Thrombosis Research 151, Suppl. 1 (2017) S11–S15

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Gender-related differences in the outcome of patients with venous thromboembolism and thrombophilia

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ARTICLE INFO

Keywords:
Gender
Venous thromboembolism
Thrombophilia
Factor V Leiden
Prothrombin 20210 G-A polymorphism

ABSTRACT

Background: In patients with venous thromboembolism (VTE) and factor V Leiden (FVL) or prothrombin 20210 G-A mutation (PTM), the influence of gender on outcome has not been consistently studied.
Methods: We used the RIETE (Registro Informatizado Enfermedad TromboEmbolica) database to assess the existence of gender differences in the rate of VTE recurrences (deep vein thrombosis [DVT] or pulmonary embolism [PE]) or major bleeding during the course of anticoagulation and after its discontinuation in FVL and PTM carriers.
Results: From March 2001 to September 2016, 11,224 VTE patients underwent thrombophilia testing. Of these, 1,563 were FVL carriers (863 men and 700 women) and 1,231 were PTM carriers (659 men and 572 women). During the course of anticoagulant therapy, men with FVL had a 6-fold higher rate of VTE recurrences than major bleeds (31 vs. 5 events). In women with FVL, the rate of VTE recurrences was 2-fold higher (16 vs. 8), as was in men (17 vs. 8) or women (17 vs. 9) with PTM. After discontinuing anticoagulation, men with FVL had a 3-fold higher rate of DVT recurrences than women (hazard ratio [HR]: 3.13; 95% CI: 1.79–5.67), with no differences in PE recurrences. Among patients with PTM, there were no gender differences in the rate of DVT (HR: 1.89; 95% CI: 1.00–3.65) or PE recurrences (HR: 1.82; 95% CI: 0.83–4.12).
Conclusions During the anticoagulation course, men with FVL are at a much higher risk for VTE recurrences than bleeding. After discontinuing anticoagulation, men with FVL are at an increased risk for DVT recurrences.

1. Introduction

Factor V Leiden (FVL) and prothrombin 20210 G-A mutations (PTM) are the most common genetic causes of thrombophilia in Caucasian population [1,2]. In a recent study by our group, FVL carriers with VTE were found to have half the risk of major bleeding during the course of anticoagulant therapy (and a similar risk for VTE recurrences) than non-carriers [3]. After discontinuing anticoagulant therapy, there is some controversy on the role of these mutations on the risk for VTE recurrences [4–6]. Furthermore, in another study by our group, women had a higher rate of major bleeding and lower rate of VTE recurrences during the course of anticoagulation than men [7]. The influence of gender on the outcome in patients with FVL or PTM has not been consistently studied.

RIETE (Registro Informatizado de Enfermedad TromboEmbólica) is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Macedonia, United States, Canada, Brazil and Ecuador) observational registry of consecutive patients with symptomatic, objectively confirmed, VTE (ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate acute management and long-term outcome of VTE patients [8–10]. In the current analysis, we used the RIETE database to assess the existence of gender differences in the rate of VTE recurrences or major bleeding appearing during the

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course of anticoagulant therapy and after its discontinuation in FVL and PTM carriers.

2. Patients and methods

2.1. Inclusion criteria

Consecutive patients with acute, symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) with or without DVT confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical CT-scan, ventilation-perfusion lung scintigraphy or angiography for PE) were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

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.

2.2. 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 FVL or PTM were included in this study. We assessed for any influence of gender on their clinical characteristics, laboratory findings, treatment and outcome during the course of anticoagulant therapy and after its discontinuation. The major outcome was the rate of symptomatic, objectively confirmed VTE and major bleeding. 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. Each episode of clinically suspected DVT or PE was investigated by compression ultrasonography, contrast venography, ventilation-perfusion lung scanning, computerized tomographic pulmonary angiography (CTPA) scan or conventional contrast pulmonary angiography as appropriate.

2.3. 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 VTE; laboratory data; treatment received upon VTE 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 $\geq$4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent a surgical intervention in the 2 months prior to VTE. Recent bleeding was defined as a major bleeding episode <30 days prior to VTE.

2.4. 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 VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, ventilation–perfusion lung scanning, CTPA 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).

2.5. 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.

