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Venous Thromboembolism Characteristics and Outcomes Among RIETE Patients Tested & Untested for Inherited Thrombophilia

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Abstract:
Inherited thrombophilia (IT) workup is commonly pursued in venous thromboembolism (VTE) patients. Recent American Society of Hematology (ASH) guidelines recommend a selective approach to IT testing, nevertheless, evidence on whether thrombophilia testing can actually improve patient-important outcomes through tailored management is limited. Data from the large prospective RIETE registry was analyzed to compare VTE risk factors, management and outcomes between patients who were tested for IT and untested patients, during anticoagulant treatment and following its discontinuation. Among 103,818 patients enrolled in RIETE, 21,089 (20.3%) were tested for IT, 8,422 (8.1%) tested positive, and 82,729 (79.7%) were not tested. IT testing was more frequent in patients with VTE provoked by minor risk factors, and less common in those with major risk factors like surgery or active cancer. Choices of anticoagulant treatment did not differ based on IT testing results. Untested patients exhibited inferior outcomes across all VTE categories, with higher rates of VTE recurrence, major bleeding, mortality, and notably, cancer-related mortality. After treatment discontinuation, IT-negative patients with surgically provoked VTE showed lower recurrence rates. For immobilization-related VTE as well as in estrogen-related VTE, no significant differences in recurrence rates were observed between IT-negative and IT-positive patients. However IT-negative patients with pregnancy or postpartum-related VTE, had significantly lower recurrence rates. Patients with unprovoked VTE, particularly those testing positive for IT, had high recurrence rates post-treatment. These findings underscore the complex role of IT testing in managing VTE, supporting personalized treatment strategies that consider VTE risk factors and comorbidities.

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Key points

- In a RIETE registry analysis of 103,818 VTE patients, 20.3% were tested for IT, showing a substantial variance in outcomes.
- A thoughtful IT testing approach should consider patients’ VTE risk factors and comorbidities.

Abstract

Inherited thrombophilia (IT) workup is commonly pursued in venous thromboembolism (VTE) patients. Recent American Society of Hematology (ASH) guidelines recommend a selective approach to IT testing, nevertheless, evidence on whether thrombophilia testing can actually improve patient-important outcomes through tailored management is limited. Data from the large prospective RIETE registry was analyzed to compare VTE risk factors, management and outcomes between patients who were tested for IT and untested patients, during anticoagulant treatment and following its discontinuation. Among 103,818 patients enrolled in RIETE, 21,089 (20.3%) were tested for IT, 8,422 (8.1%) tested positive, and 82,729 (79.7%) were not tested. IT testing was more frequent in patients with VTE provoked by minor risk factors, and less common in those with major risk factors like surgery or active cancer. Choices of anticoagulant treatment did not differ based on IT testing results. Untested patients exhibited inferior outcomes across all VTE categories, with higher rates of VTE recurrence, major bleeding, mortality, and notably, cancer-related mortality. After treatment discontinuation, IT-negative patients with surgically provoked VTE showed lower recurrence rates. For immobilization-related VTE as well as in estrogen-related VTE, no significant differences in recurrence rates were observed between IT-negative and IT-positive patients. However IT-negative patients with pregnancy or postpartum-related VTE, had significantly lower recurrence rates. Patients with unprovoked VTE, particularly those testing positive for IT, had high recurrence rates post-treatment. These findings underscore the complex role of IT testing in managing VTE, supporting personalized treatment strategies that consider VTE risk factors and comorbidities.

Keywords:

Venous thrombosis, Venous thromboembolism, Anticoagulants, Thrombophilia, Hereditary

Introduction

Inherited thrombophilia (IT) is a hereditary predisposition to venous thromboembolism (VTE), and genetic defects in this clinical contexts include deficiencies of the endogenous anticoagulants antithrombin (AT), protein C (PC), and protein S (PS), and gain-of-function polymorphisms in factor V (factor V Leiden, FVL) and prothrombin (PT G20210A) [**1-5**]. Thrombophilia testing is commonly conducted in patients with VTE, especially in those who are young, experience recurrent episodes, have thrombosis at unusual sites, or have a family history of VTE. While testing VTE patients or their relatives may result in positive findings, the incremental value of identifying thrombophilia is potentially low. Despite the growing understanding of VTE etiology, testing for IT often does not aid in guiding clinical decisions and, therefore, should not be conducted routinely [**1,2**]. Current guidelines on VTE treatment recommend indefinite anticoagulant treatment for most patients after a first episode of unprovoked VTE [**6-8**]. In light of this, IT testing should be performed in a highly selective manner. Recent guidelines put forth by the American Society of Hematology (ASH) recommend restricting IT testing to patients who have experienced VTE associated with substantial transient or hormonal risk factors, those with thrombosis occurring at unusual sites, individuals who are considering thromboprophylaxis due to minor provoking risk factors associated with familial severe IT, pregnant women with a family history of severe IT, and certain cancer patients with a family history of VTE. In most other cases, the practice of IT testing is discouraged [**9**]. Nevertheless, evidence on whether thrombophilia testing can actually improve patient-important outcomes through tailored management is limited yet. Recognizing the gaps in current knowledge, we used data from the prospective, international RIETE (Registro Informatizado de Enfermedad TromboEmbólica) [**10**] to explore and compare clinical characteristics and VTE outcomes between patients who were tested for IT and patients who were not tested.

Methods

Study design and participants

RIETE is an ongoing registry of acute VTE patients, spanning 194 centers across 26 countries in Europe, the Americas and Asia (ClinicalTrials.gov identifier: NCT02832245). The rationale, design and methodology of RIETE has been previously described [**10**]. The study included patients with objectively confirmed VTE consecutively enrolled in RIETE. All diagnostic and therapeutic decisions were determined solely by the attending physicians, as the study protocol did not mandate any specific medical interventions. Patients participating in ongoing blinded randomized controlled trials addressing VTE treatment are excluded from RIETE. Written informed consent was obtained from all participants in compliance with local ethical standards.

Data acquisition

The participating centers in RIETE attempt to enroll consecutive patients diagnosed with VTE. At each collaborating center, attending physicians gather and record data using a computer-based case report form, which is then securely transmitted to the registry's coordinating center via a dedicated website. To uphold confidentiality, a distinct identification number is assigned to each patient. The coordinating center of RIETE is responsible for data management and quality control, including thorough checks for inconsistencies or errors, resolved through direct communication with local coordinators. The RIETE reporting system tracks the duration of anticoagulant treatment, noting the start and end dates, and systematically updates outcomes and their occurrence dates during follow-up visits. Patients are eligible for inclusion if they have a minimum follow-up period of 80 days. Data for this study were extracted from the registry database on May 31, 2023, covering patient enrolments since 2001.

