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Risk stratification for predicting recurrent venous thromboembolism after discontinuation of anticoagulation: a post-hoc analysis of a French prospective multicenter study

Brief Title: Venous thromboembolism and recurrences

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*In memory of Karine Lacut

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Refined ISTH classification based on recurrence risk intensity of individual factors discriminates between low and high recurrence risk.

ABSTRACT

Background: We aimed to validate and to refine current recurrent venous thromboembolism (VTE) risk classification.

Methods: We performed a post-hoc analysis of a multicentre cohort, including 1,881 patients with a first symptomatic VTE prospectively followed after anticoagulation discontinuation. The primary objective was to validate the International Society of Thrombosis and Haemostasis (ISTH) risk classification in predicting recurrence risk. Secondary objective was to evaluate a refined ISTH classification based on recurrence risk estimate for each individual risk factors.

Results: During a 4.8-year median follow-up after anticoagulation discontinuation, symptomatic recurrent VTE occurred in 230 patients (12.2%). Based on ISTH classification, patients with unprovoked VTE or VTE with minor or major persistent risk factor had a 2-fold increased recurrence risk as compared to those with VTE and major transient risk factor. Recurrence risk was not increased in patients with minor transient factor (Hazard Ratio[HR] 1.31;95%CI0.84-2.06). Individual risk factors analysis identified hormone-related VTE (pregnancy: HR 0.26; 95%CI0.08-0.82; estrogens: HR 0.25; 95%CI0.14-0.47) and amyotrophic lateral sclerosis (HR 5.84; 95%CI1.82-18.70). After reclassification of these factors as major transient for the former and major persistent for the latter, refined ISTH classification allowed to accurately discriminate between patients at low-risk (i.e., with major transient risk factor) and those at high-risk of recurrence (i.e., without major transient risk factors).

Conclusions: Among patients who stopped anticoagulation after a first VTE, a refined ISTH classification based on recurrence risk intensity of individual factors allowed to discriminate between patients at low-recurrence risk, including hormonal exposure in women, and patients at high-recurrence risk.

Key Words: pulmonary embolism, recurrent venous thromboembolism, risk factors

INTRODUCTION

Anticoagulation is the mainstay of venous thromboembolism (VTE) treatment and it should be administered for a minimal duration of three months to reduce the risk of recurrent VTE (1–4). Beyond three months, the decision to prolong anticoagulant therapy is based on the risk of recurrent VTE after stopping anticoagulation, the risk of bleeding while maintaining anticoagulation and patients' preference. Based on high level of evidence, international guidelines recommend stopping anticoagulation when VTE was provoked by a major transient risk factor (e.g., surgery) and prolonging anticoagulant therapy (no scheduled date to stop) in cases of recurrent unprovoked (i.e., no major nor minor risk factors of recurrence) VTE or VTE with major persistent risk factor (i.e., mainly active cancer)(1,3,4). In contrast, in patients with a first VTE occurring in the absence of major risk factors, the decision to prolong anticoagulation or not remains challenging, despite the results of several randomized trials (5–8).

Subgroup of patients with VTE and no major risk factors is heterogeneous, gathering patients with minor transient or persistent risk factors and those with no identifiable clinical risk factors (i.e., unprovoked VTE) (5,7). In 2016, the International Society of Thrombosis and Haemostasis (ISTH) established a recurrence risk classification, including a definition of transient/persistent and major/minor risk factors in order to guide physicians on optimal duration of anticoagulation (9). However, the impact of "minor" risk factors remains uncertain, which translates into diverging guidelines recommendations (1,3,10–21). Hence, in patients with VTE provoked by a minor transient risk factor, the CHEST Guideline and Expert Panel Report recommends stopping anticoagulation whereas the European society of cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend considering indefinite anticoagulation if the risk of bleeding is low or moderate (1,10). Such discrepancies might be explained by misclassification of some factors (2), such as hormonal exposure in

young women, which has been shown to be associated with a particular low risk of recurrence (11). Thus, categorizing risk factors of recurrence as minor or major based on the risk of a first VTE and the risk of recurrence (9), rather than the risk of recurrence only, might be inaccurate.

In the present multicentre prospective study, we performed a post-hoc analysis with the primary aim to validate the ISTH classification in predicting the risk of recurrent VTE after a first episode of VTE according to the 5 predefined classes (9). Then, we aimed to determine the influence of individual clinical factors on the risk of recurrent VTE into ISTH classification sub-groups, in order to refine and to evaluate a modified ISTH classification only based on recurrence risk.

Methods

Study design

The study is a multicentre prospective cohort study, including patients recruited between 2001 and 2019 with symptomatic PE or deep vein thrombosis (DVT) and followed up for an indefinite period of time. The design has been previously described (17,22). The Ethics Committee of Brest University Hospital approved the study protocol (CCP-Ouest 6-390). Written informed consent was obtained from all participants before inclusion.

Eligibility

Patients aged 18 years or older who experienced a first episode of objectively confirmed symptomatic VTE initially treated for at least three months and who discontinued anticoagulation were potentially eligible. The exclusion criteria were prior VTE, indication for anticoagulation for reasons other than VTE, indefinite anticoagulation, initial anticoagulation length <90 days and no follow-up after stopping anticoagulation or follow-up of less than three months after anticoagulation discontinuation.

Diagnosis of index VTE

The diagnosis of VTE was performed using objective, standardized and validated criteria (23,24). Isolated symptomatic DVT was confirmed in cases of non-compression of leg deep vein ultrasound. Symptomatic PE was confirmed if there was: (i) a high clinical pre-test probability and a high-probability ventilation-perfusion (V/Q) lung scan according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) criteria; or (ii) a proximal DVT diagnosed on ultrasonography in a patient with symptoms of PE; or (iii) a positive computed tomography pulmonary angiography (CTPA) showing a central filling defect outlined by contrast material or a complete occlusion in a segmental or more proximal pulmonary artery.

Risk factors definition and collection

Risk factors of recurrent VTE were primarily categorized according to the ISTH classification (9). Major transient risk factors encompassed surgery with general anesthesia >30 minutes, trauma of lower limb (fracture and/or plaster cast), prolonged immobilization (>3 days) for an acute medical illness and cesarean section, all occurring in the past three months (9). Major persistent risk factor included only active cancer (9). Estrogen-containing pill, pregnancy and hormonal replacement therapy were considered as minor transient risk factors (9). All of these factors were prospectively collected in the cohort. In order to complete data on minor risk factors as defined in the ISTH classification (9), we implemented original data from the cohort with patients' medical history, ICD-10 and ICD 9 (International Classification of Diseases, tenth, and nine editions) code and keywords were retrospectively collected in the hospitals database, and crossed with the cohort study database, then confirmed manually (**Table S1**).

Study outcomes

The primary outcome was symptomatic recurrent VTE during entire follow-up after anticoagulation discontinuation. Symptomatic recurrent VTE was defined as PE (fatal or non-fatal) or isolated proximal or distal DVT (17,25–27). The diagnosis of symptomatic recurrent DVT was confirmed in case of a new or contralateral non-compression of a deep vein on legs ultrasound. The diagnosis of symptomatic recurrent PE was based on a clinical suspicion of recurrence associated with: (i) a high PIOPED probability V/Q lung scan showing the presence of a new or enlarged segmental perfusion defect with normal ventilation; or (ii) an intraluminal filling defect in a segmental or more proximal pulmonary artery on CTPA, in an area where no thrombus (normal perfusion on previous V/Q lung scan or no intraluminal defect on previous CTPA) on lung test performed at the time of initial diagnosis of PE or during follow-up prior the suspicion of recurrence; or (iii) a recurrent proximal DVT (new or contralateral non-compression of a deep vein). Secondary outcome was all-cause mortality. All initial VTE events, recurrences and deaths were adjudicated by an independent clinical event committee. (17,25–27).

Statistical analyses

Continuous variables were expressed as mean (standard deviation [SD]) and median (interquartile range [IQR]) and categorical variables as numbers and percentages. The Student t-test was used to compare means between groups in cases of normal distribution and the Mann–Whitney test was used in cases of non-normal distribution. The Chi-squared test or exact Fisher test was used to compare proportions, as appropriate. Considering the competitive situation, we used an Aalen-Johansen estimator to evaluate the cumulative probability of VTE recurrence or death during the entire follow-up period after stopping anticoagulation. The Gray’s K-sample method was used to compare cumulative incidences of recurrent VTE.

For the primary post-hoc analysis, clinical risk factors were gathered according to the

ISTH classification into the following 5-class hierarchical categorization: major transient, minor transient, minor persistent, major persistent and unprovoked VTE. For the univariable analysis, a Cause Specific Cox semi-proportional hazard model was performed to evaluate the impact of each variable on the probability of recurrence. Then, the multivariable model (model 1) was built including the ISTH classification and variables non-related to ISTH classification with a p-value <0.15 and prevalence ≥3%.