2.6. Statistical analysis

Student t-tests and nonparametric tests were used to compare means and medians of continuous variables. Categorical variables were compared using the chi-square test (two-sided) and Fisher's exact test (two-sided). Incidence rates of recurrent VTE, major bleeding and death were calculated as cumulative incidence (events/100 patient-years). We compared the cumulative incidence of these events according to sex using the Kaplan-Meier technique. 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.

3. Results

From March 2001 to September 2016, 11,224 VTE patients underwent thrombophilia testing. Of these, 1,563 were FVL carriers (863 men and 700 women) and 1,231 were PTM carriers (659 men and 572 women). In both subgroups, men were 4 years (as a mean) older than women, weighed 10 kg more and were more likely to have unprovoked VTE (Table 1).

Table 1
Clinical characteristics according to thrombophilia testing and gender.

	FVL carriers		PTM carriers	
	Men	Women	Men	Women
Patients, *N*	863	700	659	572
Clinical characteristics				
Age (mean years ± SD)	52 ± 16	48 ± 19‡	52 ± 15	48 ± 19‡
Age >50 years	473 (55%)	294 (42%)‡	361 (55%)	247 (43%)‡
Body weight (mean kg ± SD)	84 ± 15	72 ± 15‡	83 ± 14	72 ± 15‡
Risk factors for VTE				
Surgery	62 (7.2%)	57 (8.1%)	67 (10%)	66 (12%)
Immobility ≥4 days	118 (14%)	105 (15%)	120 (18%)	75 (13%)*
Estrogen therapy	1 (0.12%)	215 (31%)‡	2 (0.30%)	175 (31%)‡
Pregnancy or puerperium	0	55 (7.9%)‡	0	58 (10%)‡
Cancer	52 (6.0%)	54 (7.7%)	51 (7.7%)	47 (8.2%)
None of the above	647 (75%)	275 (39%)‡	437 (66%)	222 (39%)‡
Prior VTE	235 (27%)	164 (23%)	138 (21%)	103 (18%)
Initial VTE presentation				
Pulmonary embolism	274 (32%)	253 (36%)	323 (49%)	274 (48%)
In patients with PE				
SBP levels <90 mm Hg	3 (1.1%)	1 (0.40%)	10 (3.1%)	7 (2.6%)
Heart rate >110 per minute	43 (17%)	43 (18%)	62 (20%)	60 (23%)
Sat O_2 <90%	17 (11%)	11 (8.1%)	32 (17%)	38 (25%)

Comparisons are made using men as reference: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; SD, standard deviation; VTE, venous thromboembolism; PE, pulmonary embolism; SBP, systolic blood pressure.

Table 2
Therapeutic strategies.

	FVL carriers		PTM carriers	
	Men	Women	Men	Women
Patients, N	863	700	659	572
Initial therapy				
Low-molecular-weight heparin	775 (90%)	614 (88%)	595 (90%)	513 (90%)
Mean LMWH doses (IU/kg/day)	175 ± 41	181 ± 40*	176 ± 40	183 ± 37†
Unfractionated heparin	31 (3.6%)	38 (5.4%)	34 (5.2%)	36 (6.3%)
Fondaparinux	29 (3.4%)	20 (2.9%)	10 (1.5%)	9 (1.6%)
Rivaroxaban	16 (1.9%)	15 (2.1%)	5 (0.76%)	3 (0.52%)
Thrombolytics	7 (0.81%)	8 (1.1%)	14 (2.1%)	7 (1.2%)
Vena cava filter	10 (1.2%)	21 (3.0%)*	8 (1.2%)	17 (3.0%)*
Long-term therapy				
Vitamin K-antagonists	677 (78%)	521 (74%)	534 (81%)	441 (77%)
Low-molecular-weight heparin	129 (15%)	129 (18%)	100 (15%)	108 (19%)
Mean LMWH doses (IU/kg/day)	146 ± 40	154 ± 44	145 ± 49	151 ± 43
Rivaroxaban	36 (4.2%)	39 (5.6%)	17 (2.6%)	11 (1.9%)
Duration of therapy				
Mean days (± SD)	432 ± 573	381 ± 531	464 ± 575	437 ± 586
Median days (IQR)	241 (144–441)	215 (139–381)	266 (171–457)	238 (165–414)

Comparisons are made using men as reference: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: FVL, Factor V Leiden; PTM, prothrombin mutation; LMWH, low-molecular-weight heparin; IU, international units; SD, standard deviation; IQR, interquartile range.

