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Outcome of patients with venous thromboembolism and Factor V Leiden or Prothrombin 20210 carrier mutations during the course of anticoagulation

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Clinical Research Study

Outcome of patients with venous thromboembolism and Factor V Leiden or Prothrombin 20210 carrier mutations during the course of anticoagulation

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And the RIETE Investigators*

**A full list of the RIETE investigators is given in the appendix*

Running title: **Venous thromboembolism outcome in factor V Leiden carriers on anticoagulants**

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Abstract

Abstract

***Background*:** Individuals with factor V Leiden or prothrombin G20210A mutations are at a higher risk to develop venous thromboembolism. However, the influence of these polymorphisms on patient outcome during anticoagulant therapy has not been consistently explored.

***Methods*:** We used the RIETE database to compare rates of venous thromboembolism recurrence and bleeding events occurring during the anticoagulation course in factor V Leiden carriers, prothrombin mutation carriers and non-carriers.

***Results*:** Between 03.2001 and 12.2015, 10139 patients underwent thrombophilia testing. Of these, 1384 were factor V Leiden carriers, 1115 prothrombin mutation carriers and 7640 non-carriers. During the anticoagulation course, 160 patients developed recurrent deep vein thrombosis and 94 – pulmonary embolism (16 died); 154 had major bleeding (10 died) and 291 had non-major bleeding. On multivariable analysis, factor V Leiden carriers had a similar rate of venous thromboembolism recurrence (adjusted hazard ratio [HR]: 1.16; 95%CI: 0.82-1.64), half the rate of major bleeding (adjusted HR: 0.50; 95%CI: 0.25-0.99) and a non-significantly lower rate of non-major bleeding (adjusted HR: 0.66; 95%CI: 0.43-1.01) than non-carriers. Prothrombin mutation carriers and non-carriers had a comparable rate of venous thromboembolism recurrence (adjusted HR: 1.00; 95%CI: 0.68-1.48), major bleeding (adjusted HR: 0.75; 95%CI: 0.42-1.34) and non-major bleeding events (adjusted HR: 1.10; 95%CI: 0.77-1.57).

***Conclusions*:** During the anticoagulation course, factor V Leiden carriers had a similar risk for venous thromboembolism recurrence and half the risk for major bleeding compared to non-carriers. This finding may contribute to decision-making regarding anticoagulation duration in selected factor V Leiden carriers with venous thromboembolism.

Keywords*:* thrombophilia, anticoagulant therapy, venous thromboembolism, bleeding

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Introduction

Factor V Leiden and prothrombin 20210G-A mutations are the most common genetic causes of thrombophilia in Caucasian population (1, 2). Carriers of these mutations are at an increased risk to develop acute venous thromboembolism, particularly in the presence of concomitant risk factors such as estrogen use, pregnancy, surgery or immobility (3, 4). However, the influence of factor V Leiden and prothrombin 20210G-A mutations on the natural history of venous thromboembolism is still a matter of debate (5). In the past, some studies suggested that venous thromboembolism patients with factor V Leiden or prothrombin 20210G-A mutations were at an increased risk for venous thromboembolism recurrence after discontinuing anticoagulant therapy (6-9), influencing the American College of Chest Physicians (ACCP) guidelines recommendation that these patients should receive anticoagulant therapy for 6-12 months and their suggestion of indefinite therapy (10). However, subsequent research led to a change in the more recent ACCP guidelines and the presence of hereditary thrombophilia was no longer taken into consideration when the duration of anticoagulant therapy was determined (11-13).

Moreover, it has also been suggested that factor factor V Leiden and prothrombin 20210G-A mutations may contribute to an evolutionary advantage by reducing the risk of life-threatening bleeding, such as during childbirth, warfare, or other high risk activities (14, 15). A number of studies have suggested that these mutations may be associated with a significantly lower bleeding rate in patients with hemophilia (16-18), and a decreased hemorrhagic risk in patients undergoing surgery (19, 20).