The secondary analyses were conducted in two steps. First, the risk of recurrent VTE associated with each individual risk factors into ISTH classification was estimated in univariable analysis based on a Cause Specific Cox semi-proportional hazard model. The multivariable model (model 2) was built by selecting variables with a p-value <0.15 and a prevalence ≥3%. Interactions between variables were systematically studied. In order to build the modified ISTH classification, only variables initially considered as minor transient or minor persistent risk factors with a p-value <0.05 and a Hazard Ratio (HR) <0.5 or >2 were reclassified as major transient (if HR <0.5) or major persistent (if HR >2) in the refined ISTH classification. Second, the multivariable model (model 3) was built including the refined ISTH classification and variables non-related to ISTH classification with a p-value <0.15 and prevalence ≥3%.

All tests were two-sided and a p-value less than 0.05 was considered statistically significant. Statistical analyses were done using R version 4.0 - © 2009-2017 R Studio, Inc.

RESULTS

Between January 1st 2000 and June 21st 2019, 4512 patients were enrolled and prospectively followed in the cohort. Of them, 2631 presented one or more exclusion criteria (**Figure 1**). The most frequent exclusion criteria were long-term anticoagulation (n=1983) and initial anticoagulant therapy duration <90 days (n=258).

Baseline characteristics

Among the 1881 included patients, mean (SD) age was 56.9 years (19.3) and 1043 patients (55.4%) were female. According to the ISTH classification, VTE was provoked by one or more major transient risk factor in 501 patients and by a major persistent risk factor (i.e., active cancer) in 129. Among the remaining 1251 patients in whom VTE was not provoked by a major risk factor, 467 had VTE provoked by one or more minor transient risk factor, 57 by one or more minor persistent risk factor and 727 were considered unprovoked. Demographic and clinical characteristics are presented in **Tables 1** and **2**.

Primary outcome

During a median (IQR) follow-up period of 4.8 years (2.5-8.0) after anticoagulation discontinuation, symptomatic recurrent VTE occurred in 230 patients (12.2%): 117 events (52.2%) were non-fatal PE, three were fatal PE (1.3%) and 110 were isolated DVT (47.8%). The cumulative VTE recurrence rate in the overall population was 8.10% (95%CI, 8.09-8.11) at 1 year, 9.47% (95%CI, 9.46 - 9.48) at 2 years and 12.49 % (95%CI, 12.48-12.50) at 5 years.

Primary analysis on original ISTH classification

In univariable analysis, among variables non-related to ISTH classification, index events presenting as PE (associated or not with DVT) *versus* isolated DVT, age >65 years, female gender and anticoagulation duration were associated with a p-value <0.15 and were selected for the multivariable model 1. In this multivariable model 1, unprovoked VTE and VTE with major or minor persistent risk factors were associated with a 2-fold increased risk of recurrence as compared to VTE with major transient risk factors (**Table 3**). The risk of recurrence was not increased in patients with VTE and minor transient risk factor (HR 1.22; 95%CI, 0.78-1.90) (**Table 3**).

Secondary analyses on modified ISTH classification

Impact of individual risk factors. In univariable analysis, cancer, peripheral artery disease (PAD) and amyotrophic lateral sclerosis (ALS) were associated with an increased risk of recurrent VTE (HR >2) (**Table 4**). In contrast, plaster cast or fracture, prolonged (>3 days) hospitalization, estrogen-containing pill and pregnancy were associated with a lower risk of recurrent VTE (HR <0.5). In multivariable analysis (model 2), variables associated with VTE recurrences were age >65 (HR 2.28; 95%CI, 1.62 -3.20), cancer (HR 1.57; 95%CI, 1.00-2.46) and ALS (HR 5.74; 95%CI, 1.79-18.37) whereas estrogen-containing pill (HR 0.25; 95%CI, 0.14-0.47), pregnancy or post-partum (HR 0.26;95%CI 0.08-0.82) and prolonged hospitalization (HR 0.49; 95%CI, 0.33-0.71) were associated with decreased risk of recurrence (**Table 4**).

Influence of the modified ISTH classification on recurrent VTE. The 5-class ISTH classification was modified as follows: hormone-related factors (i.e., pregnancy, post-partum and estrogen containing pill) were considered as major transient risk factors and ALS as a major persistent risk factor (**Table S2**). Based on this modified 5-class risk classification, unprovoked VTE, VTE with major or minor persistent risk factors and VTE with minor transient risk factors were all associated with a 2-fold increased risk of recurrent VTE, as compared to VTE with major transient risk factor in multivariable analysis (model 3)(**Table 3**).

The 5-year cumulative incidences of recurrent VTE and survival curves of recurrence are shown in **Table 5** and **Figure 2**.

Mortality

During the median follow-up period of 4.8 years, 373 patients (19.83%) died yielding a 5-year cumulative mortality rate of 15.70 (95%CI, 13.90-17.50). Adjudicated causes of death were available for 241 patients (64.61%)(**Table S3**): death was considered as certainly and probably due to PE in 3 and in 32 (8.58%), respectively. The other most frequent causes of

death were acute respiratory failure, cancer and septic shock.

DISCUSSION

In this prospective cohort, including 1881 patients with a first symptomatic VTE and followed during a median length of 4.8 years after anticoagulation discontinuation, the primary post-hoc analysis on ISTH classification showed a 2-fold increased risk of recurrent VTE in patients with unprovoked VTE or VTE with persistent, minor or major, risk factors as compared to patients with VTE provoked by major or minor transient risk factor. In the secondary analysis on individual risk factors, most of them considered as minor in the original ISTH classification were not found to significantly influence the risk of recurrence, excepted hormone-related VTE that was associated with a particular low risk of recurrence (HR <0.5); among patients with unprovoked VTE, ALS which was associated with a high risk of recurrence (HR >2). After reclassification of hormonal exposure as major transient and ALS as major persistent, the refined ISTH classification allowed to accurately discriminate between patients at low risk (i.e., presence of major transient risk factor, HR<0.5) and those at high risk of recurrence (i.e., absence of major transient risk factors, HR >2).

Regarding the influence of major transient risk factors as defined by the ISTH classification, we confirmed a 2 to 3-fold reduced risk of recurrence in patients with prolonged hospitalization and plaster cast, the latter being associated with a non-significant HR of 0.26 probably due to under-representation. Surprisingly, major surgery was not found associated with a lower risk of recurrence. Although a high risk of recurrent VTE has also been reported in some large cohorts of unselected patients, particularly during the first year of follow-up after anticoagulation discontinuation (28-30), this result is likely related to selection biases (referral bias). As shown in the **Table S4**, a high proportion of these patients had associated risk factors for VTE (cancer (11%), familial history (23%)) and comorbidities

(chronic cardio-respiratory diseases (24%), chronic renal insufficiency (6.4%) or stroke sequelae (5.2%)) that expose patients to an increased risk of further prothrombotic circumstances (e.g., re-hospitalizations for an acute organ failure)(31). In our study, participating hospital centres are all public hospitals having intensive care units, which is not the case in private hospitals. Therefore, severe patients who are hospitalized for major surgery are more often addressed to public hospital than to private hospitals.

Regarding the influence of minor transient risk factors, one of the important findings is the confirmation of a very low risk of recurrence in women with hormone-related VTE (i.e., estrogen-containing pill and pregnancy: HR of 0.25 [95% CI 0.14-0.47] and of 0.26 [95% CI 0.08-0.82], respectively); this observation is consistent and complementary to other studies (11,32-34). Thus, given the potential major impact on anticoagulation (i.e., cumulative recurrence risk not high enough to justify extending anticoagulation)(1,2,11,32-34), hormonal exposure was included in the "major transient risk factor" subgroup in the modified ISTH classification. Consequently, the one-year cumulative incidence of recurrent VTE in patients with minor transient risk factors in the modified ISTH classification was higher to that observed in the original classification (10.40% [95% CI 10.27-10.53] and 4.99% [95% CI 4.97-5.01], respectively)(**Table 5**) and close to that of patients with unprovoked VTE. Regarding individual minor transient risk factors other than hormonal exposure, we failed to identify additional predictors for recurrence, which is consistent with the results of the post-hoc analysis of the Einstein-Choice trial (**Table S5**)(34). Finally, in subgroup of patients with minor transient factors (when excluding hormonal exposure), there is no suggestion in this post-hoc analysis that anticoagulation could be safely stopped after the initial 3 to 6 months of anticoagulation (4,34).

