CLINICAL RESEARCH STUDY

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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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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 Registro Informatizado de Enfermedad TromboEmbólica 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 noncarriers.

RESULTS: Between March 2001 and December 2015, 10,139 patients underwent thrombophilia testing. Of these, 1384 were factor V Leiden carriers, 1115 were prothrombin mutation carriers, and 7640 were noncarriers. During the anticoagulation course, 160 patients developed recurrent deep vein thrombosis and 94 patients developed pulmonary embolism (16 died); 154 patients had major bleeding (10 died), and 291 patients had nonmajor bleeding. On multivariable analysis, factor V Leiden carriers had a similar rate of venous thromboembolism recurrence (adjusted hazard ratio [HR], 1.16; 95% confidence interval [CI], 0.82-1.64), half the rate of major bleeding (adjusted HR, 0.50; 95% CI, 0.25-0.99) and a nonsignificantly lower rate of nonmajor bleeding (adjusted HR, 0.66; 95% CI, 0.43-1.01) than noncarriers. Prothrombin mutation carriers and noncarriers 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 nonmajor 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 with noncarriers. This finding may contribute to decision-making regarding anticoagulation duration in selected factor V Leiden carriers with venous thromboembolism.

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Factor V Leiden and prothrombin 20210G-A mutations are the most common genetic causes of thrombophilia in the 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, and 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 patients with venous thromboembolism 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 guidelines recommendation that these patients should receive anticoagulant therapy for 6 to 12 months and their suggestion of indefinite therapy.[10] However, subsequent research led to a change in the more recent American College of Chest Physicians guidelines, and the presence of hereditary thrombophilia was no longer taken into consideration when the duration of anticoagulant therapy was determined.[11-13]

CLINICAL SIGNIFICANCE

- 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.

Moreover, it has been suggested that 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 Registro Informatizado de Enfermedad TromboEmbólica (RIETE) 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 noncarriers.

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 in 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 2 units of blood or more, or were retroperitoneal, spinal, or intracranial, or when they were fatal. Nonmajor 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, computed tomography 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 on venous thromboembolism diagnosis (drugs, doses, and duration); and the outcome during the course of anticoagulant therapy. Immobilized patients were defined as nonsurgical patients who had been immobilized (ie, total bed rest with bathroom privileges) for ≥4 days in the 2-month period before venous thromboembolism diagnosis. Surgical patients were defined as those who underwent a surgical intervention in the 2 months before venous thromboembolism. Recent bleeding was defined as a major bleeding episode <30 days before venous thromboembolism.

Treatment and Follow-up

Patients were managed according to the clinical practice of each participating hospital (ie, 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, computed tomography 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 (<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

Table 1 Clinical Characteristics and Treatment According to Thrombophilia Testing

	FVL Carriers	PTM Carriers	Noncarriers
Patients, N	1384	1115	7640
Clinical characteristics			
Age (mean y ± SD)	50 ± 18	50 ± 17	56 ± 18
Age >50 y	669 (48%)	536 (48%)	4707 (62%)
Gender (male)	750 (54%)	597 (54%)	3822 (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%)	1631 (21%)
Recent major bleeding	6 (0.43%)	21 (1.9%)	111 (1.5%)
Anemia	207 (15%)	226 (20%)	1894 (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 d	200 (14%)	179 (16%)	1400 (18%)
Estrogen therapy (N = 1173)	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%)	1200 (16%)
Initial VTE presentation			
Pulmonary embolism	463 (33%)	536 (48%)	3829 (50%)
In patients with PE			
SBP levels <90 mm Hg	3 (0.65%)	15 (2.8%)	139 (3.6%)
Heart rate >110 beats/min	77 (17%)	110 (21%)	937 (25%)
Saturated oxygen <90%	25 (9.6%)	63 (20%)	755 (30%)
Prognostic scores			
PESI <65 points	243 (52%)	262 (49%)	1230 (32%)
Simplified PESI <1 point	300 (65%)	325 (61%)	1779 (46%)
RIETE <1 point	247 (53%)	263 (49%)	1344 (35%)

CrCl = creatinine clearance; FVL = Factor V Leiden; PE = pulmonary embolism; PESI = pulmonary embolism severity index; PTM = prothrombin mutation; RIETE = Registro Informatizado de Enfermedad TromboEmbólica; SBP = systolic blood pressure; SD = standard deviation; VTE = venous thromboembolism.