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international (Spain, Belgium, Canada, Czech Republic, Ecuador, France, Greece, Israel, Italy, Latvia, Portugal, Republic of Macedonia and Switzerland) observational registry of consecutive patients with objectively confirmed acute venous thromboembolism. Data from this registry have been used to evaluate outcomes after acute venous thromboembolism, such as the frequency of recurrent venous thromboembolism, bleeding and

mortality, and risk factors for these outcomes (21-23). The aim of the current study was to compare the rate of symptomatic venous thromboembolism recurrence and bleeding events during the course of anticoagulant therapy in factor V Leiden carriers, prothrombin 20210G-A mutation carriers and non-carriers.

Patients and Methods

Inclusion criteria

Consecutive patients with acute, symptomatic, objectively proven venous thromboembolism were enrolled in RIETE. For this analysis, only patients undergoing thrombophilia tests were considered. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. This analysis was approved by the Ethics Committees of the UZ Gasthuisberg Hospital in Leuven, Belgium (B70721111790) and the Hospital Clinic of Barcelona, Spain (Reg. HCB/2015/0386).

Physicians participating in the RIETE registry made all efforts to enroll consecutive patients. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management.

Study design

Although thrombophilia testing was not routinely performed in RIETE, in those patients who were tested the analyses were performed according to the protocol of each participating hospital. Only patients tested for thrombophilia who were found to have factor V Leiden, prothrombin 20210G-A mutation or none of these polymorphisms were included in this study. We excluded from the study all the patients with other thrombophilic states. In particular, patients with protein C or protein S deficiencies, those with antithrombin deficiency and those with antiphospholipid syndrome were not included in the analysis. We compared their clinical characteristics, laboratory findings, treatment and outcome during the course of anticoagulant therapy. The major outcome was

the rate of symptomatic, objectively confirmed venous thromboembolism and bleeding complications occurring during the course of anticoagulation. Bleeding complications were classified as 'major' if they were overt and required a transfusion of two units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal. Non-major bleeding was defined as any overt bleed requiring medical assistance but not filling the criteria for major bleeding. Each episode of clinically suspected pulmonary embolism or deep vein thrombosis was investigated by ultrasonography, contrast venography, ventilation-perfusion lung scanning, computerized tomographic pulmonary angiography scan or conventional contrast pulmonary angiography as appropriate. Fatal pulmonary embolism, in the absence of autopsy, was defined as any death appearing within 10 days after symptomatic pulmonary embolism diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

Baseline variables

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; risk factors for venous thromboembolism; laboratory data; treatment received upon venous thromboembolism diagnosis (drugs, doses and duration) and the outcome during the course of anticoagulant therapy. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the 2-month period prior to venous thromboembolism diagnosis. Surgical patients were defined as those who underwent a surgical intervention in the 2 months prior to venous thromboembolism. Recent bleeding was defined as a major bleeding episode <30 days prior to venous thromboembolism.

Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). Patients were followed-up for at least 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting symptomatic venous thromboembolism

recurrence or bleeding complications were noted. Each episode of clinically suspected recurrent venous thromboembolism was investigated by repeat compression ultrasonography, ventilation-perfusion lung scanning, computerized tomographic pulmonary angiography scan or conventional contrast pulmonary angiography, as appropriate. Most outcomes were classified as reported by the clinical centers. However, if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

Data collection and monitoring

The primary investigator ensured a consecutive enrollment of qualified patients. The data collected were recorded electronically using the RIETE report form accessible to each of the participating hospitals and medical offices and were submitted securely to the central coordinating center. Data were encrypted to ensure confidentiality and security and patients were assigned a unique number by the study's coordinating center. Quality measures were utilized regularly and electronically documented to expose errors or inconsistencies.