Regarding the influence of minor persistent risk factors, cumulative incidence rate of recurrent VTE was particularly high, possibly due to under-representation (only 107 patients)

and to selection bias as half of all of these patients with minor risk factors remained on indefinite anticoagulation (**Table S7**) (34). Although an association with autoimmune diseases and a first VTE has been reported (35-38), we did not observe an increased risk of recurrence in these patients, as reported in the RIETE registry (39). Whether these conditions might reinforce or not indication for indefinite anticoagulation remains to be investigated in large studies.

Consistent with several randomized trials, we confirmed a high risk of recurrence in patients with unprovoked VTE (5-8); consistent with other studies, the risk was particularly high the first year of follow-up after stopping anticoagulation (5-8). However, this subgroup is heterogeneous, many patients having associated comorbidities that might influence the risk of recurrence (e.g., PAD, bronchectiasis, ILD). Interestingly, secondary analysis identified ALS as a potential major persistent risk factor of recurrence. In a prospective cohort of 50 ALS patients, an annual incidence rate of a first DVT of 11.2% has been reported (40), however, the risk of recurrence has not been studied yet. In our study, the magnitude of the recurrence risk is possibly over-estimated due to the small number of ALS patients; nevertheless, this signal warrants further investigation in dedicated studies. Given the high risk of recurrence, we considered this factor as major persistent in the modified ISTH classification, contributing to the high cumulative incidence rate of recurrent VTE in this group (one-year cumulative incidence of 14.30% (95% CI 14.11-14.49)(**Table 5**). Lastly, cancer-associated VTE patients had a moderate risk of recurrence in the multivariable model on individual risk factors (**Table 4**) as the majority of these patients remained on long-term anticoagulation (**Table S6 and S7**).

The strengths of this study include: (i) a prospective enrollment of consecutive patients with a first documented VTE; (ii) objective criteria for all cases of recurrent VTE, adjudicated by physicians not involved in patient's care; and (iii), a long follow-up period

after anticoagulation discontinuation.

Some limitations need to be underlined. First, as the decision to prolong or not anticoagulation was left to physician's decision, almost 50% of patients of the entire cohort could not be included in the analysis. As mentioned above, this selection bias could have led to over-estimate HR for recurrence in patients with VTE provoked by a major transient risk factor or a minor persistent risk factor or to under-estimate HR for recurrence (unprovoked VTE). Second, the sample size, although substantial, is underpowered to be able to obtain precise estimates regarding many potential minor risk factors. Third, anticoagulation durations were heterogeneous, however, we systematically adjusted on anticoagulant therapy duration in all analyses. Fourth, imaging and biological parameters, not available for all patients, were not evaluated.

Conclusion

In a post-hoc analysis of a large cohort of patients with first episode of VTE who stopped anticoagulation after a minimum of three months of therapy, the refinement of the ISTH classification, only based on the recurrence risk intensity of individual risk factors, allowed to accurately discriminate between patients at low recurrence risk, i.e., presence of major transient risk factor, including hormonal exposure in women, and patients at high recurrence risk, i.e. absence of major transient risk factor. These results should be interpreted as hypothesis-generating, and well-designed studies are needed to precisely estimate the recurrence risk associated with a number of minor risk factors.

Table 1. Baseline patients' characteristics

Variables n (%)	Total (n = 1881) n (%)	Non-recurrent VTE (n=1651) n (%)	Recurrent VTE (n= 230) n (%)	P-value
Age (years), mean (SD)	56.85 (19.33)	55.98 (19.45)	63.16(17.14)	<0.001
<50	709 (37.7)	655 (39.7)	54 (23.6)	<0.001
50-65	419 (22.3)	364 (22.0)	55 (24.0)	
>65	752 (40.0)	632 (38.3)	120 (52.4)	
Gender (women)	1043 (55.4)	931 (56.4)	112 (48.7)	0.033
BMI, mean (SD)	26.42 (5.07)	26.45 (5.15)	26.17 (4.47)	0.39
Underweight <18.5	47 (2.6)	42 (2.6)	5 (2.2)	0.91
Normal [18.5-25]	752 (40.9)	657 (40.8)	95 (41.7)	
Overweight >25	1040 (56.6)	912 (56.6)	128 (56.1)	
Blood group				
A	752 (50.1)	664 (50.2)	88 (48.9)	0.95
B	197 (13.1)	172 (13.0)	25 (13.9)	
AB	65 (4.3)	56 (4.2)	9 (5.0)	
O	488 (32.5)	430 (32.5)	58 (32.2)	
Rh -	1197 (83.0)	1051 (82.6)	146 (85.4)	0.60
Rh +	223 (15.5)	201 (15.8)	22 (12.9)	
Tobacco	863 (46.7)	764 (47.2)	99 (43.8)	0.38
Pack-year, mean (SD)	13.0 (10.4)	12.7 (10.1)	14.6 (11.7)	0.19
Family history of VTE	490 (26.3)	425 (26.1)	65 (28.3)	0.53
Characteristics of VTE at diagnosis				<0.001
Isolated proximal DVT	782 (41.7)	686 (41.7)	96 (41.7)	
Isolated PE	530 (28.3)	485 (29.5)	45 (19.6)	
PE + DVT	562 (30.0)	473 (28.8)	89 (38.7)	
Concomitant drugs				
Platelet aggregation inhibitors	189 (10.1)	168 (10.2)	21 (9.1)	0.70
Statins	174 (9.3)	152 (9.2)	22 (9.6)	0.97
Follow-up, mean (SD)	6.18 (4.0)	6.15 (4.0)	6.39 (4.1)	0.40
Length of anticoagulation (days)				0.001
90-180	547 (29.1)	473 (28.6)	74 (32.2)	
180-360	871 (46.3)	748 (45.3)	123 (53.5)	
>360	463 (24.6)	430 (26.0)	33 (14.3)	

BMI: body mass index; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; Rh: rhesus system

Table 2. Baseline patients' risk factors according to ISTH classification

Variables n (%)	Total (n = 1881) n (%)	Non-recurrent VTE (n=1651) n (%)	Recurrent VTE (n= 230) n (%)	P-value
MAJOR TRANSIENT				
Major surgery	266 (14.1)	235 (14.2)	31 (13.5)	0.84
Plaster cast/fracture of lower limb	66 (3.5)	64 (3.9)	2 (0.9)	0.033
Hospitalization [a]	387 (20.6)	354 (21.5)	33(14.3)	0.016
MINOR TRANSIENT				
Pregnancy or post-partum	95 (9.1)	92 (9.9)	3 (2.7)	0.02
Estrogen-containing pill	297 (28.5)	285 (30.6)	12 (10.7)	<0.001
Hormonal replacement therapy	60 (5.8)	51 (5.5)	9 (8.0)	0.38
Medically assisted procreation	3 (0.3)	2 (0.2)	1(0.9)	0.74
Travel in the past 3 months	237 (12.6)	210 (12.7)	27 (11.8)	0.77
>6 hours	171 (74.3)	152 (74.5)	19 (73.1)	0.99
Surgery with general anesthesia < 30 minutes	64 (3.4)	57 (3.5)	7 (3.0)	0.90
Minor leg injury	26 (1.4)	26 (1.6)	0 (0.0)	0.106
Length of splint (mean days (SD))	29.71 (13.6)	29.71 (13.6)		
MAJOR PERSISTANT				
Cancer	129 (6.9)	107 (6.5)	22 (9.6)	0.111
MINOR PERSISTENT				
Inflammatory diseases	25 (1.3)	22 (1.3)	3 (1.3)	0.99
Autoimmune diseases	82 (4.4)	72 (4.4)	10 (4.3)	0.99
OTHER CONDITIONS [b]	980	861	119	0.13
Stroke				
Paresis from ischemic stroke	37 (2.0)	33 (2.0)	4 (1.7)	0.99
Paresis from hemorrhagic stroke	8 (0.4)	8 (0.5)	0 (0.0)	0.61
Hemiplegia	25 (1.3)	21 (1.3)	4 (1.7)	0.79
Congestive heart failure	31 (1.6)	28 (1.7)	3 (1.3)	0.87
Chronic heart diseases	139 (7.4)	129 (7.8)	10(4.3)	0.34
Valvular cardiopathy	2 (0.1)	2 (0.1)	0 (0)	0.34
Ischemic cardiopathy	73 (3.9)	67 (4.1)	6 (2.6)	0.34
Rhythmic cardiopathy	48 (2.6)	44 (2.7)	4 (1.7)	0.34
Other cardiopathy	16(0.9)	16(1.0)	0 (0.0)	0.34
PAD	52 (2.8)	41 (2.5)	11 (4.8)	0.071
Chronic lung diseases	147 (7.8)	125 (7.6)	22 (9.6)	0.36
COPD	113 (6.0)	96 (5.8)	17 (7.4)	0.43
Asthma	15 (0.8)	15 (0.9)	0 (0.0)	0.29
Restrictive diseases	22 (1.2)	20 (1.2)	2 (0.9)	0.90
ILD	14 (0.7)	11 (0.7)	3 (1.3)	0.52
Bronchiectasis	23 (1.2)	18 (1.1)	5 (2.2)	0.28
OSA	64 (3.4)	59 (3.6)	5 (2.2)	0.37
Hypothyroidism	43 (2.3)	38 (2.3)	5 (2.2)	0.99
Hyperthyroidism	10 (0.5)	8 (0.5)	2 (0.9)	0.79
Chronic liver diseases	7 (0.4)	6 (0.4)	1 (0.4)	0.99
Parkinson disease	18 (1.0)	16 (1.0)	2 (0.9)	0.99
Amyotrophic lateral sclerosis	6 (0.3)	3 (0.2)	3 (1.3)	0.027
Renal chronic diseases	67 (3.6)	57 (3.5)	10 (4.3)	0.62
No risk factor nor comorbidity	0	0	0	

PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; OSA: obstructive sleep apnea

[a]*Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness in the past three months before VTE first event.*
[b]*Other conditions: no major or minor, transient or persistent risk factors*

Table 3. Risk of recurrent VTE according to the original (model 1) and the modified (model 3) ISTH risk classification

	Original ISTH classification				Modified ISTH classification			
Variables	**Univariable analysis [a] HR (95%CI)**	**P-value**	**Multivariable analysis (model 1) [a] HR (95%CI)**	**P-value**	**Univariable analysis [b] HR (95%CI)**	**P-value**	**Multivariable analysis (model 3) [b] HR (95%CI)**	**P-value**
Major transient risk factors	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Major persistent risk factors	2.39 (1.43-3.97)	0.001	2.15 (1.28-3.60)	0.004	3.32 (2.08-5.31)	<0.001	2.65 (1.61-4.37)	<0.001
Minor persistent risk factors	1.85 (0.90-3.77)	0.093	2.06 (1.001-4.23)	0.05	2.74 (1.31-5.73)	0.008	2.35 (1.11-4.97)	0.026
Minor transient risk factors	0.92 (0.60-1.40)	0.69	1.31 (0.84-2.06)	0.24	2.13 (1.37-3.34)	0.001	2.04 (1.28-3.24)	0.003
Unprovoked VTE	1.77 (1.25-2.49)	0.001	1.79 (1.26-2.53)	0.001	2.21 (1.61-3.03)	<0.001	1.97 (1.40-2.77)	<0.001
Age (years)								
<50	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
50-65	1.88 (1.29-2.74)	0.001	1.66 (1.11-2.46)	0.013	1.88 (1.29-2.74)	0.001	1.43 (0.97-2.12)	0.08
>65	2.47 (1.79-3.42)	<0.001	2.18 (1.26-3.13)	<0.001	2.47 (1.79-3.42)	<0.001	1.91 (1.35-2.70)	<0.001
Gender (women)	0.74 (0.57-0.95)	0.02	0.80 (0.61-1.07)	0.13	0.74 (0.57-0.95)	0.02	0.87 (0.66-1.14)	0.32
Characteristics of VTE at diagnosis								
Isolated DVT	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
Isolated PE	0.75 (0.53-1.07)	0.112	1.27 (0.94-1.72)	0.12	0.75 (0.53-1.07)	0.112	0.73 (0.51-1.05)	0.09
PE + DVT	1.40 (1.05-1.87)	0.022	0.74 (0.51-1.06)	0.10	1.40 (1.05-1.87)	0.022	1.25 (0.92-1.69)	0.15
Length of anticoagulation (days)								
>360	*Ref.*		*Ref.*		*Ref.*		*Ref.*	
180-360	1.76 (1.20-2.59)	0.004	1.93 (1.31-2.84)	0.001	1.76 (1.20-2.59)	0.004	1.95 (1.33-2.87)	0.001
90-180	1.64 (1.09-2.48)	0.018	2.08 (1.35-3.19)	0.001	1.64 (1.09-2.48)	0.018	2.10 (1.37-3.22)	0.001

VTE: venous thromboembolism; DVT: deep vein thrombosis; PAD: peripheral arterial disease; PAD: peripheral artery disease; ALS: amyotrophic lateral sclerosis

[a] Uni and multivariable model 1 includes variables defined as major/minor, transient/persistent or no risk factors (unprovoked VTE) according to the original ISTH classification.

[b] Uni and multivariable model 3 includes variables defined as major/minor, transient/persistent or no risk factors (unprovoked VTE) according to the refined ISTH classification. Following analyses on individual risk factors (model 2, Table 3), hormone related variables (estrogen containing pill, pregnancy and post-partum) were classified as major transient risk factors and ALS was classified as a major persistent risk factor.

Table 4. Individual risk factors associated with VTE recurrence (model 2)

Variables	Univariable analysis HR (95%CI)	P-value	Multivariable Analysis (model 2) HR (95%CI)	P-value
Age (years)				
<50	*Ref.*		*Ref.*	
50-65	1.88 (1.29-2.74)	0.001	1.68 (1.13-2.48)	0.01
>65	2.47 (1.29-2.74)	0.001	2.28 (1.62-3.20)	<0.01
Gender (women)	0.74 (0.57-0.95)	0.020	0.78 (0.59-1.02)	0.07
BMI				
Normal [18.5-25]	*Ref.*			
Underweight <18.5	0.87 (0.35-2.14)	0.759		
Overweight >25	0.96 (0.74-1.26)	0.788		
Blood group				
A/B/AB	*Ref.*			
O	1.02 (0.75-1.40)	0.900		
Rh +	Ref.			
Rh -	1.25 (0.80-1.96)	0.331		
Tobacco	0.90 (0.69-1.18)	0.447		
Pack-year	1.02 (1.00-1.04)	0.09		
Family history of VTE	1.05 (0.79-1.40)	0.729		
Characteristics of VTE at diagnosis				
Isolated DVT	*Ref.*		*Ref.*	
Isolated PE	0.75 (0.53-1.07)	0.112	0.73 (0.51-1.05)	0.09
PE + DVT	1.40 (1.05-1.87)	0.022	1.25 (0.92-1.70)	0.16
Concomitant drugs				
Platelet aggregation inhibitors	1.00 (0.64-1.57)	0.996		
Statins	1.07 (0.69-1.66)	0.770		
Length of anticoagulation				
>360	*Ref.*		*Ref.*	
180-360 days	1.76 (1.20-2.59)	0.004	1.85 (1.22-2.72)	<0.001
90-180 days	1.64 (1.09-2.48)	0.018	2.01 (1.31-3.08)	<0.001
MAJOR TRANSIENT FACTOR [a]				
Major surgery	0.90 (0.61-1.31)	0.57		
Plaster cast/fracture of lower limb	0.22 (0.06-0.90)	0.04	0.26 (0.07-1.07)	0.06
Hospitalization [b]	0.65 (0.45-0.93)	0.02	0.50 (0.34-0.73)	<0.001
MINOR TRANSIENT FACTOR [a]				
Pregnancy or post-partum	0.26 (0.08-0.81)	0.021	0.26 (0.08-0.82)	0.02
Estrogen-containing pill	0.26 (0.14-0.47)	<0.001	0.25 (0.14-0.47)	<0.001
Hormonal replacement therapy	1.30 (0.66-2.57)	0.45		
Medically assisted procreation	3.67 (0.51-26.34)	0.20		
Travel in the past 3 months	0.90 (0.60-1.35)	0.615		
>6 hours	0.88 (0.37-2.11)	0.776		
Surgery with general anesthesia < 30 minutes	0.93 (0.44-1.98)	0.860		
Minor leg injury	0.00 (0.00-0.00)	0.99		
MAJOR PERSISTENT [a]				
Cancer	1.82 (1.17-2.82)	0.008	1.57 (1.00-2.46)	0.05
MINOR PERSISTENT [a]				
Auto immune diseases	0.95 (0.31-2.98)	0.934		
Inflammatory diseases	1.05 (0.56-1.97)	0.888		
NO MINOR OR MAJOR FACTOR [a]				
Stroke [c]				
Paresis from ischemic stroke	0.96 (0.36-2.57)	0.927		
Paresis from hemorrhagic stroke	(0.00-0.00)	0.990		
Hemiplegia	1.50 (0.56-4.03)	0.422		
Parkinson disease	0.91 (0.23-3.66)	0.893		
Amyotrophic lateral sclerosis	6.44 (2.06-20.13)	0.001	5.74 (1.79-18.37)	<0.001

