromboembolism.

[a] Adjusted for age, sex, major surgery during the last 3 months prior to index VTE, pulmonary embolism as index VTE, diabetes mellitus, chronic heart failure, low physical activity, systolic blood pressure < 100 mm Hg, anemia, and periods of anticoagulation.