Statistical analysis

We used Student's t test and X^2 test (or Fisher's exact test where appropriate) to compare continuous or categorical variables. Then, we carried out a multivariable analysis through a logistic regression model trying to identify independent predictors for venous thromboembolism recurrence and for major- and non-major bleeding during the course of anticoagulant therapy. Covariates entering in the model were selected by a significance level of $p < 0.10$ on univariable analysis, or by a well–known association reported in the literature. SPSS software (version 20, SPSS Inc. Chicago, Illinois) was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

Results

From March 2001 to March 2016, 64690 venous thromboembolism patients were recruited into the registry. Of these, 10139 (16%) were tested for thrombophilia: 1384 patients were positive for factor V Leiden and 1115 were

positive for prothrombin 20210G-A mutation. Carriers of either factor V Leiden or prothrombin 20210G-A mutations were younger and with slight male predominance compared to non-carriers (Table I). They were less likely to have chronic heart failure, lung disease, renal insufficiency or anemia, but more frequently were users of hormonal therapy or pregnant than non-carriers. Additionally, factor V Leiden carriers (but not prothrombin 20210G-A mutation carriers) were less likely to have recent major bleeding, surgery or immobilization and pulmonary embolism at baseline (compared to deep vein thrombosis alone) than non-carriers. Among patients initially presenting with pulmonary embolism, factor V Leiden carriers were less likely to have severe symptoms associated with their pulmonary embolism (i.e., hypotension, hypoxemia or tachycardia) than non-carriers and scored lower in PESI (pulmonary embolism severity index) and RIETE scores(24, 25).

The majority of patients in all the three subgroups (89%, 90% and 86%, respectively) received initial therapy with low molecular weight heparin (LMWH), at similar daily doses, transitioned immediately to vitamin K antagonists (VKA) (Table II). Notably, the duration of anticoagulation was longer in carriers of factor V Leiden or prothrombin 20210G-A mutation than in non-carriers (397±508 days per 100 patient-years in factor V Leiden carriers, 420±502 days in prothrombin 20210G-A mutation carriers and 303±377 days in non-carriers; p <0.001).

During the course of anticoagulant therapy, 160 patients developed deep vein thrombosis recurrence, 94 pulmonary embolism recurrence, 154 had major bleeding (gastrointestinal tract n=47, brain n=28, retroperitoneal n=11), 291 presented with non-major bleeding and 151 died (Table III). Compared with non-carriers, factor V Leiden carriers had a similar rate of venous thromboembolism recurrence (rate ratio [RR]: 0.96; 95%CI: 0.68-1.33) and a significantly lower rate of major bleeding (RR: 0.32; 95%CI: 0.16-0.59) and non-major bleeding (RR: 0.46; 95%CI: 0.30-0.68). Prothrombin 20210G-A mutation carriers had a comparable rate of venous thromboembolism recurrence (RR: 0.86; 95%CI: 0.58-1.24) and a lower rate of major bleeding (RR: 0.49; 95%CI:

0.27-0.84), but their rate of non-major bleeding was similar to that observed in non-carriers (RR: 0.78; 95%CI: 0.54-1.10).

On multivariable analysis, factor V Leiden carriers had a similar rate of venous thromboembolism recurrences (adjusted hazard ratio [HR]: 1.16; 95%CI: 0.82-1.64), half the rate of major bleeding (adjusted HR: 0.50; 95%CI: 0.25-0.99) and a non-significantly lower rate of non-major bleeding (adjusted HR: 0.66; 95%CI: 0.43-1.01) compared to non-carriers. Both prothrombin 20210G-A mutation carriers and non-carriers had a similar rate of venous thromboembolism recurrences (adjusted HR: 1.00; 95%CI: 0.68-1.48), major bleeding (adjusted HR: 0.75; 95%CI: 0.42-1.34) and non-major bleeding (adjusted HR: 1.10; 95%CI: 0.77-1.57) (Table IV).

The assessment of patients with double heterozygosity for factor V Leiden and prothrombin 20210G-A mutations, or with homozygosity for factor V Leiden or prothrombin 20210G-A mutation did not reveal any measurable difference in the outcome compared with non-carriers, but there were only 203 patients in this category (Table V).