Variables and outcomes definitions

The variables recorded in RIETE include patient baseline characteristics, coexisting medical conditions, risk factors for VTE, treatment following VTE diagnosis, and outcomes during anticoagulant treatment and after its discontinuation. Immobility is defined as at least 4 days of complete bed rest, including bathroom privileges, within the 2 months before VTE diagnosis. Surgical patients are defined as those undergoing surgery within 2 months prior to VTE. Active cancer refers to newly diagnosed or ongoing malignancy not in remission, or when patients are receiving anti-neoplastic treatment. A history of cancer is noted when the disease is in remission and no cancer treatment has been administered for at least 90 days before VTE diagnosis. Hormonal therapy includes treatments with estrogen, progesterone, combined oral contraceptives, and selective estrogen receptor modulators. VTE following in-vitro fertilization procedures involving such hormonal therapies within 2 months is also categorized under hormonal therapy. Unprovoked VTE is identified in the absence of factors like active cancer, recent immobility, surgery, central venous catheters, hormone use, pregnancy, postpartum status, or prolonged air travel. Patients are documented as having FVL and PT G20210A mutation, whether heterozygous or homozygous carriers, or low activated protein C resistance (APCR) in the case of FVL. Combined thrombophilia refers to patients with more than one positive test for IT.

Primary clinical outcomes include all-cause mortality, confirmed VTE recurrence, and major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) [**11**]. Non-major bleeding is any overt bleeding not meeting major bleeding criteria. Recurrent VTE is a new VTE event occurring after the initial diagnosis, regardless of completed previous treatment. Fatal PE is death within ten days of PE diagnosis when no other cause of death is evident. Supplementary data on the cause of death and the nature of bleeding are also collected, although outcome adjudication is not centrally conducted.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation (SD) or median [interquartile range (IQR) or range, as appropriate]. Categorical variables are presented as counts and percentages. The chi-square test (two-sided) and Fisher's Exact Test (two-sided) were used for comparing categorical variables, considering a *p*-value of 0.05 or less as statistically significant. Student's t-test and the Mann-Whitney U test were used for continuous variables, as applicable. The incidence rates of outcomes (VTE recurrences, major bleeding, and mortality) during anticoagulant treatment and following its discontinuation were calculated as cumulative incidence (events per 100 patient-years). Patients tested for IT were compared with those not tested. Untested patients serve as the reference group for all comparisons. To further assess the impact of IT testing on clinical outcomes, subgroup analyses were conducted based on the categorization of VTE events into unprovoked VTE, VTE provoked by specific risk factors, and VTE at unusual sites, adhering to the framework suggested by the ASH guidelines on IT testing [**9**]. All statistical analyses were conducted with the SPSS (Statistical Package for Social Sciences) program (SPSS for Windows version 25.0, SPSS Inc. Chicago, Illinois, USA).

Role of the funding source

The sponsors of RIETE have not been involved in designing the registry, nor do they possess any rights to access the database, or to review or comment on studies from RIETE prior to publication.

The study was approved by the IRB at Sheba Medical Center and at each center participating in RIETE. Written informed consent was obtained from all participants in compliance with local ethical standards.

Results

Patient characteristics and VTE risk factors

Out of 103,818 VTE patients enrolled in RIETE by May 31st, 2023, 21,089 (20.3%) were tested for IT. Baseline characteristics of these patients are presented in **Table 1**. Tested individuals were notably younger, with a higher prevalence of isolated deep venous thrombosis (DVT) and less pulmonary embolism (PE) compared to untested patients ($p<0.001$). Unusual site thrombosis involving the splanchnic or cerebral veins was also more prevalent amongst patients who underwent IT testing ($p<0.001$). IT testing varied with VTE risk factors, being more common in patients with prior VTE events, estrogen exposure, or pregnancy-related events, and less frequent in those with surgery, immobilization, or cancer.

VTE treatment strategies

Most patients (86%) initially received parenteral anticoagulants (low molecular-weight heparin [LMWH], unfractionated heparin [UFH], and fondaparinux), with no significant differences in rates between those tested for IT and untested patients. Similar patterns were observed in the rates of thrombolysis and the insertion of inferior vena cava filters across these groups. Most also transitioned to oral anticoagulants for long-term treatment. Among IT-tested patients, vitamin K antagonists (VKAs) were preferred (65%), with direct oral anticoagulants (DOACs) used less frequently compared to untested patients ($p<0.001$). Percentage rates of patients treated with LMWH, VKAs, and DOACs were comparable between those who tested positive for IT and those who tested negative (**Table 2**).

Clinical outcomes during anticoagulant treatment and following its discontinuation

VTE-outcomes during anticoagulant treatment and following its discontinuation are presented in **Table 3**. During anticoagulant therapy, untested patients showed higher VTE recurrence rates (3.46 [3.31-3.62]) compared to those tested for IT (2.58 [2.38-2.80]), regardless of IT status (p<0.001). They also exhibited higher rates of major bleeding (4.44 [4.27-4.61]), all-cause mortality (16.2 [15.9-16.5]), PE-related mortality (1.32 [1.23-1.41]), and bleeding-related mortality (0.65 [0.58-0.71]), compared with tested patients (p<0.001). Major bleeding and all-cause mortality rates were the lowest in patients with FVL and PT G20210A mutations.

Anticoagulant treatment was discontinued in 36,097 patients, of whom 10,048 (27.8%) were tested for IT, 3,488 were positive. Untested patients continued to exhibit higher incidences of VTE recurrence (8.69 [8.35-9.05]), major bleeding (1.14 [1.03-1.27]), and all-cause mortality (13.1 [12.7-13.5]), PE-related mortality (0.17 [0.13-0.22]) and bleeding-related mortality (0.62 [0.54-0.72]) than tested patients (p<0.001).

These higher rates of adverse outcomes remained evident even after excluding cancer patients from the analysis, albeit to a lesser extent. Nonetheless, untested patients uniformly exhibited higher cancer-related mortality both during anticoagulation treatment (6.15 [5.96-6.36] vs. 0.82 [0.71-0.94], p<0.001) and following its discontinuation (5.18 [4.92-5.44] vs. 0.97 [0.84-1.12], p<0.001) compared to tested patients, indicating a substantial impact of cancer on outcomes.

Outcomes according to IT testing and patient groups of interest

VTE-related outcomes according to IT-testing across various patient groups of interest, are presented in **Table 4**. Across all VTE patient groups, the duration of anticoagulant treatment was consistently longer for those tested for IT (p<0.001). Across all categories, untested patients experienced higher rates of major bleeding, all-cause and VTE-related mortality, and notably, cancer-related mortality. Excluding patients with splanchnic vein thrombosis, IT-positive individuals typically exhibited the lowest rates of major bleeding.