Congestive heart failure	1.00 (0.32-3.12)	0.999		
Chronic heart diseases				
Valvular cardiopathy	0.00 (0.00-0.00)	0.996		
Ischemic cardiopathy	0.67 (0.30-1.51)	0.331		
Rhythmic cardiopathy	0.86 (0.32-2.30)	0.760		
Other cardiopathy	0.00 (0.00-0.00)	0.99		
PAD	2.13 (1.16-3.91)	0.014	1.72 (0.93-3.18)	0.08
Chronic lung diseases	1.42 (0.20-10.10)	0.125		
COPD	1.39 (0.85-2.29)	0.188		
Asthma	0.00 (0.00-0.00)	0.991		
Restrictive diseases	0.91 (0.23-3.67)	0.898		
ILD	2.34 (0.75-7.31)	0.144	1.66 (0.50-5.47)	0.41
Bronchiectasis	2.13 (0.88-5.17)	0.095	2.09 (0.82-5.29)	0.12
OSA	0.64 (0.26-1.55)	0.323		
Hypothyroidism	0.98 (0.41-2.38)	0.969		
Hyperthyroidism	2.11 (0.52-8.48)	0.294		
Chronic liver diseases	1.42 (0.20-10.10)	0.728		
Renal chronic diseases	1.36 (0.72-2.57)	0.339		

BMI: body mass index; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; Rh: rhesus system PAD: peripheral artery occlusive disease; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; OSA: obstructive sleep apnea

[a] *Risk factor are classified as minor, major, transient and persistent risk factors are based on the original ISTH classification; however, in this model 2, only the influence of each individual risk factor was analyzed, not the influence of risk classification.*
[b] *Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness in the past three months before VTE first event.*
[c] *These patients developed an acute VTE more than 3 months after ischemic or hemorrhagic stroke.*

Table 5. Cumulative incidence of VTE recurrence according to original and modified ISTH risk classifications

Variables	Cumulative incidence rate, % (95%CI)		
	1 year	2 years	5 years
Model 1 (Original ISTH categorization) [1]			
Major transient risk factors	5.49 (5.47-5.51)	6.56 (6.53-6.58)	9.37 (9.33-9.41)
Major persistent risk factors	12.52 (12.34-12.70)	15.35 (15.13-15.57)	21.40 (21.03-21.77)
Minor transient risk factors	4.99 (4.97-5.01)	5.67 (5.65-5.69)	8.77 (8.73-8.81)
Minor persistent risk factors	14.37 (13.93-14.82)	14.37 (13.93-14.82)	16.64 (16.12-17.16)
Unprovoked VTE	10.68 (10.65-10.70)	12.59 (12.56-12.62)	15.44 (15.40-15.48)
Model 3 (Modified ISTH categorization) [2]			
Major transient risk factors	3.85 (3.84-3.86)	4.94 (4.92-4.95)	7.66 (7.64-7.68)
Major persistent risk factors	14.30 (14.11-14.49)	17.01(16.78-17.24)	22.83 (22.47-23.19)
Minor transient risk factors	10.40 (10.27-10.53)	10.40 (10.27-10.53)	14.41(14.23-14.59)
Minor persistent risk factors	16.00 (15.38-16.62)	16.00 (15.38-16.62)	18.92 (18.17-19.66)
Unprovoked VTE	10.44 (10.42-10.47)	12.36 (12.33-12.39)	15.22 (15.18-15.26)

[1]*Cumulative incidences based on model 1 includes variables defined as major/minor transient/persistent according to the ISTH classification.*
[2]*Cumulative incidence of recurrent VTE based on model 3: following analyses on individual risk factors (model 2, Table 3), hormone related variables (estrogen containing pill, pregnancy and post-partum) were classified as major transient risk factors and ALS was classified as a major persistent risk factor.*
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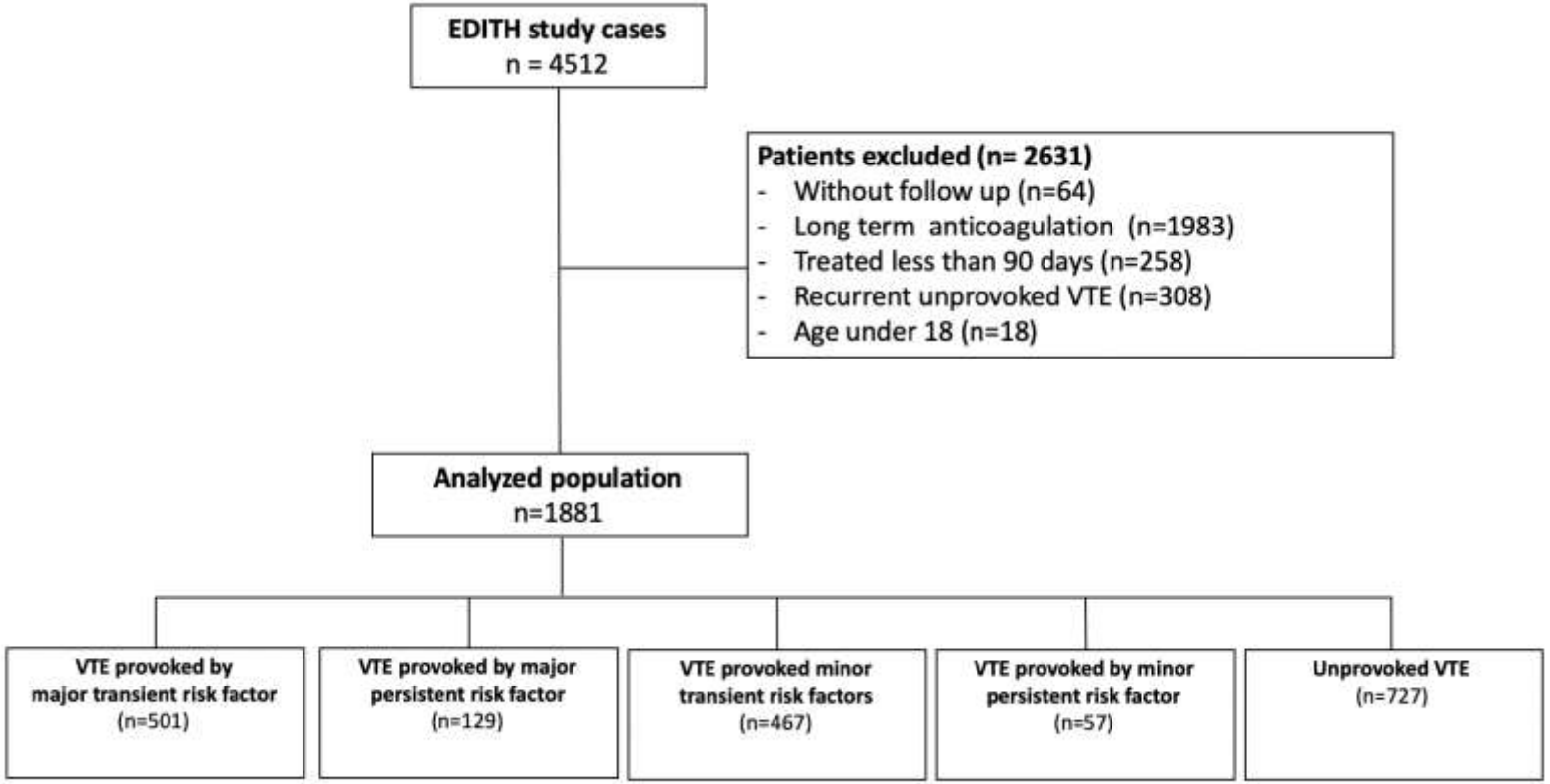
Figure 1. Flow chart



Classification of risk factors according to ESC/ERS and ISTH guidelines:
Major transient risk factor (including surgery with general anesthesia for greater than 30 min, plaster, confined to bed in hospital for at least 3 days with acute illness, cesarean section)
Major persistent risk factor (cancer)
Minor transient risk factors (including surgery with general anesthesia for less than 30 min, estrogen containing pill, hormone replacement therapy, pregnancy or puerperium, medically assisted procreation, leg injury associated with reduced mobility for at least 3 days, travel greater than 6 hours)
Minor persistent risk factor (including auto immune diseases, inflammatory diseases),
Unprovoked (none of the risk factors listed above

Figure 2. Cumulative incidence of VTE recurrence according to original (figure 2A) and refined ISTH classification (figure 2B)