Discussion

Most guidelines of antithrombotic therapy issued before 2008 recommended performing thrombophilia testing in venous thromboembolism patients with specific clinical conditions, including a first episode of spontaneous venous thromboembolism, age under 50 years or recurrent venous thromboembolism during the course of anticoagulant therapy(5, 10). However, the latest guidelines did recommend against such testing, since it did not provide added value for patient management(11-13, 26). Our findings, obtained from a large series of consecutive patients with venous thromboembolism, demonstrated that in real life one in every 6-7 patients with venous thromboembolism did undergo thrombophilia testing, and that factor V Leiden or prothrombin 20210G-A mutation carriers did receive anticoagulant therapy for longer periods of time than non-carriers. We failed to find a measurable difference in the rate of venous thromboembolism recurrence during the course of anticoagulant therapy, but factor V Leiden carriers did bleed significantly less.

We consistently found a lower rate of bleeding in factor V Leiden carriers than in non-carriers: they had a decreased rate of major bleeding immediately prior to venous thromboembolism (odds ratio: 0.30; 95%CI: 0.12-0.63), and during the course of anticoagulation they had a lower rate of major bleeding (RR: 0.32; 95%CI: 0.16-0.59) and non-major bleeding (RR: 0.46; 95%CI: 0.30-0.68) relative to non-carriers. This lower risk of bleeding was confirmed on multivariable analysis, after adjusting for potentially confounding variables. Thus, our findings suggest that the presence of factor V Leiden mutation should be considered in future studies aiming to identify venous thromboembolism patients at risk for bleeding during the course of anticoagulant therapy. We also found that factor V Leiden carriers less likely presented with pulmonary embolism at baseline compared with non-carriers (as already reported)(27-31). These findings might suggest against the benefit from prolonging anticoagulation in factor V Leiden carriers. However, we found no differences in the rate of pulmonary embolism recurrence between the three subgroups.

We failed to find a lower rate of bleeding in prothrombin 20210G-A mutation carriers. Their rate of major bleeding prior to the baseline venous thromboembolism and their rate of non-major bleeding during the course of anticoagulant therapy were similar to those in non-carriers. They certainly had a lower rate of major bleeding during the course of anticoagulant therapy (RR: 0.49; 95%CI: 0.27-0.84), but any difference disappeared on multivariable analysis. We also failed to find any difference in the outcome of patients heterozygous for both mutations or in those who were homozygous. Most likely, this absence of differences could be attributed to the small number of patients in each subgroup.

Our study has several limitations that should be addressed. Testing for thrombophilia was performed according to the protocol of each participating hospital, which could cause a bias. However, the proportion of patients found to harbor these polymorphisms in our series was similar to that reported in several prospective studies (8, 32, 33). Of note, unlike the careful patient selection that characterizes some prospective studies performed in academic centers, our

patient population reflects routine, unmonitored medical practice involving a broad spectrum of patients with venous thromboembolism. The RIETE registry provides data on the management of patients with venous thromboembolism in a real-world situation with an unselected patient population. To that end, it may help to identify factors associated with patient outcomes. However, as an observational database, RIETE is not designed to answer questions regarding the efficiency of thrombophilia testing. Data from the registry are hypothesis-generating and provide feedback from real-world clinical situations which may be of help when designing new randomized clinical studies.

In summary, factor V Leiden carriers had half the risk for major and non-major bleeding during the course of anticoagulant therapy as did non-carriers. This finding can contribute to the evaluation of risk and benefit of prolonged secondary venous thromboembolism prevention in patients with venous thromboembolism.

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Conflict of interest statement: The authors have no conflicts to declare.

Author Contributions:

Inna Tzoran: Conception and design, critical revision of the article for important intellectual content, final approval of the article

Manolis Papadakis: Analysis and interpretation of the data, drafting of the article, final approval of the article

Benjamin Brenner: Conception and design, critical revision of the article for important intellectual content, final approval of the article

Ángeles Fidalgo: Collection and assembly of data, final approval of the article

Agustina Rivas: Collection and assembly of data, final approval of the article

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María Dolores Adarraga: Collection and assembly of data, final approval of the article

Farès Moustafa: Collection and assembly of data, final approval of the article

Manuel Monreal: Conception and design, critical revision of the article for important intellectual content, final approval of the article

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References:

1. Herrmann FH, Koesling M, Schroder W, et al. Prevalence of factor V Leiden mutation in various populations. Genet Epidemiol. 1997;14(4):403-11.

2. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88(10):3698-703.

3. Simioni P, Tormene D, Prandoni P, et al. Incidence of venous thromboembolism in asymptomatic family members who are carriers of factor V Leiden: a prospective cohort study. Blood. 2002;99(6):1938-42.

4. Piazza G. Thrombophilia testing, recurrent thrombosis, and women's health. Circulation. 2014;130(3):283-7.

5. Roldan V, Lecumberri R, Munoz-Torrero JF, et al. Thrombophilia testing in patients with venous thromboembolism. Findings from the RIETE registry. Thromb Res. 2009;124(2):174-7.

6. Ruiz-Irastorza G, Hunt BJ, Khamashta MA. A systematic review of secondary thromboprophylaxis in patients with antiphospholipid antibodies. Arthritis Rheum. 2007;57(8):1487-95.

7. Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. JAMA. 2009;301(23):2472-85.

8. Marchiori A, Mosena L, Prins MH, Prandoni P. The risk of recurrent venous thromboembolism among heterozygous carriers of factor V Leiden or prothrombin G20210A mutation. A systematic review of prospective studies. Haematologica. 2007;92(8):1107-14.

9. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med. 2003;349(12):1133-8.

10. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):401S-28S.

11. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed:

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e419S-94S.

12. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-84S.

13. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315-52.

14. Lindqvist PG. On the evolutionary advantage of coagulation factor V Leiden (FVL). Curr Med Chem. 2015;22(32):3676-81.

15. Zivelin A, Griffin JH, Xu X, et al. A single genetic origin for a common Caucasian risk factor for venous thrombosis. Blood. 1997;89(2):397-402.

16. Kurnik K, Kreuz W, Horneff S, et al. Effects of the factor V G1691A mutation and the factor II G20210A variant on the clinical expression of severe hemophilia A in children--results of a multicenter studys. Haematologica. 2007;92(7):982-5.

17. Lee DH, Walker IR, Teitel J, et al. Effect of the factor V Leiden mutation on the clinical expression of severe hemophilia A. Thromb Haemost. 2000;83(3):387-91.

18. Tizzano EF, Soria JM, Coll I, et al. The prothrombin 20210A allele influences clinical manifestations of hemophilia A in patients with intron 22 inversion and without inhibitors. Haematologica. 2002;87(3):279-85.

19. Donahue BS, Gailani D, Higgins MS, et al. Factor V Leiden protects against blood loss and transfusion after cardiac surgery. Circulation. 2003;107(7):1003-8.

20. Sweeney JD, Blair AJ, Dupuis MP, et al. Aprotinin, cardiac surgery, and factor V Leiden. Transfusion. 1997;37(11-12):1173-8.

21. Arcelus JI, Caprini JA, Monreal M, et al. The management and outcome of acute venous thromboembolism: a prospective registry including 4011 patients. J Vasc Surg. 2003;38(5):916-22.

22. Tzoran I, Saharov G, Brenner B, et al. Silent pulmonary embolism in patients with proximal deep vein thrombosis in the lower limbs. J Thromb Haemost. 2012;10(4):564-71.

23. Tzoran I, Brenner B, Sakharov G, et al. Clinical outcome in patients with venous thromboembolism receiving concomitant anticoagulant and antiplatelet therapy. Eur J Intern Med. 2014;25(9):821-5.

24. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med. 2010;170(15):1383-9.

25. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. J Thromb Haemost. 2010;8(7):1509-14.

26. Howard LS, Hughes RJ. NICE guideline: management of venous thromboembolic diseases and role of thrombophilia testing. Thorax. 2013;68(4):391-3.