VTE provoked by surgery:

Rates of VTE recurrence on treatment were similar between tested (4.63 [3.78-5.62]) and untested patients (5.46 [4.78-6.20]). Following treatment discontinuation, IT-negative patients had significantly lower VTE recurrence rates (3.42 [2.57-4.48]), while IT-positive patients had higher rates (7.25 [5.42-9.50]), although not statistically significant when compared to untested patients.

VTE provoked by immobilization for 4 days or more due to non-surgical reasons:

Patients tested for IT and IT-negative patients had lower recurrence rates on anticoagulant treatment than untested patients (2.67 [2.15-3.29] and 2.26 [1.64-3.03] vs. 3.57 [3.24-3.94], $p<0.05$ and $p<0.01$, respectively). After discontinuation of anticoagulant treatment, while tested patients maintained lower recurrence rates, the difference between IT-negative (6.09 [5.06-7.27]) and IT-positive (6.95 [5.38-8.83]) patient was not statistically significant.

VTE provoked by estrogen use, pregnancy and post-partum

In estrogen-related VTE, tested patients had lower recurrence rates during treatment (1.56 [1.08-2.17]) than untested ones (2.55 [1.96-3.26], $p<0.05$), with IT-negative patients exhibiting even lower rates (1.36 [0.79-2.20], $p<0.05$). Post-therapy recurrence rates were similar between IT-negative (2.31 [1.63-3.17]) and IT-positive (2.43 [1.56-3.62]) groups.
In pregnancy or postpartum-related VTE, recurrence rates during treatment were comparable between untested patients and tested patients, regardless of testing results. Upon treatment discontinuation, IT-negative patients had significantly lower recurrence rates (0.23 [0.01-1.11]) as opposed to IT-positive patients (2.27 [1.05-4.31], $p<0.01$).

Unprovoked DVT and PE

On-treatment VTE recurrence rates did not significantly differ between those tested and untested for IT, as well as between IT-positive and IT-negative patients, yet AT deficiency was specifically associated with the highest on-treatment recurrence rates (3.46 [1.51-6.84], $p<0.001$). Following the discontinuation of anticoagulant treatment, the recurrence rates spiked, highlighting a continuous risk, particularly for IT-positive patients (9.90 [8.83-11.07]).

Unusual site thrombosis

Among patients with splanchnic vein thrombosis, rates of recurrence during anticoagulant treatment did not significantly differ among all groups. Following treatment discontinuation, tested patients, irrespective of their IT status, exhibited significantly lower recurrence rates (1.00 [0.17-3.31]) compared to those untested (7.39 [4.11-12.32], $p<0.01$), with no reported recurrences in IT-positive patients. Similarly, in patients with CSVT, rates of on-treatment VTE recurrence were comparable between the groups, and these similarities persisted following treatment discontinuation, although rate of recurrent events was low, with no reported recurrences in IT-positive patients.

Discussion

In this study, we report the differences in characteristics, treatment, and VTE outcomes between patients enrolled in the large prospective RIETE registry who were tested for IT and those who were not. Approximately one fifth of RIETE patients were tested for IT, at their physician's discretion. These patients were generally younger and more likely to present with unusual site thrombosis, events provoked by estrogen exposure, or pregnancy-related events or have prior VTE events. IT testing was less frequent among VTE patients with pro-thrombotic risk factors like recent surgery, immobilization, or active cancer. The impact of IT-testing results on post-treatment outcomes varied across subgroups, depending on the risk factors leading to the initial VTE event, highlighting a complex interplay between IT testing and patient outcomes that extends beyond mere diagnostic assessment.

Untested patients showed higher rates of VTE recurrence, major bleeding, and mortality during anticoagulant treatment and following its discontinuation. Furthermore, untested patients consistently showed higher rates of cancer-related mortality, underscoring the profound impact of cancer on their outcomes. Notably, most (91.5%) RIETE patients with cancer were not tested for IT. Specifically, guidelines on VTE management recognize active cancer as a persistent risk factor for VTE, thus warranting long-term anticoagulant treatment and reducing the need for IT testing [**12-14**].

Similarly, patients with unprovoked VTE have a substantial risk of recurrent thrombotic events, and are likely to benefit from extended anticoagulant treatment [**15,16**]. Only 22.9% of RIETE patients with unprovoked VTE underwent IT testing. The utility of IT testing in these patients is reduced because, while patients with IT exhibit higher rates of VTE recurrence following treatment discontinuation, those without IT also continue to face a consistently high risk of recurrence. Guidelines on VTE management typically advise indefinite anticoagulant treatment for most patients with unprovoked VTE [**6-8**], reflecting a broad approach that prioritizes long-term prevention of recurrence over selective testing outcomes. In such cases, a strategy of thrombophilia testing followed by tailored treatment may result in fewer patients receiving indefinite anticoagulation but potentially increases the risk of recurrent VTE in patients discontinued based on negative IT results [**9**].

Surgical and immobilization-related VTE showed little variance in recurrence rates across IT testing groups during anticoagulant treatment. Post-treatment, recurrence rates were lower in IT-negative patients for surgical VTEs, while the effect of IT appeared less pronounced in patients where the VTE was triggered by prolonged immobilization. These findings only partially align with the ASH guideline panel's recommendations, which suggest against IT testing in patients who have completed primary treatment for surgically provoked VTEs, but suggest IT testing in patients with VTE provoked by a non-surgical major transient risk factors, and prescribing indefinite anticoagulant treatment only to those testing positive [**9**]. Nevertheless, while most patients with VTE provoked by temporary risk factors are recommended to discontinue anticoagulant therapy after primary treatment, testing for thrombophilia would lead to indefinite anticoagulant treatment for patients with IT, increasing bleeding risk and potentially reducing overall clinical benefit. Reflecting a similar trend in clinical practice, only 18.7% of RIETE patients with VTE following recent surgery and 16.4% with VTE after immobilization were tested for IT. This pattern in the RIETE cohort, predating the 2023 guidelines, suggests a longstanding clinical inclination towards selective IT testing in these patient categories. It should be noted, however, that IT-positive patients still exhibited considerable recurrence rates following treatment discontinuation, therefore suggesting that in cases of a known thrombophilia, extending anticoagulant treatment indefinitely may be considered, diverging from current management guidelines [**6-8**].