Table 3
Clinical outcomes during the course of anticoagulant therapy.

	Men		Women		Hazard ratio (95% CI)
	N	*N* per 100 patient-years	*N*	*N* per 100 patient-years	
Factor V Leiden					
Patients, *N*	863		700		
Recurrent DVT	21	2.09 (1.33–3.14)	9	1.26 (0.61–2.31)	1.66 (0.77–3.82)
Recurrent PE	10	1.00 (0.51–1.79)	7	0.97 (0.42–1.91)	1.04 (0.39–2.89)
Recurrent VTE	31	3.16 (2.19–4.43)	16	2.25 (1.33–3.58)	1.40 (0.77–2.62)
Major bleeding	5	0.49 (0.18–1.09)	8	1.10 (0.51–2.09)	0.44 (0.13–1.37)
Gastrointestinal	3	0.29 (0.07–0.80)	0	–	–
Cerebral	2	0.20 (0.03–0.65)	1	0.14 (0.01–0.68)	1.43 (0.11–42.2)
Haematoma	0	–	2	0.27 (0.05–0.91)	–
Death	5	0.49 (0.18–1.09)	9	1.23 (0.60–2.26)	0.40 (0.12–1.19)
Prothrombin mutation					
Patients, *N*	659		572		
Recurrent DVT	10	1.22 (0.62–2.18)	10	1.50 (0.76–2.67)	0.82 (0.33–2.01)
Recurrent PE	8	0.97 (0.45–1.85)	7	1.04 (0.45–2.05)	0.94 (0.33–2.72)
Recurrent VTE	17	2.11 (1.27–3.32)	17	2.58 (1.56–4.05)	0.82 (0.41–1.62)
Major bleeding	8	0.97 (0.45–1.85)	9	1.34 (0.65–2.46)	0.73 (0.27–1.93)
Gastrointestinal	3	0.36 (0.09–0.99)	3	0.44 (0.11–1.20)	0.82 (0.14–4.79)
Cerebral	2	0.24 (0.04–0.79)	1	0.15 (0.01–0.72)	1.63 (0.12–48.1)
Haematoma	1	0.12 (0.01–0.59)	2	0.29 (0.05–0.97)	0.41 (0.01–5.37)
Death	6	0.72 (0.29–1.49)	7	1.02 (0.45–2.03)	0.70 (0.22–2.16)

Abbreviations: CI, confidence intervals; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Most patients in all subgroups received initial therapy with low-molecular-weight heparin (LMWH), though men received significantly lower daily doses of LMWH than women (Table 2). Then, the proportion of patients switching to vitamin K antagonists was similar in both genders. Men in all two subgroups were less likely to undergo a vena cava filter insertion than women. Mean duration of therapy was similar.

During the course of anticoagulant therapy, there were no gender differences in the rate of VTE recurrences or major bleeding in any subgroup (Table 3). However, the rate of VTE recurrences in men with FVL was 6-fold higher than the rate of major bleeding (31 vs. 5 events, respectively). In women with FVL the rate of VTE recurrences was "only" 2-fold higher than the rate of major bleeding (16 vs. 8 events, respectively). Among patients with PTM, the rate of VTE recurrences was also 2-fold higher than the rate of major bleeding in both men and women.

After discontinuing anticoagulant therapy, men with FVL had a 3-fold higher rate of DVT recurrences than women (hazard ratio [HR]: 3.13; 95% CI: 1.79–5.67), with no gender differences in the rate of PE recurrences or death (Table 4). Among patients with PTM, the rate of DVT and PE recurrences was non-significantly higher in men than in women (HR: 1.89; 95% CI: 1.00–3.65, and HR: 1.82; 95% CI: 0.83–4.12, respectively).

4. Discussion

Our findings, obtained from a large series of consecutive patients with VTE and FVL or PTM, reveal the existence of some non-previously reported gender differences in clinical characteristics, treatment and outcome that might be of interest to guide therapy. In our series, there were more men than women with FVL or PTM, and men were older and more likely to have unprovoked VTE than women. Men received fewer daily doses of LMWH than women, and less likely underwent vena cava filter placement. During the course of anticoagulant therapy, men with FVL had 6 times more VTE recurrences than major bleeding. These data suggest that men with FVL could probably benefit from a more aggressive anticoagulant therapy. After its discontinuation, the rate of DVT recurrences in men with FVL (12 events per 100 patient-years) was much higher than the rate in women with FVL or in PTM carriers (men or

Table 4
Clinical outcome after discontinuing anticoagulant therapy.