27. van Stralen KJ, Doggen CJ, Bezemer ID, et al. Mechanisms of the factor V Leiden paradox. Arterioscler Thromb Vasc Biol. 2008;28(10):1872-7.

28. van Langevelde K, Flinterman LE, van Hylckama Vlieg A, et al. Broadening the factor V Leiden paradox: pulmonary embolism and deep-vein thrombosis as 2 sides of the spectrum. Blood. 2012;120(5):933-46.

29. Margaglione M, Brancaccio V, De Lucia D, et al. Inherited thrombophilic risk factors and venous thromboembolism: distinct role in peripheral deep venous thrombosis and pulmonary embolism. Chest. 2000;118(5):1405-11.

30. Ordonez AJ, Carreira JM, Alvarez CR, et al. Comparison of the risk of pulmonary embolism and deep vein thrombosis in the presence of factor V Leiden or prothrombin G20210A. Thromb Haemost. 2000;83(2):352-4.

31. Martinelli I, Cattaneo M, Panzeri D, Mannucci PM. Low prevalence of factor V:Q506 in 41 patients with isolated pulmonary embolism. Thromb Haemost. 1997;77(3):440-3.

32. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet. 2003;362(9383):523-6.

33. Palareti G, Legnani C, Cosmi B, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation. 2003;108(3):313-8.

Table I. Clinical characteristics and treatment according to thrombophilia testing

	FVL carriers	PTM carriers	Non-carriers
Patients, N	***1,384***	***1,115***	***7,640***
Clinical characteristics			
Age (mean years±SD)	50±18	50±17	56±18
Age >50 years	669 (48%)	536 (48%)	4,707 (62%)
Gender (male)	750 (54%)	597 (54%)	3,822 (50%)
Body weight (mean kg±SD)	78±16	78±16	77±16
Underlying diseases			
Chronic heart failure	23 (1.7%)	23 (2.1%)	373 (4.9%)
Chronic lung disease	88 (6.4%)	64 (5.7%)	766 (10%)
CrCl levels <60 mL/min	163 (12%)	131 (12%)	1,631 (21%)
Recent major bleeding	6 (0.43%)	21 (1.9%)	111 (1.5%)
Anaemia	207 (15%)	226 (20%)	1,894 (25%)
Concomitant medications			
Antiplatelets	100 (7.2%)	91 (8.2%)	805 (11%)
Risk factors for VTE			
Surgery	107 (7.7%)	125 (11%)	887 (12%)
Immobility ≥4 days	200 (14%)	179 (16%)	1,400 (18%)
Estrogen therapy (N=1,173)	195 (31%)	162 (31%)	816 (21%)
Pregnancy/puerperium (N=299)	53 (8.4%)	53 (10%)	193 (5.1%)
Cancer	86 (6.2%)	92 (8.3%)	807 (11%)
Prior VTE	347 (25%)	215 (19%)	1,200 (16%)
Initial VTE presentation,			
Pulmonary embolism	463 (33%)	536 (48%)	3,829 (50%)
In patients with PE,			
SBP levels <90 mm Hg	3 (0.65%)	15 (2.8%)	139 (3.6%)
Heart rate >110 per minute	77 (17%)	110 (21%)	937 (25%)
Sat O_2 <90%	25 (9.6%)	63 (20%)	755 (30%)
Prognostic scores,			
PESI <65 points	243 (52%)	262 (49%)	1,230 (32%)
sPESI <1 point	300 (65%)	325 (61%)	1,779 (46%)
RIETE <1 point	247 (53%)	263 (49%)	1,344 (35%)

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; SD, standard deviation; CrCl, creatinine clearance; VTE, venous thromboembolism; SBP, systolic blood pressure; PESI, pulmonary embolism severity index; sPESI, simplified PESI score; CI, confidence intervals

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Table II. Therapeutic strategies