In RIETE, 40.5% of women with estrogen-associated VTE and 47.3% with pregnancy-associated VTE or VTE during the postpartum period were tested for IT, highlighting a focus on testing in these specific patient groups. Additionally, IT-negative women with pregnancy or postpartum-related VTE experienced significantly lower recurrence rates after treatment discontinuation, indicating a potential to safely stop anticoagulant treatment in this subgroup. However, IT-positive women maintained higher recurrence rates, supporting the need for continued anticoagulation. These findings align with ASH guidelines, which suggest IT testing for women with estrogen, pregnancy or postpartum-related VTE after completing primary treatment, and indefinite anticoagulant treatment for those diagnosed with an IT [**9**]. This approach underscores the value of IT testing in personalizing treatment plans, potentially enhancing safety and efficacy by adjusting the duration of therapy based on IT testing.

The relationship between IT testing and subsequent treatment outcomes in patients with unusual site thromboses, is more complex. While on-treatment recurrence rates showed no differences across IT testing groups, post-treatment outcomes were inferior for untested patients, suggesting the impact of comorbidities, especially among patients with splanchnic vein thrombosis. While tested patients generally had better outcomes, even IT-positive individuals had no recurrences, although the overall number of events was low. Therefore, while the definitive role of IT testing in guiding treatment duration for unusual site thrombosis is still unclear, it is advisable that patients with persistent risk factors and those with unprovoked thromboses at unusual sites might be considered for indefinite anticoagulant treatment [**17,18**]. In patients with unusual site thrombosis planning to discontinue anticoagulant treatment, the ASH guidelines suggest testing for IT as well as acquired types of thrombophilia, with indefinite anticoagulation in patients testing positive [**9**].

RIETE data indicates comparable treatment outcomes between the subgroup of patients who tested negative for IT and the broader group who underwent IT testing, suggesting that comorbidities and treatment protocols may impact outcomes more than IT itself. Furthermore, VTE treatment across patient groups was consistent, irrespective of IT status, thereby suggesting that IT detection may not substantially alter VTE management.

The current study presents several strengths, including a comprehensive, prospective data collection from the large RIETE cohort, providing insights into the implications of IT testing during and post-anticoagulant therapy. The inclusion of patients with all types of IT, the high rates of successful follow-up while reflecting real-world management strategies, contribute to the study's external validity. Limitations include the observational nature of the registry, with IT testing reported by individual centers without central verification and the absence of central adjudication for events and outcomes.

This study uniquely demonstrates the complex interplay between IT testing and VTE recurrence in diverse patient subgroups, offering valuable real-world evidence that may inform future revisions of clinical guidelines and practices. Overall, our findings highlight an intricate role of IT testing in tailoring VTE management strategies, indicating that knowledge of IT status may occasionally assist clinicians in stratifying patients more precisely by their risk of recurrence following treatment discontinuation. This underscores the need for a thoughtful approach to IT testing, one that is adapted to specific patient groups where it can meaningfully affect management decisions and outcomes, given the critical importance of VTE risk factors and underlying conditions.

Author contributions

Study conception and design: L Waldman Radinsky, O Cohen, M Monreal; Interpretation of the data: all authors; Drafting of the manuscript: L Waldman Radinsky, O Cohen; Critical revision of the manuscript: all authors; Final approval of the manuscript: all authors.

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COI notes

The authors declare no competing interests.

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APPENDIX
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Table 1: Baseline characteristics of VTE patients in RIETE, according to inherited thrombophilia testing and its results.

	Not tested	**Tested**	**Positive IT (ALL IT types)**	**Protein C deficiency only**	**Protein S deficiency only**	**Anti-thrombin deficiency only**	**Factor V Leiden only**	**Pro-thrombin mutation only**	**Combined IT**	**Negative IT**
Patients, N	***82,729***	***21,089***	***8,422***	***294***	***726***	***240***	***2,248***	***1,434***	***3,480***	***12,667***
Demographics										
Male gender	40,214 (49%)	11,021 (52%)‡	4,592 (55%)‡	167 (57%)†	327 (45%)	147 (61%)‡	1,271 (57%)‡	755 (53%)†	1,925 (55%)‡	6,429 (51%)
Age (mean years±SD)	68±16	55±18‡	53±18‡	52±17‡	52±19‡	50±19‡	50±17‡	52±17‡	57±18‡	56±18‡
Body weight (mean kg±SD)	76±16	78±16‡	78±17‡	77±14	75±16	79±18†	80±17‡	79±16‡	78±17‡	78±16‡
Initial VTE presentation										
Pulmonary embolism	44,225 (53%)	10,164 (48%)‡	3,747 (44%)‡	136 (46%)*	316 (44%)‡	117 (49%)	779 (35%)‡	685 (48%)‡	1,714 (49%)‡	6,417 (51%)
Isolated lower-limb DVT	32,057 (39%)	9,116 (43%)‡	3,968 (47%)‡	135 (46%)*	353 (49%)‡	102 (43%)	1,264 (56%)‡	642 (45%)‡	1,472 (42%)‡	5,148 (41%)
Isolated upper-limb DVT	3,494 (4.2%)	891 (4.2%)	306 (3.6%)†	9 (3.1%)	20 (2.8%)	7 (2.9%)	91 (4.0%)	38 (2.6%)†	141 (4.1%)	585 (4.6%)
Splanchnic vein thrombosis	386 (0.47%)	223 (1.1%)‡	93 (1.1%)‡	4 (1.4%)	9 (1.2%)†	8 (3.3%)‡	6 (0.27%)	23 (1.6%)‡	43 (1.2%)‡	130 (1.0%)‡
Superficial vein thrombosis	1,777 (2.1%)	441 (2.1%)	199 (2.4%)	5 (1.7%)	20 (2.8%)	5 (2.1%)	84 (3.7%)‡	26 (1.8%)	59 (1.7%)	242 (1.9%)
Cerebral sinus vein thrombosis	95 (0.11%)	105 (0.50%)‡	47 (0.56%)‡	0	4 (0.55%)*	1 (0.42%)	7 (0.31%)*	14 (0.98%)‡	21 (0.60%)‡	58 (0.46%)‡
Other locations	695 (0.84%)	149 (0.71%)	62 (0.74%)	5 (1.7%)	4 (0.55%)	0	17 (0.76%)	6 (0.42%)	30 (0.86%)	87 (0.69%)
Risk factors for VTE										
Recent surgery	9,018 (11%)	2,075 (9.8%)‡	761 (9.0%)‡	26 (8.8%)	76 (10%)	20 (8.3%)	164 (7.3%)‡	155 (11%)	320 (9.2%)†	1,314 (10%)
Immobilization ≥4 days	19,199 (23%)	3,762 (18%)‡	1,313 (16%)‡	45 (15%)†	127 (17%)‡	30 (13%)‡	297 (13%)‡	229 (16%)‡	585 (17%)‡	2,449 (19%)
Active cancer	17,124 (21%)	1,595 (7.6%)‡	619 (7.3%)‡	14 (4.8%)‡	42 (5.8%)‡	12 (5.0%)‡	106 (4.7%)‡	88 (6.1%)‡	357 (10%)‡	976 (7.7%)
Estrogen use	3,466 (4.2%)	2,365 (11%)‡	917 (11%)‡	20 (6.8%)*	79 (11%)‡	16 (6.7%)	286 (13%)‡	200 (14%)‡	316 (9.1%)‡	1,448 (11%)
Pregnancy or postpartum	676 (0.8%)	608 (2.9%)‡	295 (3.5%)‡	11 (3.7%)‡	43 (5.9%)‡	15 (6.3%)‡	75 (3.3%)‡	58 (4.0%)‡	93 (2.7%)‡	313 (2.5%)
None of the above (unprovoked)	40,190 (49%)	11,945 (57%)‡	4,986 (59%)‡	186 (63%)‡	404 (56%)‡	156 (65%)‡	1,426 (63%)‡	801 (56%)‡	2,013 (58%)‡	6,959 (55%)
Prior VTE	11,300 (14%)	3,769 (18%)‡	1,976 (23%)‡	96 (33%)‡	175 (24%)‡	81 (34%)‡	580 (26%)‡	292 (20%)‡	752 (22%)‡	1,793 (14%)