	Men		Women		Hazard ratio (95% CI)
	N	*N* per 100 patient-years	*N*	*N* per 100 patient-years	
Factor V Leiden					
Patients, *N*	349		302		
Recurrent DVT	46	12.1 (9.00–16.1)	16	3.89 (2.30–6.18)	3.13 (1.79–5.67)
Recurrent PE	10	2.61 (1.33–4.65)	11	2.66 (1.40–4.63)	0.98 (0.40–2.35)
Major bleeding	1	0.26 (0.01–1.28)	0	–	–
Cerebral	1	0.26 (0.01–1.28)	0	–	–
Death	6	1.56 (0.63–3.25)	5	1.21 (0.44–2.68)	1.29 (0.38–4.59)
Prothrombin mutation					
Patients, *N*	272		237		
Recurrent DVT	26	7.56 (5.04–10.9)	15	4.00 (2.33–6.46)	1.89 (1.00–3.65)
Recurrent PE	17	4.84 (2.91–7.59)	10	2.66 (1.35–4.75)	1.82 (0.83–4.12)
Major bleeding	0	–	0	–	–
Death	4	1.14 (0.36–2.74)	7	1.86 (0.82–3.69)	0.61 (0.16–2.11)

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; CI, confidence intervals.

women). These data suggest that men with FVL could probably benefit from a longer duration of anticoagulant therapy.

The observed higher rate of VTE recurrences than bleeding in men with FVL (compared to women) might partly be explained by the fact that they received lower doses of LMWH per body weight. However, we failed to find similar gender differences in patients with PTM (and men with PTM also received lower LMWH doses). The higher rate of DVT recurrences after discontinuing anticoagulation in men with FVL could partly be attributed to the fact that the proportion of men with unprovoked VTE was 2-fold higher than among women. We also failed to find similar differences among patients with PTM. As in our series, a meta-analysis including 10 studies found that VTE patients with FVL (but not those with PTM) had a 40% higher risk to develop VTE recurrences than non-carriers [5]. A minor, statistically insignificant, difference in the duration of anticoagulation treatment between men and women did not contribute to the variance in the rate of major outcomes among the groups.

To our knowledge, this is the first real-life study reporting the existence of gender differences in VTE patients with thrombophilia. A number of studies reported a higher rate of VTE recurrences in men after discontinuing anticoagulant therapy [11–14]. Moreover, a study in thrombophilic families reported a higher rate of VTE recurrences in men [15].

Our study has several limitations that should be addressed. Baseline imaging at the completion of anticoagulant therapy was not systematically conducted and this may have influenced the validity of the diagnosis of recurrent VTE. However, imaging of the pathological site at the end of treatment is not required according to the International Guidelines on "Antithrombotic Therapy for VTE Disease" [16]. Patient outcome events were not independently adjudicated, but the evaluations were performed at academic hospitals providing high standards of care. 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 [5,17,18]. 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 VTE. The RIETE registry provides data on the management of patients with VTE in a real-world situation with an unselected patient population. To that end, it may help to identify factors associated with patient outcomes. 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, men with FVL had a higher rate of VTE recurrences (during and after discontinuing anticoagulation) than women with FVL and than men or women with PTM. This finding can contribute to decision-making regarding the duration of anticoagulant therapy in men with FVL.

Acknowledgements

We express our gratitude to Sanofi Spain for supporting this Registry with an unrestricted educational grant. We also express our gratitude to Bayer Pharma AG for supporting this Registry. Bayer Pharma AG's support was limited to the part of RIETE outside Spain, which accounts for a 23.52% of the total patients included in the RIETE Registry. We also thank the RIETE Registry Coordinating Center, S & H Medical Science Service, for their quality control data, logistic and administrative support and Prof. Salvador Ortiz, Universidad Autónoma de Madrid and Statistical Advisor S& H Medical Science Service for the statistical analysis of the data presented in this paper.

Conflict of interest statement

The authors declare that they have no relevant conflicts of interest with this manuscript.

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