	FVL carriers	PTM carriers	Non-carriers
Patients, N	***1,384***	***1,115***	***7,640***
Initial therapy,			
Low-molecular-weight heparin	1,231 (89%)	1,007 (90%)	6,538 (86%)
Mean LMWH doses (IU/Kg/day)	178±40	179±38	180±37
Unfractionated heparin	66 (4.8%)	66 (5.9%)	657 (8.6%)
Fondaparinux	46 (3.3%)	17 (1.5%)	158 (2.1%)
Rivaroxaban	18 (1.3%)	3 (0.27%)	78 (1.0%)
Thrombolytics	15 (1.1%)	20 (1.8%)	170 (2.2%)
Vena cava filter	28 (2.0%)	23 (2.1%)	155 (2.0%)
Long-term therapy,			
Vitamin K-antagonists	1,102 (80%)	898 (81%)	5,985 (78%)
Low-molecular-weight heparin	212 (15%)	187 (17%)	1,341 (18%)
Mean LMWH doses (IU/Kg/day)	149±44	149±47	149±48
Rivaroxaban	45 (3.3%)	20 (1.8%)	176 (2.3%)
Duration of therapy,			
Mean days (±SD)	397±508	420±502	303±377
Median days (IQR)	229 (146-398)	246 (166-411)	199 (132-349)

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; LMWH, low-molecular-weight heparin; IU, international units; SD, standard deviation; IQR, interquartile range.

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Table III. Clinical outcome during the course of anticoagulant therapy

	FVL carriers		PTM carriers		Non-carriers	
	N	**N per 100 patient-years**	**N**	**N per 100 patient-years**	**N**	**N per 100 patient-years**
Patients, N	***1,384***		***1,115***		***7,640***	
Events,						
Recurrent DVT	25	1.69 (1.12-2.46)	17	1.36 (0.82-2.13)	118	1.90 (1.58-2.27)
Recurrent PE	16	1.08 (0.64-1.72)	14	1.11 (0.63-1.82)	64	1.02 (0.79-1.29)
Recurrent VTE	41	2.83 (2.06-3.80)	31	2.52 (1.75-3.54)	182	2.95 (2.54-3.41)
Major bleeding	10	0.67 (0.34-1.19)‡	13	1.03 (0.57-1.71)†	131	2.09 (1.75-2.47)
Gastrointestinal	2	0.13 (0.02-0.44)†	4	0.31 (0.10-0.76)	41	0.65 (0.47-0.87)
Haematoma	2	0.13 (0.02-0.44)*	3	0.23 (0.06-0.64)	31	0.49 (0.34-0.69)
Cerebral	3	0.20 (0.05-0.54)	2	0.16 (0.03-0.52)	23	0.36 (0.24-0.54)
Retroperitoneal	1	0.07 (0.00-0.33)	0	-	10	0.16 (0.08-0.28)
Haemopericardias	0	-	0	-	4	0.06 (0.02-0.15)
Non-major bleeding	25	1.70 (1.12-2.47)‡	36	2.91 (2.07-3.98)	230	3.72 (3.26-4.23)
Gastrointestinal	4	0.27 (0.08-0.64)*	10	0.79 (0.40-1.41)	51	0.81 (0.61-1.05)
Hematuria	2	0.13 (0.02-0.44)‡	4	0.31 (0.10-0.76)*	54	0.85 (0.65-1.11)
Haematoma	5	0.33 (0.12-0.74)	4	0.31 (0.10-0.76)	38	0.60 (0.43-0.82)
Menorhagia	3	0.20 (0.05-0.55)	2	0.16 (0.03-0.52)	20	0.32 (0.20-0.48)
Death	13	0.86 (0.48-1.44)†	11	0.86 (0.45-1.49)†	127	2.00 (1.68-2.37)
Pulmonary embolism	1	0.07 (0.00-0.33)	3	0.23 (0.06-0.64)	12	0.19 (0.10-0.32)
Bleeding	1	0.07 (0.00-0.33)	0	-	9	0.14 (0.07-0.26)
Cerebral	0	-	0	-	4	0.06 (0.02-0.15)
Gastrointestinal	1	0.07 (0.00-0.33)	0	-	2	0.03 (0.01-0.10)

Differences between FVL carriers or PTM carriers and non-carriers (reference): $^{*}p < 0.05$; $^{†}p < 0.01$; $^{‡}p < 0.001$

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; IQR, inter-quartile range; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

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Table IV. Multivariable analyses for VTE recurrences, major bleeding or death during the course of anticoagulant therapy.