Patients not tested for inherited thrombophilia were used as reference for all comparisons with the remaining subgroups
$^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$.

Abbreviations: DVT, Deep venous thrombosis; IT, Inherited thrombophilia; PE, Pulmonary embolism; SD, Standard deviation; VTE, Venous thromboembolism

Table 2: VTE treatment strategies according to inherited thrombophilia testing, its results, and by thrombophilia subgroups.

	Not tested	**Tested**	**Positive IT (ALL IT types)**	**Protein C deficiency only**	**Protein S deficiency only**	**Anti-thrombin deficiency only**	**Factor V Leiden only**	**Pro-thrombin mutation only**	**Combined IT**	**Negative IT**
Patients, N	***82,729***	***21,089***	***8,422***	***294***	***726***	***240***	***2,248***	***1,434***	***3,480***	***12,667***
Initial therapy										
LMWH	71,327 (86%)	18,097 (86%)	7,387 (88%)‡	258 (88%)	649 (89%)*	206 (86%)	1,946 (87%)	1,276 (89%)†	3,052 (88%)*	10,710 (85%)‡
UFH	4,402 (5.3%)	1,201 (5.7%)*	411 (4.9%)	19 (6.5%)	31 (4.3%)	21 (8.8%)*	77 (3.4%)‡	69 (4.8%)	194 (5.6%)	790 (6.2%)‡
Fondaparinux	1,883 (2.3%)	417 (2.0%)†	192 (2.3%)	3 (1.0%)	7 (1.0%)*	7 (2.9%)	77 (3.4%)‡	28 (2.0%)	70 (2.0%)	225 (1.8%)‡
DOACs	3,193 (3.9%)	759 (3.6%)	225 (2.7%)‡	7 (2.4%)	17 (2.4%)*	2 (0.8%)*	99 (4.4%)	25 (1.7%)‡	75 (2.2%)‡	534 (4.2%)
Rivaroxaban	2,122 (2.6%)	637 (3.0%)‡	175 (2.1%)†	5 (1.7%)	12 (1.7%)	2 (0.8%)	82 (3.6%)†	20 (1.4%)†	54 (1.6%)‡	462 (3.6%)‡
Apixaban	969 (1.2%)	112 (0.5%)‡	45 (0.53%)‡	2 (0.7%)	4 (0.5%)	0	15 (0.7%)*	5 (0.3%)†	19 (0.5%)‡	67 (0.5%)‡
Systemic thrombolysis	472 (0.6%)	92 (0.5%)†	38 (0.49%)	1 (0.4%)	3 (0.4%)	4 (1.8%)	7 (0.3%)	6 (0.4%)	17 (0.5%)	54 (0.5%)*
Mechanical thrombolysis	343 (1.1%)	94 (1.3%)	43 (1.6%)*	0	7 (3.1%)*	1 (1.4%)	9 (1.2%)	9 (1.9%)	17 (1.7%)	51 (1.1%)
Inferior vena cava filter	2,167 (2.6%)	421 (2.0%)‡	170 (2.0%)‡	7 (2.4%)	19 (2.6%)	10 (4.2%)	38 (1.7%)†	24 (1.7%)*	72 (2.1%)*	251 (2.0%)‡
No anticoagulant therapy	319 (0.4%)	44 (0.2%)‡	18 (0.21%)*	0	4 (0.5%)	0	5 (0.2%)	4 (0.3%)	5 (0.1%)*	26 (0.2%)†
Long-term therapy										
LMWH	25,872 (31%)	4,634 (22%)‡	1,773 (21%)‡	35 (12%)‡	176 (24%)‡	51 (21%)‡	443 (20%)‡	303 (21%)‡	765 (22%)‡	2,861 (23%)‡
VKAs	40,548 (49%)	13,629 (65%)‡	5,588 (66%)‡	224 (76%)‡	467 (64%)‡	165 (69%)‡	1,434 (64%)‡	962 (67%)‡	2,336 (67%)‡	8,041 (63%)‡
DOACs	11,790 (15%)	2,399 (11%)‡	884 (11%)‡	28 (9.7%)*	69 (9.6%)‡	14 (5.9%)‡	323 (14%)	154 (11%)‡	296 (8.6%)‡	1,515 (12%)‡
Rivaroxaban	5,946 (7.2%)	1,508 (7.2%)	523 (6.2%)‡	19 (6.5%)	41 (5.6%)	12 (5.0%)	205 (9.1%)‡	76 (5.3%)†	170 (4.9%)‡	985 (7.8%)*
Apixaban	4,049 (4.9%)	514 (2.4%)‡	203 (2.4%)‡	8 (2.7%)	13 (1.8%)‡	0	65 (2.9%)‡	37 (2.6%)‡	80 (2.3%)‡	311 (2.5%)‡
Edoxaban	1,442 (1.7%)	279 (1.3%)‡	113 (1.3%)†	1 (0.3%)	11 (1.5%)	1 (0.4%)	35 (1.6%)	30 (2.1%)	35 (1.0%)†	166 (1.3%)‡
Dabigatran	353 (0.4%)	98 (0.5%)	45 (0.53%)	0	4 (0.5%)	1 (0.4%)	18 (0.8%)*	11 (0.8%)	11 (0.3%)	53 (0.4%)
Fondaparinux	830 (1.0%)	148 (0.7%)‡	80 (0.95%)	2 (0.7%)	3 (0.4%)	5 (2.1%)	25 (1.1%)	7 (0.5%)	38 (1.1%)	68 (0.5%)‡
No anticoagulant therapy	634 (0.8%)	64 (0.3%)‡	24 (0.28%)‡	2 (0.7%)	1(0.14%)	2 (0.8%)	7 (0.3%)*	3 (0.2%)*	9 (0.3%)‡	40 (0.3%)‡

Patients not tested for inherited thrombophilia were used as reference for all comparisons with the remaining subgroups
$^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$.