Figure 2A

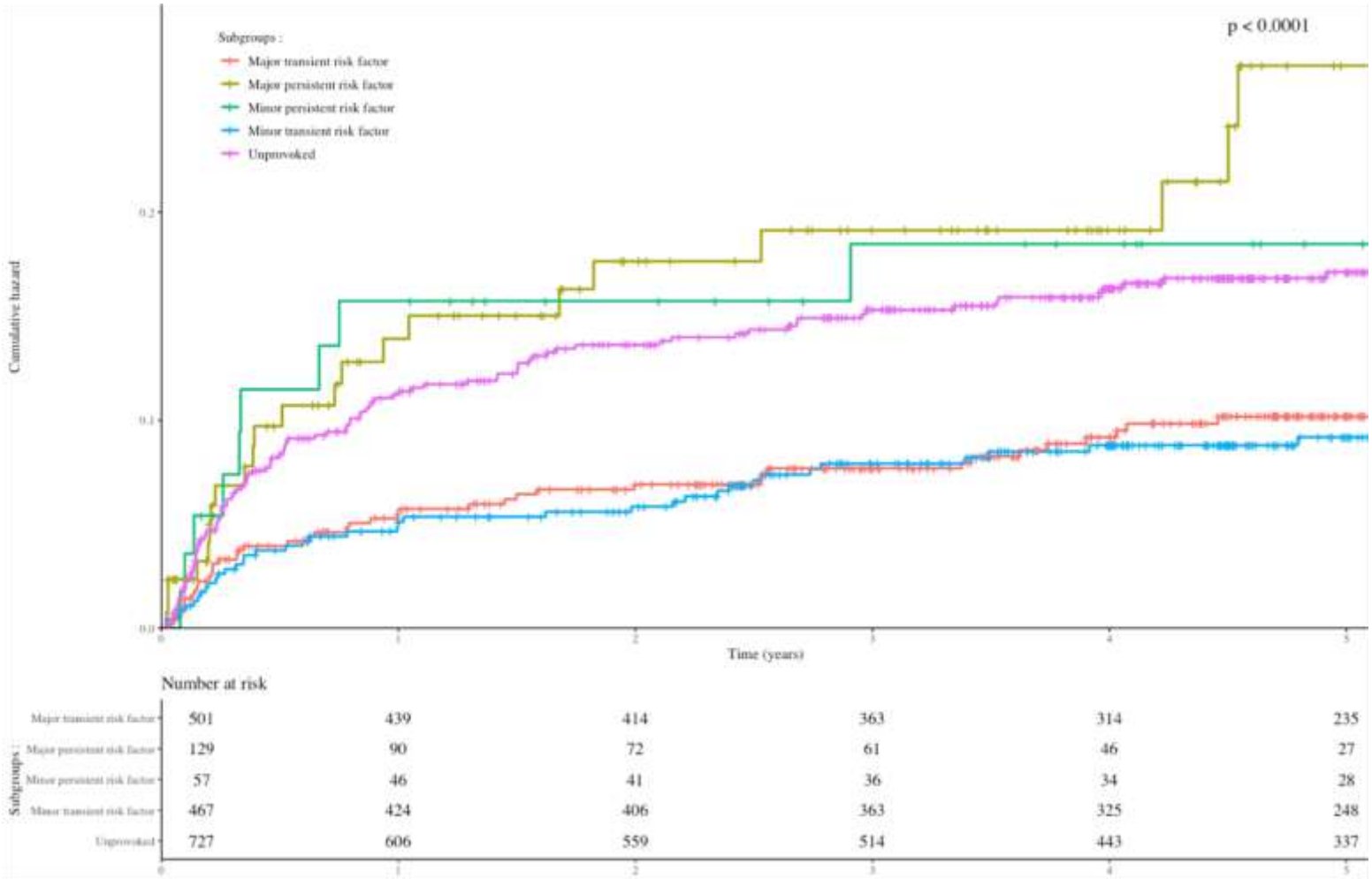
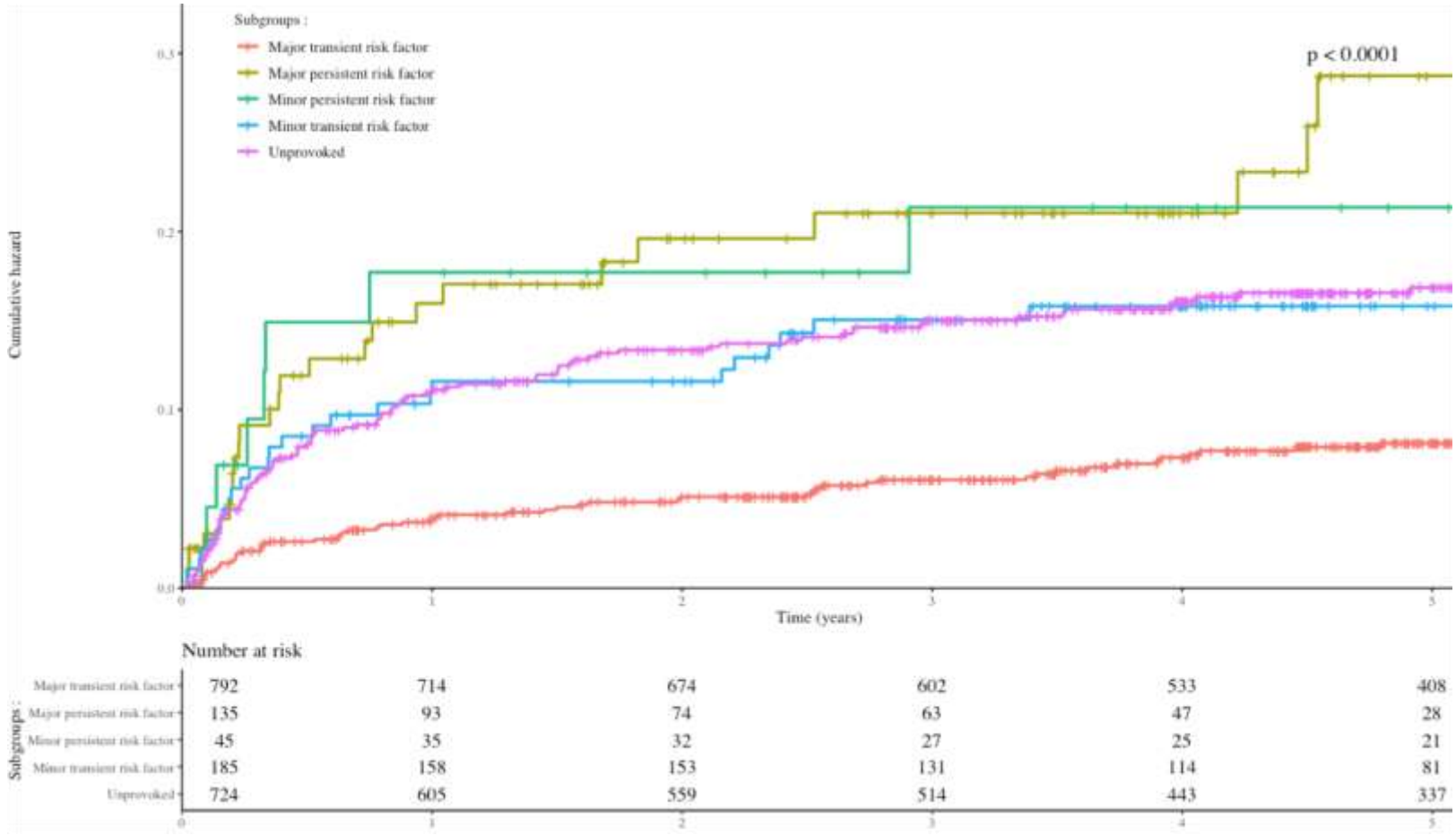


Figure 2B


Subgroups :
Major transient risk factor
Major persistent risk factor
Minor persistent risk factor
Minor transient risk factor
Unprovoked
p < 0.0001
Cumulative hazard
0.0
0.1
0.2
0.3
0
1
2
3
4
5
Time (years)
Number at risk
Subgroups
Major transient risk factor 792 714 674 602 533 408
Major persistent risk factor 135 93 74 63 47 28
Minor persistent risk factor 45 35 32 27 25 21
Minor transient risk factor 185 158 153 131 114 81
Unprovoked 724 605 559 514 443 337

Supplement data

Table S1. Detailed study variable collected

Categories	Collected variables
Minor transient risk factors (ISTH classification)	
Surgery condition	- Date of surgery - Length - Type of intervention - Organ site
Minor leg injury without plaster	- Date of leg injury - Time of reduced mobility
Travel	- Date of travel - length
Minor persistent risk factors (ISTH classification)	
Auto-immune disease	- Date of diagnosis - Rheumatoid arthritis - Ankylosing spondylitis - Rheumatic pseudo polyarthritis - Autoimmune hepatitis - Autoimmune thyroiditis - Systemic sclerosis - Necrotizing vasculopathy, - Polymyositis - Autoimmune pancreatitis, - Autoimmune angiocholitis - Nephritic syndrome - Autoimmune hypothyroidism, - Autoimmune hyperthyroidism - Auto thyroiditis - Lupus - Autoimmune myopathy
Inflammatory diseases	- Date of diagnosis - Sarcoidosis - Multiple sclerosis - Crohn’s disease - Ulcerative colitis
Other risk factors - comorbidities	
Organ dysfunction	Date of diagnosis - Congestive heart failure - Chronic heart diseases including: o Valvular cardiopathy o Rhythmic cardiopathy o Other cardiopathy Chronic respiratory diseases: - Chronic obstructive pulmonary disease - Asthma - Restrictive disease - Bronchiectasis - Interstitial lung disease