	VTE recurrences	P value	Major bleeding	P value	Non-major bleeding	p_value
Clinical characteristics,						
Age >50 years	0.73 (0.55-1.01)	0.054	1.43 (0.92-2.23)	0.112	1.57 (1.16-2.12)	0.003
Underlying diseases,						
CrCl levels <60 mL min	1.01 (0.71-1.44)	0.944	1.52 (1.02-2.28)	0.040	1.45 (1.09-1.93)	0.011
Recent major bleeding	2.80 (1.35-5.81)	0.005	1.64 (0.66-4.11)	0.287	1.79 (0.94-3.43)	0.079
Anemia	1.28 (0.95-1.72)	0.110	2.45 (1.72-3.48)	0.000	1.35 (1.03-1.75)	0.028
Concomitant medications,						
Antiplatelets	1.30 (0.90-1.89)	0.164	0.99 (0.58-1.69)	0.966	0.93 (0.62-1.40)	0.733
Risk Factors for VTE,						
Unprovoked	Reference	0.000	Reference	0.157	Reference	0.408
Cancer with metastases	2.84 (1.67-4.84)	0.000	1.39 (0.61-3.19)	0.432	0.93 (0.46-1.87)	0.831
Cancer without metastases	1.60 (1.08-2.38)	0.020	1.73 (1.06-2.82)	0.029	1.17 (0.78-1.75)	0.453
Transient risk factors	0.61 (0.44-0.85)	0.003	1.05 (0.70-1.56)	0.824	1.25 (0.95-1.64)	0.114
Initial VTE presentation,						
Symptomatic PE	1.12 (0.87-1.45)		1.50 (1.06-2.12)	0.021	1.41 (1.11-1.79)	0.005
Thrombophilia testing,						
Non-carriers	Reference	0.659	Reference	0.111	Reference	0.114
FVL carriers	1.16 (0.82-1.64)	0.363	0.50 (0.25-0.99)	0.042	0.66 (0.43-1.01)	0.054
PTM carriers	1.00 (0.68-1.48)	0.974	0.75 (0.42-1.34)	0.327	1.10 (0.77-1.57)	0.599

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance; PE, pulmonary embolism; FVL, Factor V Leiden; PTM, prothrombin mutation.

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Table V. Clinical outcome during the course of anticoagulant therapy in some subgroups of patients with thrombophilia. Results expressed as number of events per 100 patient-years

	N	Age	VTE recurrences		Major bleeding	
Non-carriers	7,640	56.4±18.4	181	2.95 (2.54-3.41)	131	2.09 (1.75-2.47)
Heterozigous FVL	1,326	50.2±17.9‡	41	2.99 (2.18-4.02)	10	0.70 (0.36-1.26)‡
Heterozigous PTM	970	50.7±17.4‡	25	2.43 (1.61-3.53)	9	0.84 (0.41-1.55)†
Heterozigous FVL and PTM	106	47.1±17.2‡	5	3.14 (1.15-6.97)	2	1.21 (0.20-3.99)
Homozygous FVL	58	47.4±15.6‡	0	-	0	-
Homozygous PTM	39	47.1±17.4†	1	2.58 (0.13-12.7)	2	5.56 (0.93-18.4)

Comaprisons between non-carriers and other subgroups: *p <0.05; †p <0.01; ‡p <0.001

Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; VTE, venous thromboembolism

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Highlights

- During anticoagulation, the risk of major bleeding was 50% lower in factor V Leiden carriers
- During anticoagulation, factor V Leiden presence did not affect venous thromboembolism recurrence risk
- Factor V Leiden presence should be considered in decision-making on anticoagulation duration

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APPENDIX

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