Abbreviations: DVT, Deep venous thrombosis; DOACs, Direct oral anticoagulants; IT, Inherited thrombophilia; LMWH, Low-molecular-weight heparin; PE, Pulmonary embolism; UFH, Unfractionated heparin; VKAs; Vitamin K antagonists; VTE, Venous thromboembolism

Table 3: VTE-related outcomes during anticoagulation and after its discontinuation, by thrombophilia subgroups.

	Patients not tested for IT		Tested patients (all)		Negative IT		All positive IT		Protein C deficiency		Protein S deficiency		AT deficiency		FVL		PT G20210A		Combined IT	
	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
During anticoagulation																				
Patients, N		***82,729***		***21,089***		***12,667***		***8,422***		***294***		***726***		***240***		***2,248***		***1,434***		***3,480***
Duration of therapy																				
Mean days (±SD)		264±371		407±594[‡]		362±533[‡]		475±670[‡]		520±702[‡]		554±712[‡]		507±695[‡]		444±644[‡]		477±667[‡]		471±672[‡]
Median days (IQR)		164 (97-282)		216 (133-398)[‡]		204 (125-373)[‡]		244 (146-467)[‡]		270 (154-545)[‡]		275 (151-609)[‡]		277 (129-572)[‡]		230 (133-434)[‡]		254 (159-472)[‡]		241 (148-462)[‡]
Outcomes																				
VTE recurrences	2,016	3.46 (3.31-3.62)	581	2.58 (2.38-2.80)[‡]	310	2.57 (2.29-2.87)[‡]	271	2.59 (2.30-2.92)[‡]	8	1.95 (0.91-3.70)	25	2.38 (1.57-3.46)	16	5.31 (3.15-8.45)[‡]	70	2.69 (2.11-3.38)[*]	35	1.95 (1.38-2.68)[‡]	117	2.73 (2.27-3.26)[†]
Recurrent DVT	1,054	1.79 (1.68-1.90)	360	1.57 (1.42-1.74)[*]	191	1.56 (1.35-1.79)	169	1.59 (1.36-1.84)	6	1.45 (0.59-3.02)	17	1.60 (0.96-2.51)	11	3.45 (1.81-5.99)[*]	45	1.71 (1.26-2.26)	22	1.20 (0.77-1.79)	68	1.56 (1.22-1.96)
Recurrent PE	1,006	1.70 (1.60-1.81)	235	1.02 (0.89-1.15)[‡]	126	1.02 (0.85-1.21)[‡]	109	1.01 (0.84-1.22)[‡]	2	0.48 (0.08-1.59)[*]	9	0.83 (0.40-1.52)[*]	5	1.58 (0.58-3.51)	25	0.93 (0.62-1.35)[†]	14	0.76 (0.43-1.25)[‡]	54	1.23 (0.93-1.59)[*]
Major bleeding	2,614	4.44 (4.27-4.61)	364	1.57 (1.41-1.73)[‡]	234	1.89 (1.66-2.14)[‡]	130	1.20 (1.00-1.42)[‡]	5	1.20 (0.44-2.67)[‡]	16	1.47 (0.87-2.34)[‡]	4	1.20 (0.38-2.90)[†]	19	0.70 (0.43-1.07)[‡]	17	0.91 (0.55-1.43)[‡]	69	1.55 (1.22-1.95)[‡]
All-cause mortality	9,692	16.2 (15.9-16.5)	449	1.91 (1.74-2.09)[‡]	248	1.97 (1.74-2.23)[‡]	201	1.84 (1.60-2.11)[‡]	6	1.43 (0.58-2.98)[‡]	14	1.27 (0.72-2.08)[‡]	12	3.60 (1.95-6.12)[‡]	28	1.03 (0.70-1.46)[‡]	15	0.80 (0.47-1.29)[‡]	126	2.81 (2.35-3.33)[‡]
Causes of death,																				
PE	788	1.32 (1.23-1.41)	19	0.08 (0.05-0.12)[‡]	11	0.09 (0.05-0.15)[‡]	8	0.07 (0.03-0.14)[‡]	0	-	0	-	0	-	1	0.04 (0.00-0.18)[‡]	3	0.16 (0.04-0.44)[‡]	4	0.09 (0.03-0.22)[‡]
Bleeding	386	0.65 (0.58-0.71)	22	0.09 (0.06-0.14)[‡]	11	0.09 (0.05-0.15)[‡]	11	0.10 (0.05-0.17)[‡]	0	-	1	0.09 (0.00-0.45)[†]	1	0.30 (0.02-1.48)	1	0.04 (0.00-0.18)[‡]	0	-	8	0.18 (0.08-0.34)[‡]
Cancer	3,676	6.15 (5.96-6.36)	192	0.82 (0.71-0.94)[‡]	100	0.80 (0.65-0.96)[‡]	92	0.84 (0.68-1.03)[‡]	2	0.48 (0.08-1.58)[‡]	4	0.36 (0.12-0.88)[‡]	4	1.20 (0.38-2.89)[‡]	11	0.40 (0.21-0.70)[‡]	4	0.21 (0.07-0.52)[‡]	67	1.49 (1.17-1.89)[‡]
After anticoagulation discontinuation																				
Patients, N		***26,049***		***10,048***		***6,560***		***3,488***		***92***		***266***		***68***		***958***		***632***		***1,472***
Duration of follow-up																				
Mean days (±SD)		423±623		688±891[‡]		673±869[‡]		717±930[‡]		790±1,175[†]		661±811[‡]		695±887[*]		722±897[‡]		773±996[‡]		696±928[‡]
Median days (IQR)		193 (64-516)		370 (127-903)[‡]		373 (130-891)[‡]		368 (123-938)[‡]		254 (88-984)		419 (130-927)[‡]		382 (111-997)[*]		393 (147-955)[‡]		430 (144-949)[‡]		331 (112-903)[‡]
Outcomes																				
VTE recurrences	2,390	8.69 (8.35-9.05)	1,172	6.99 (6.59-7.40)	711	6.58 (6.11-7.08)	461	7.72 (7.04-8.45)	18	11.8 (7.20-18.3)	27	6.12 (4.11-8.77)	9	7.86 (3.83-14.4)	135	8.09 (6.81-9.54)	92	8.06 (6.54-9.84)	180	7.34 (6.33-8.48)[*]
Recurrent DVT	1,283	4.46 (4.22-4.71)	692	3.89 (3.61-4.19)[†]	400	3.50 (3.17-3.85)[‡]	292	4.61 (4.10-5.16)	10	5.77 (2.93-10.3)	21	4.67 (2.97-7.02)	4	3.18 (1.01-7.68)	99	5.65 (4.62-6.85)[*]	57	4.62 (3.53-5.94)	101	3.88 (3.18-4.70)
Recurrent PE	1,141	3.96 (3.73-4.19)	501	2.80 (2.56-3.05)[‡]	324	2.83 (2.54-3.15)[‡]	177	2.74 (2.36-3.16)[‡]	9	5.11 (2.49-9.37)	7	1.48 (0.65-2.93)[†]	5	4.23 (1.55-9.36)	39	2.16 (1.56-2.92)[‡]	35	2.82 (1.99-3.87)[*]	82	3.09 (2.48-3.82)[*]
Major bleeding	342	1.14 (1.03-1.27)	98	0.52 (0.43-0.63)[‡]	60	0.50 (0.38-0.64)[‡]	38	0.56 (0.40-0.76)[‡]	1	0.50 (0.03-2.49)	2	0.42 (0.07-1.38)	0	-	6	0.32 (0.13-0.66)[‡]	7	0.53 (0.23-1.04)[*]	22	0.79 (0.51-1.18)
All-cause	3,949	13.1	460	2.43	288	2.38	172	2.51	1	0.50	19	3.95	6	4.64	25	1.32	24	1.80	97	3.46