	Obstructive sleep apnea Chronic renal disease Chronic hepatic disease Hyperthyroidism Hypothyroidism
Parkinson disease	- Date of diagnosis
Amyotrophic lateral sclerosis	- Date of diagnosis
Paresis or hemiplegia from stroke	- Date of diagnosis - Ischemic - Hemorrhagic - Associated persistent hemiplegia

Table S2. Components of subgroups in original and modified ISTH classification

Original ISTH classification	Modified ISTH classification
MAJOR TRANSIENT FACTOR	**MAJOR TRANSIENT FACTOR**
Major surgery	Major surgery
Plaster cast/fracture of lower limb	Plaster cast/fracture of lower limb
Hospitalization	Hospitalization
	+ Pregnancy or post-partum
	+ Estrogen-containing pill
MINOR TRANSIENT FACTOR	**MINOR TRANSIENT FACTOR**
Pregnancy or post-partum	
Estrogen-containing pill	
Hormonal replacement therapy	Hormonal replacement therapy
Medically assisted procreation	Medically assisted procreation
Travel in the past 3 months	Travel in the past 3 months
>6 hours	>6 hours
Surgery with general anesthesia < 30 minutes	Surgery with general anesthesia < 30 minutes
Minor leg injury	Minor leg injury
MAJOR PERSISTENT	**MAJOR PERSISTENT**
Cancer	Cancer
	+ Amyotrophic lateral sclerosis
MINOR PERSISTENT	**MINOR PERSISTENT**
Auto immune diseases	Auto immune diseases
Inflammatory diseases	Inflammatory diseases
NO MINOR OR MAJOR FACTOR	
Stroke [c]	Stroke [c]
Paresis from ischemic stroke	Paresis from ischemic stroke
Paresis from hemorrhagic stroke	Paresis from hemorrhagic stroke
Hemiplegia	Hemiplegia
Parkinson disease	Parkinson disease
Amyotrophic lateral sclerosis	
Congestive heart failure	Congestive heart failure
Chronic heart diseases	Chronic heart diseases
Valvular cardiopathy	Valvular cardiopathy
Ischemic cardiopathy	Ischemic cardiopathy
Rhythmic cardiopathy	Rhythmic cardiopathy
Other cardiopathy	Other cardiopathy
PAD	PAD
Chronic lung diseases	Chronic lung diseases
COPD	COPD
Asthma	Asthma
Restrictive diseases	Restrictive diseases
ILD	ILD
Bronchiectasis	Bronchiectasis
OSA	OSA
Hypothyroidism	Hypothyroidism
Hyperthyroidism	Hyperthyroidism
Chronic liver diseases	Chronic liver diseases
Renal chronic diseases	Renal chronic diseases

BMI: body mass index; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; Rh: rhesus system PAD: peripheral artery occlusive disease; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; OSA: obstructive sleep apnea

[ac]These patients developed an acute VTE more than 3 months after ischemic or haemorragic stroke

Table S3. Adjudicated causes of death

Subjects, n (%)	N=373
Certainly not due to PE	64 (17.16)
Certainly due to PE	3 (0.80)
Probably not due to PE	142 (38.07)
Probably due to PE	32 (8.58)
Missing data	132 (35.39)
Causes of death	
Acute cardiac failure	16 (4.29)
Acute respiratory failure	43 (11.53)
Arrhythmia	5 (1.34)
Bleeding	14 (3.75)
Cancer	56 (15.01)
Kidney failure	8 (2.14)
Myocardial infarction	7 (1.88)
Septic shock	34 (9.12)
Stroke	14 (3.75)
Trauma	7 (1.88)

PE, pulmonary embolism

Table S4. Characteristics of the 266 patients with major surgery

Variables	n (%)
Age (years), mean (SD)	58.3 (17.7)
<50	80 (30.1)
50-65	76 (28.6)
>65	110 (41.4)
Sex Female	126 (47.4)
BMI, mean (SD)	22 (41)
Tobacco	132 (50.8)
Pack-year, mean (SD)	12.3 (9.7)
Family history of VTE	60 (22.9)
Characteristics of VTE at diagnosis	
Isolated proximal DVT	120 (45.1)
Isolated PE	74 (27.8)
PE + DVT	72 (27.1)
Concomitant drugs	
Platelet aggregation inhibitors	21 (8.0)
Statins	37 (14.0)
Plaster cast/fracture of lower limb	14 (5.3)
Hormone replacement therapy	9 (7.1)
Hospitalization[a]	142 (53.4)
Cancer	29 (10.9)
Stroke	
Paresis from ischemic stroke	6 (2.3)
Paresis from hemorrhagic stroke	2 (0.8)
Hemiplegia	2 (0.8)
Chronic heart diseases	
Valvular cardiopathy	1 (0.4)
Ischemic cardiopathy	16 (6.0)
Rhythmic cardiopathy	6 (2.3)
Other cardiopathy	1 (0.4)
PAD	9 (3.4)
Chronic lung diseases	
COPD	12 (4.5)
Asthma	1 (0.4)
Restrictive diseases	2 (0.8)
ILD	1(0.4)
Bronchiectasis	2(0.8)
OSA	12 (4.5)
Hypothyroidism	4 (1.5)
Hyperthyroidism	0 (0.0)
Chronic Liver diseases	0 (0.0)
Renal chronic diseases	17 (6.4)
Parkinson disease	2 (0.8)
Amyotrophic lateral sclerosis	1 (0.4)
Autoimmune diseases	4 (1.5)
Inflammatory diseases	10 (3.8)
Death	16 (6.0)
VTE recurrence	31 (11.7)

BMI: body mass index; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; Rh: rhesus system PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; OSA: obstructive sleep apnea

[a] *Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness in the past three months before VTE first event.*