Table 2 Therapeutic Strategies

	FVL Carriers	PTM Carriers	Noncarriers
Patients, N	1384	1115	7640
Initial therapy			
Low-molecular-weight heparin	1231 (89%)	1007 (90%)	6538 (86%)
Mean LMWH doses (IU/kg/d)	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	1102 (80%)	898 (81%)	5985 (78%)
Low-molecular-weight heparin	212 (15%)	187 (17%)	1341 (18%)
Mean LMWH doses (IU/kg/d)	149 ± 44	149 ± 47	149 ± 48
Rivaroxaban	45 (3.3%)	20 (1.8%)	176 (2.3%)
Duration of therapy			
Mean d (± SD)	397 ± 508	420 ± 502	303 ± 377
Median d (IQR)	229 (146-398)	246 (166-411)	199 (132-349)

FVL = Factor V Leiden; IQR = interquartile range; LMWH = low-molecular-weight heparin; PTM = prothrombin mutation; SD = standard deviation.

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 used regularly and electronically documented to expose errors or inconsistencies.

Statistical Analysis

We used the Student *t* test and chi-square test (or Fisher exact test when appropriate) to compare continuous or categoric 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 nonmajor bleeding during the course of anticoagulant therapy. Covariates entering in the model were selected by a significance level of $P < .10$ on univariable analysis or by a well-known association reported in the literature. SPSS software (version 20, SPSS Inc, Chicago, Ill) was used for the statistical management of the data, and a 2-sided $P < .05$ was considered to be statistically significant.

RESULTS

From March 2001 to March 2016, 64,690 patients with venous thromboembolism were recruited into the registry. Of these, 10,139 (16%) were tested for thrombophilia; 1384 patients were positive for factor V Leiden, and 1115 patients were positive for prothrombin 20210G-A mutation. Carriers of factor V Leiden or prothrombin 20210G-A mutations were younger and with slight male predominance compared with noncarriers (Table 1). 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 noncarriers. In addition, 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 with deep vein thrombosis alone) than noncarriers. Among patients initially presenting with pulmonary embolism, factor V Leiden carriers were less likely to have severe symptoms associated with their pulmonary embolism (ie, hypotension, hypoxemia, or tachycardia) than noncarriers and scored lower in pulmonary embolism severity index and RIETE scores.[24,25]

The majority of patients in all the 3 subgroups (89%, 90%, and 86%, respectively) received initial therapy with low-molecular-weight heparin, at similar daily doses, transitioned immediately to vitamin K antagonists (Table 2). Of note, the duration of anticoagulation was longer in carriers of factor V Leiden or prothrombin 20210G-A mutation than in noncarriers (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 noncarriers; $P < .001$).

During the course of anticoagulant therapy, 160 patients developed deep vein thrombosis recurrence, 94 patients developed pulmonary embolism recurrence, 154 patients had major bleeding (gastrointestinal tract n = 47, brain n = 28, retroperitoneal n = 11), 291 patients presented with nonmajor bleeding, and 151 patients died (Table 3). Compared with noncarriers, factor V Leiden carriers had a similar rate of venous thromboembolism recurrence (rate ratio [RR], 0.96; 95% confidence interval [CI], 0.68-1.33) and a significantly lower rate of major bleeding (RR, 0.32; 95% CI, 0.16-0.59) and nonmajor 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%

Table 3 Clinical Outcome During the Course of Anticoagulant Therapy

	FVL Carriers		PTM Carriers		Noncarriers	
	N	N per 100 Patient-y	N	N per 100 Patient-y	N	N per 100 Patient-y
Patients, N	1384		1115		7640	
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)
Hematoma	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)
Hemopericardias	0	-	0	-	4	0.06 (0.02-0.15)
Nonmajor 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)
Hematoma	5	0.33 (0.12-0.74)	4	0.31 (0.10-0.76)	38	0.60 (0.43-0.82)
Menorrhagia	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 noncarriers (reference): *P <.05; †P <.01; ‡P <.001.

DVT = deep vein thrombosis; FVL = Factor V Leiden; IQR = interquartile range; PE = pulmonary embolism; PTM = prothrombin mutation; VTE = venous thromboembolism.