mortality		(12.7-13.5)		(2.22-2.66)‡		(2.12-2.67)‡		(2.16-2.91)‡		(0.03-2.48)‡		(2.45-6.05)‡		(1.88-9.64)†		(0.87-1.92)‡		(1.18-2.63)‡		(2.82-4.20)‡
Causes of death,																				
PE	51	0.17 (0.13-0.22)	13	0.07 (0.04-0.11)†	6	0.05 (0.02-0.10)†	7	0.10 (0.04-0.20)	0	-	0	-	0	-	1	0.05 (0.00-0.26)	0	-	6	0.21 (0.09-0.45)
Bleeding	188	0.62 (0.54-0.72)	27	0.14 (0.10-0.20)‡	15	0.12 (0.07-0.20)‡	12	0.18 (0.09-0.30)‡	0	-	1	0.21 (0.01-1.02	0	-	2	0.11 (0.02-0.35)‡	2	0.15 (0.03-0.49)*	7	0.25 (0.11-0.49)†
Cancer	1,560	5.18 (4.92-5.44)	184	0.97 (0.84-1.12)‡	124	1.03 (0.86-1.22)‡	60	0.88 (0.67-1.12)‡	0	-	5	1.04 (0.38-2.30)‡	1	0.77 (0.04-3.81)*	12	0.63 (0.34-1.08)‡	5	0.37 (0.14-0.83)‡	37	1.32 (0.94-1.80)‡

Patients not tested for inherited thrombophilia were used as reference for all comparisons with the remaining subgroups
***p < 0.05; †p < 0.01; ‡p < 0.001.**

Abbreviations: AT; Antithrombin; DVT, Deep venous thrombosis; FVL, Factor V Leiden; IQR, Interquartile range; PE, Pulmonary embolism; SD, Standard deviation; VTE, Venous thromboembolism.

Table 4: VTE-related outcomes during anticoagulation and after its discontinuation, according to inherited thrombophilia testing, and patient groups of interest:

Patient Population	Thrombophilia Status	Number of Patients	Duration of AC Therapy (Months) Median, IQR	Recurrent VTE on AC (Events/100 PY)	Recurrent VTE after AC Discontinuation (Events/100 PY)	Major Bleeding Events (Events/100 PY)	Mortality (Events/100 PY)	VTE-related mortality (Events/100 PY)	Bleeding-related mortality (Events/100 PY)	Cancer-related mortality (Events/100 PY)	Notes
Patients with VTE provoked by recent surgery	Patients not tested for IT	9,018	4.70 (3.15-7.69)	3.18 (2.73-3.67)	5.46 (4.78-6.20)	3.58 (3.22-3.97)	10.8 (10.2-11.5)	0.62 (0.48-0.79)	0.46 (0.34-0.61)	4.22 (3.83-4.63)	
	Tested patients (all)	2,075	6.41 (4.01-11.0)‡	3.72 (2.92-4.69)	4.63 (3.78-5.62)	1.21 (0.91-1.58)‡	1.79 (1.42-2.22)‡	0.07 (0.02-0.19)‡	0.07 (0.02-0.19)‡	0.93 (0.67-1.25)‡	
	Negative thrombophilia	1,314	6.23 (3.91-9.63)‡	3.91 (2.82-5.29)	3.42 (2.57-4.48)†	1.28 (0.90-1.78)‡	1.64 (1.20-2.18)‡	0.04 (0.00-0.19)‡	0.08 (0.01-0.25)†	0.84 (0.54-1.25)‡	
	All positive thrombophilia	761	7.00 (4.21-12.6)‡	3.51 (2.41-4.95)	7.25 (5.42-9.50)	1.10 (0.67-1.70)‡	2.03 (1.43-2.80)‡	0.12 (0.02-0.39)†	0.06 (0.00-0.29)†	1.07 (0.66-1.66)‡	
Patients with VTE provoked by immobilization ≥4 days	Patients not tested for IT	19,199	4.47 (3.02-7.59)	3.57 (3.24-3.94)	8.38 (7.65-9.16)	5.31 (4.98-5.67)	25.3 (24.5-26.0)	1.98 (1.78-2.19)	1.15 (1.00-1.32)	5.95 (5.60-6.32)	
	Tested patients (all)	3,762	6.14 (3.61-11.1)‡	2.67 (2.15-3.29)*	6.36 (5.48-7.35)†	1.52 (1.24-1.85)‡	3.65 (3.21-4.14)‡	0.16 (0.08-0.28)‡	0.19 (0.10-0.32)‡	0.90 (0.69-1.16)‡	
	Negative thrombophilia	2,449	5.82 (3.52-9.03)‡	2.26 (1.64-3.03)†	6.09 (5.06-7.27)†	1.54 (1.19-1.97)‡	3.53 (2.98-4.15)‡	0.13 (0.05-0.28)‡	0.15 (0.06-0.31)‡	0.85 (0.60-1.17)‡	
	All positive thrombophilia	1,313	7.03 (4.09-13.4)‡	3.25 (2.38-4.33)	6.95 (5.38-8.83)	1.48 (1.05-2.04)‡	3.86 (3.13-4.70)‡	0.21 (0.08-0.46)‡	0.25 (0.10-0.52)‡	1.00 (0.65-1.46)‡	
Patients with VTE provoked by estrogen use	Patients not tested for IT	3,466	5.22 (3.22-8.54)	2.55 (1.96-3.26)	4.61 (3.60-5.83)	2.12 (1.70-2.62)	8.89 (7.99-9.86)	0.46 (0.28-0.71)	0.31 (0.17-0.52)	4.25 (3.65-4.94)	
	Tested patients (all)	2,365	6.54 (4.17-11.3)‡	1.56 (1.08-2.17)*	2.35 (1.80-3.03)‡	0.59 (0.40-0.84)‡	0.58 (0.39-0.84)‡	0.04 (0.01-0.14)‡	-	0.32 (0.19-0.52)‡	
	Negative thrombophilia	1,448	6.37 (4.01-9.76)‡	1.36 (0.79-2.20)*	2.31 (1.63-3.17)‡	0.83 (0.53-1.23)‡	0.59 (0.35-0.94)‡	0.04 (0.00-0.18)‡	-	0.30 (0.14-0.56)‡	
	All positive thrombophilia	917	7.03 (4.57-12.4)‡	1.78 (1.07-2.79)	2.43 (1.56-3.62)†	0.26 (0.10-0.58)‡	0.57 (0.30-0.99)‡	0.05 (0.00-0.26)†	-	0.36 (0.16-0.72)‡	
Patients with VTE provoked by pregnancy or postpartum	Patients not tested for IT	676	4.67 (3.22-7.20)	3.28 (1.72-5.70)	2.53 (1.23-4.63)	1.29 (0.63-2.38)	0.99 (0.43-1.97)	0.14 (0.01-0.70)	0.14 (0.01-0.70)	0.14 (0.01-0.70)	
	Tested patients (all)	608	6.47 (4.17-9.84)‡	3.02 (1.75-4.87)	1.13 (0.55-2.07)	0.53 (0.23-1.05)	0.08 (0.00-0.37)†	-	-	0.08 (0.00-0.37)	
	Negative	313	6.34	2.95	0.23	0.46	-	-	-	-	