Table S5. Influence of individual minor risk factors in univariable analysis

Variables	Total (n = 1881)	Non-recurrent VTE (n=1651)	Recurrent VTE (n= 230)	HR (95% CI)	P-value
Type of intervention					
Endoscopy	9 (0.5)	6 (0.4)	3 (1.3)	4.10 (1.31-12.82)	0.015
Coelioscopy	1 (0.1)	1 (0.1)	0 (0.0)	0.000	0.991
Surgery	45 (2.4)	42 (2.5)	3 (1.3)	0.54 (0.17-1.69)	0.288
Type of surgery					
Ophthalmic	3 (0.2)	3 (0.2)	0 (0.0)	0.000	0.995
Otolaryngology	0 (0.0)	0 (0.0)	0 (0.0)		
Thorax	2 (0.1)	2 (0.1)	0 (0.0)	0.000	0.997
Digestive	14 (0.7)	12 (0.7)	2 (0.9)	1.35 (0.34-5.44)	0.672
Vascular	2 (0.1)	1 (0.1)	1 (0.4)	5.88 (0.82-41.95)	0.077
Gynecologic	9 (0.5)	7 (0.4)	2 (0.9)	1.76 (0.44-7.07)	0.428
Urologic	4 (0.2)	3 (0.2)	1 (0.4)	2.198 (0.31-15.68)	0.432
Plastic	2 (0.1)	2 (0.1)	0 (0.0)	0.000	0.996
Neurologic	4 (0.2)	4 (0.2)	0 (0.0)	0.000	0.994
Orthopedic	5 (0.3)	5 (0.3)	0 (0.0)	0.000	0.993
Leg orthopedic	19 (1.0)	18 (1.1)	1 (0.4)	0.428 (0.06-3.05)	0.397
Length between surgery and VTE>30 days	36 (56.2)	30 (52.6)	6 (85.7)	4.76 (0.57-39.54)	0.149
Chronic lung disease	**147 (7.8)**	**125 (7.6)**	**22 (9.6)**	**1.42 (0.20-10.10)**	**0.125**
COPD	113 (6.0)	96 (5.8)	17 (7.4)	1.39 (0.85-2.29)	0.188
Asthma	15 (0.8)	15 (0.9)	0 (0.0)	0.000	0.991
Restrictive diseases	22 (1.2)	20 (1.2)	2 (0.9)	0.91(0.23-3.67)	0.898
ILD	14 (0.7)	11 (0.7)	3 (1.3)	2.34 (0.75-7.31)	0.144
Bronchiectasis	23 (1.2)	18 (1.1)	5 (2.2)	2.13(0.88-5.17)	0.095
Auto immune diseases	**82 (4.4)**	**72 (4.4)**	**10 (4.3)**	**1.05 (0.56-1.97)**	**0.888**
Autoimmune hypothyroidism	3 (0.2)	3 (0.2)	0 (0.0)	0.00	0.991
Auto immune hyperthyroidism	7 (0.4)	6 (0.4)	1 (0.4)	1.43 (0.20-10.19)	0.722
Systemic sclerosis	3 (0.2)	3 (0.2)	0 (0.0)	0.00	0.991
Necrotizing vasculopathy	0 (0.0)	0 (0.0)	0 (0.0)		
Polymyositis	0 (0.0)	0 (0.0)	0 (0.0)		
Autoimmune pancreatitis	5 (0.3)	4 (0.2)	1 (0.4)	1.99 (0.28-14.18)	0.493
Autoimmune cholangitis	1 (0.1)	1 (0.1)	0 (0.0)	0.000	0.991
Autoimmune hepatitis	2 (0.1)	2 (0.1)	0 (0.0)		
Lupus	6 (0.3)	6 (0.4)	0 (0.0)	0.000	0.992
Auto immune myopathy	2 (0.1)	2 (0.1)	0 (0.0)	0.000	0.992
Rhizomelic pseudo polyarthritis	20 (1.1)	18 (1.1)	2 (0.9)		
Ankylosing spondylitis	10 (0.5)	8 (0.5)	2 (0.9)		
Rheumatoid arthritis	20 (1.1)	16 (1.0)	4 (1.7)	1.84(0.31-2.98)	0.227
Inflammatory diseases	**25 (1.3)**	**22 (1.3)**	**3 (1.3)**	**0.95 (0.31-2.98)**	**0.934**
Multiple sclerosis	4 (0.2)	4 (0.2)	0 (0.0)	0.000	0.993
Sarcoidosis	6 (0.3)	5 (0.3)	1 (0.4)	1.56 (0.22-11.15)	0.656
Crohn's disease	5 (0.3)	5 (0.3)	0 (0.0)	0.000	0.991
Ulcerative colitis	11 (0.6)	9 (0.5)	2 (0.9)	1.41 (0.35-5.69)	0.626

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; OSA: obstructive sleep apnea

Table S6. Comparison between recurrence risk stratification of excluded patients with long-term anticoagulation and analyzed patients

Variables (ISTH classification)	Included patients (i.e., stopped anticoagulation) (n = 1881) n (%)	Patients on long-term anticoagulation (n= 1983) n (%)	P-value
Original five-class ISTH classification			<0.001
Major transient risk factors	501 (26.6)	374 (18.9)	
Major persistent risk factors	129 (6.9)	525 (26.5)	
Minor persistent risk factors	70 (3.7)	79 (4.0)	
Minor transient risk factors	464 (24.7)	213 (10.7)	
Unprovoked VTE	717 (38.1)	792 (39.9)	
Characteristics of VTE at diagnosis			<0.001
Isolated DVT	782 (41.7)	602 (32.9)	
Isolated PE	530 (28.3)	544 (29.7)	
PE + DVT	562 (30.0)	685 (37.4)	
Age (years)			<0.001
<50	709 (37.7)	329 (17.2)	
50-65	419 (22.3)	444 (23.2)	
>65	752 (40.0)	1138 (59.5)	
Length of anticoagulation (days)			
>360	463 (24.6)	-	
180-360	871 (46.3)	-	
90-180	547 (29.1)	-	

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis

Table S7. Comparison between baseline characteristics of excluded patients with long-term anticoagulation and included patients who stopped anticoagulation

Variables	Included patients (i.e., stopped anticoagulation) (n = 1881) n (%)	Patients on long-term anticoagulation (n= 1983) n (%)	P-value
Age (years), mean (SD)	56.85 (19.3)	66.56(16.7)	<0.001
<50	709 (37.7)	329 (17.2)	<0.001
50-65	419 (22.3)	444 (23.2)	
>65	752 (40.0)	1138 (59.5)	
Gender (women)	1043 (55.4)	964 (48.6)	<0.001
BMI			
Underweight <18.5	47 (2.6)	81(4.4)	0.006
Normal [18.5-25]	752 (40.9)	714 (38.3)	
Overweight >25	1040 (56.6)	1067 (57.3)	
Blood group			
A	752 (50.1)	683 (49.0)	0.229
B	197 (13.1)	168(12.1)	
AB	65 (4.3)	82 (5.9)	
O	488 (32.5)	460 (33.0)	
Rh -	1197 (83.0)	1089 (82.3)	0.661
Rh +	223 (15.5)	208 (15.7)	
Tobacco	863 (46.7)	979 (52.0)	0.001
Pack-year, mean (SD)	13.0 (10.4)	15.7 (11.4)	<0.001
Family history of VTE	490 (26.3)	454 (23.6)	0.059
Characteristics of VTE at diagnosis			<0.001
Isolated proximal DVT	782 (41.7)	602 (32.9)	
Isolated PE	530 (28.3)	544 (29.7)	
PE + DVT	562 (30.0)	685 (37.4)	
Concomitant drugs			
Platelet aggregation inhibitors	189 (10.1)	389 (19.9)	<0.001
Statins	174 (9.3)	277 (14.2)	<0.001
Major surgery	266 (14.1)	197 (9.9)	<0.001
Plaster cast/fracture of lower limb	66 (3.5)	23 (1.2)	<0.001
Pregnancy	52 (4.3)	11 (0.9)	<0.001
Post-partum	44 (3.7)	7 (0.6)	<0.001
Estrogen-containing pill	297 (28.5)	73 (7.6)	<0.001
Hormone replacement therapy	60 (5.8)	18 (1.9)	0.021
Medically assisted procreation	3 (0.3)	12 (1.4)	<0.001
Hospitalization[a]	387 (20.6)	503 (25.4)	<0.001
Cancer	129 (6.9)	525 (26.5)	<0.001
Travel in the past 3 months	237 (12.6)	191 (9.7)	0.004
Length > 6 hours	171 (74.3)	134 (72.8)	0.813
Surgery with general anesthesia < 1h	64 (3.4)	72 (3.6)	0.766
Minor leg injury	26 (1.4)	10 (0.5)	0.008
Length of splint (days), mean (SD)	29.71 (13.6)	18.5 (11.4)	0.056
Stroke			
Paresis from ischemic stroke	37 (2.0)	110 (5.5)	<0.001
Paresis from hemorrhagic stroke	8 (0.4)	18 (0.9)	0.102
Hemiplegia	25 (1.3)	73 (3.7)	<0.001
Congestive heart failure	31 (1.6)	85 (4.3)	<0.001
Chronic heart diseases	139 (7.4)	236 (11.9)	<0.001
Valvular cardiopathy	2 (0.1)	1 (0.1)	
Ischemic cardiopathy	73 (3.9)	129 (6.5)	
Rhythmic cardiopathy	48 (2.6)	61 (3.1)	
Other cardiopathy	16 (0.9)	45 (2.3)	
PAD	52 (2.8)	133 (6.8)	<0.001
Chronic lung diseases	147 (7.8)	192 (9.7)	0.046
COPD	113 (6.0)	138 (7.0)	0.257

Asthma	15 (0.8)	11 (0.6)	0.468
Restrictive diseases	22 (1.2)	43 (2.2)	0.022
ILD	14 (0.7)	25 (1.3)	0.149
Bronchiectasis	23 (1.2)	20 (1.0)	0.631
OSA	64 (3.4)	68 (3.4)	1.00
Hypothyroidism	43 (2.3)	75 (3.8)	0.009
Hyperthyroidism	10 (0.5)	12 (0.6)	0.929
Chronic Liver diseases	7 (0.4)	8 (0.4)	1.000
Renal chronic diseases	67 (3.6)	110 (5.5)	0.004
Parkinson disease	18 (1.0)	12 (0.6)	0.288
Amyotrophic lateral sclerosis	6 (0.3)	2 (0.1)	0.256
Autoimmune diseases	25 (1.3)	37 (1.9)	0.230
Inflammatory diseases	82 (4.4)	93 (4.7)	0.677
Death	121 (6.4)	424 (21.4)	<0.001

BMI: body mass index; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; Rh: rhesus system PAD: peripheral artery disease; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; OSA: obstructive sleep apnea

[a] *Confined to bed in hospital (only "bathroom privileges") for ≥3 days due to an acute illness, or acute exacerbation of a chronic illness in the past three months before VTE first event.*