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 nonmajor bleeding was similar to that observed in noncarriers (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%

Table 4 Multivariable Analyses for Venous Thromboembolism Recurrences, Major Bleeding, or Death During the Course of Anticoagulant Therapy

	VTE Recurrences	*P* Value	Major Bleeding	*P* Value	Nonmajor Bleeding	*P* Value
Clinical characteristics						
Age >50 y	0.73 (0.55-1.01)	.054	1.43 (0.92-2.23)	.112	1.57 (1.16-2.12)	.003
Underlying diseases						
CrCl levels <60 mL min	1.01 (0.71-1.44)	.944	1.52 (1.02-2.28)	.040	1.45 (1.09-1.93)	.011
Recent major bleeding	2.80 (1.35-5.81)	.005	1.64 (0.66-4.11)	.287	1.79 (0.94-3.43)	.079
Anemia	1.28 (0.95-1.72)	.110	2.45 (1.72-3.48)	.000	1.35 (1.03-1.75)	.028
Concomitant medications						
Antiplatelets	1.30 (0.90-1.89)	.164	0.99 (0.58-1.69)	.966	0.93 (0.62-1.40)	.733
Risk factors for VTE						
Unprovoked	Reference	.000	Reference	.157	Reference	.408
Cancer with metastases	2.84 (1.67-4.84)	.000	1.39 (0.61-3.19)	.432	0.93 (0.46-1.87)	.831
Cancer without metastases	1.60 (1.08-2.38)	.020	1.73 (1.06-2.82)	.029	1.17 (0.78-1.75)	.453
Transient risk factors	0.61 (0.44-0.85)	.003	1.05 (0.70-1.56)	.824	1.25 (0.95-1.64)	.114
Initial VTE presentation						
Symptomatic PE	1.12 (0.87-1.45)		1.50 (1.06-2.12)	.021	1.41 (1.11-1.79)	.005
Thrombophilia testing						
Noncarriers	Reference	.659	Reference	.111	Reference	.114
FVL carriers	1.16 (0.82-1.64)	.363	0.50 (0.25-0.99)	.042	0.66 (0.43-1.01)	.054
PTM carriers	1.00 (0.68-1.48)	.974	0.75 (0.42-1.34)	.327	1.10 (0.77-1.57)	.599

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

Table 5 Clinical Outcome During the Course of Anticoagulant Therapy in Some Subgroups of Patients with Thrombophilia

	N	Age, y	VTE Recurrences		Major Bleeding	
Noncarriers	7640	56.4 ± 18.4	181	2.95 (2.54-3.41)	131	2.09 (1.75-2.47)
Heterozygous FVL	1326	50.2 ± 17.9‡	41	2.99 (2.18-4.02)	10	0.70 (0.36-1.26)‡
Heterozygous PTM	970	50.7 ± 17.4‡	25	2.43 (1.61-3.53)	9	0.84 (0.41-1.55)†
Heterozygous 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)

Results are expressed as number of events per 100 patient-years.
Comparisons between noncarriers and other subgroups: †P <.01; ‡P <.001.
FVL = Factor V Leiden; PTM = prothrombin mutation; VTE = venous thromboembolism.

CI, 0.25-0.99), and a nonsignificantly lower rate of nonmajor bleeding (adjusted HR, 0.66; 95% CI, 0.43-1.01) compared with noncarriers. Both prothrombin 20210G-A mutation carriers and noncarriers 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 nonmajor bleeding (adjusted HR, 1.10; 95% CI, 0.77-1.57) (**Table 4**).

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 noncarriers, but there were only 203 patients in this category (**Table 5**).

DISCUSSION

Most guidelines of antithrombotic therapy issued before 2008 recommended performing thrombophilia testing in patients with venous thromboembolism with specific clinical conditions, including a first episode of spontaneous venous thromboembolism, age less than 50 years, or recurrent venous thromboembolism during the course of anticoagulant therapy.[5,10] However, the latest guidelines did recommend against such testing, because 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 1 in every 6 to 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 noncarriers. 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 noncarriers: They had a decreased rate of major bleeding immediately before 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 nonmajor bleeding (RR, 0.46; 95% CI, 0.30-0.68) relative to noncarriers. 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 patients with venous thromboembolism 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 noncarriers (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 among the 3 subgroups.

We failed to find a lower rate of bleeding in prothrombin 20210G-A mutation carriers. Their rate of major bleeding before the baseline venous thromboembolism and their rate of nonmajor bleeding during the course of anticoagulant therapy were similar to those in noncarriers. 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 due to the small number of patients in each subgroup.

Study Limitations

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 that may be of help when designing new randomized clinical studies.

CONCLUSIONS

Factor V Leiden carriers had half the risk for major and nonmajor bleeding during the course of anticoagulant therapy as did noncarriers. 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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SUPPLEMENTARY DATA

Supplementary appendix accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2016.11.016.

APPENDIX

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