	thrombophilia		(4.01-8.77)‡	(1.20-6.14)	(0.01-1.11)†	(0.12-1.26)					
	All positive thrombophilia	295	6.64 (4.21-11.1)‡	3.07 (1.50-5.63)	2.27 (1.05-4.31)	0.60 (0.19-1.45)	0.15 (0.01-0.73)*	-	-	0.15 (0.01-0.73)	
Unprovoked VTE	Patients not tested for IT	40,190	6.11 (3.42-11.4)	2.34 (2.18-2.51)	9.73 (9.22-10.3)	2.10 (1.97-2.23)	5.82 (5.61-6.04)	0.51 (0.45-0.57)	0.36 (0.31-0.41)	0.47 (0.41-0.54)	
	Tested patients (all)	11,945	8.10 (5.22-15.1)‡	2.24 (2.00-2.49)	8.83 (8.22-9.48)*	0.93 (0.81-1.06)‡	1.01 (0.90-1.15)‡	0.06 (0.03-0.09)‡	0.06 (0.04-0.10)‡	0.11 (0.08-0.16)‡	
	Negative thrombophilia	6,959	7.59 (5.16-13.6)‡	2.19 (1.88-2.54)	8.23 (7.49-9.02)†	1.02 (0.86-1.20)‡	0.99 (0.83-1.16)‡	0.06 (0.03-0.11)‡	0.06 (0.03-0.11)‡	0.13 (0.08-0.20)‡	
	All positive thrombophilia	4,986	9.05 (5.39-18.2)‡	2.29 (1.95-2.67)	9.90 (8.83-11.07)	0.81 (0.65-1.00)‡	1.05 (0.87-1.26)‡	0.06 (0.02-0.12)‡	0.07 (0.03-0.14)‡	0.09 (0.05-0.17)‡	
Patients with splanchnic vein thrombosis	Patients not tested for IT	611	4.67 (2.92-9.33)	3.26 (1.81-5.43)	7.39 (4.11-12.32)	7.85 (5.78-10.5)	26.6 (22.7-31.0)	0.17 (0.01-0.84)	1.52 (0.74-2.80)	14.7 (11.9-18.1)	
	Tested patients (all)	287	8.41 (3.75-20.4)‡	2.25 (1.10-4.12)	1.00 (0.17-3.31)†	1.48 (0.72-2.72)‡	1.13 (0.50-2.24)‡	-	0.16 (0.01-0.80)†	0.32 (0.05-1.07)‡	
	Negative thrombophilia	171	6.18 (3.52-16.4)*	2.66 (0.97-5.89)	1.56 (0.26-5.16)*	0.93 (0.24-2.52)‡	0.61 (0.10-2.01)‡	-	-	0.61 (0.10-2.01)‡	
	All positive thrombophilia	116	12.0 (4.11-28.8)‡	1.88 (0.60-4.54)	-	2.12 (0.86-4.41)‡	1.73 (0.64-3.85)‡	-	0.35 (0.02-1.71)	-	
Patients with cerebral sinus vein thrombosis	Patients not tested for IT	162	5.22 (3.24-10.1)	1.55 (0.26-5.11)	2.56 (0.43-8.47)	3.91 (1.82-7.42)	8.62 (5.27-13.4)	0.48 (0.02-2.36)	0.96 (0.16-3.16)	2.87 (1.16-5.97)	
	Tested patients (all)	130	9.00 (5.32-15.8)‡	1.12 (0.19-3.70)	1.76 (0.30-5.82)	1.37 (0.44-3.31)	2.35 (1.03-4.65)†	-	0.67 (0.11-2.22)	1.68 (0.62-3.72)	
	Negative thrombophilia	70	10.2 (4.58-15.9)†	1.20 (0.06-5.94)	3.06 (0.51-10.10)	2.03 (0.52-5.51)	2.60 (0.83-6.26)*	-	0.65 (0.03-3.20)	1.95 (0.50-5.30)	
	All positive thrombophilia	60	8.18 (5.82-14.9)†	1.05 (0.05-5.17)	-	0.70 (0.03-3.43)	2.09 (0.53-5.68)*	-	0.70 (0.03-3.43)	1.39 (0.23-4.59)	

Patients not tested for inherited thrombophilia were used as reference for all comparisons with the remaining subgroups
$^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$.

Abbreviations: DVT, Deep venous thrombosis; IQR, Interquartile range; IT, Inherited thrombophilia; PE, Pulmonary embolism; PY, Patient-years; VTE, Venous thromboembolism