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Venous thromboembolism in young adults: Findings from the RIETE registry

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SUMMARY

Background: Little is known on the clinical characteristics, risk factors and outcomes during anticoagulation in young patients with acute venous thromboembolism (VTE).

Methods: We used data from the RIETE (Registro Informatizado Enfermedad TromboEmbólica) registry to assess the clinical characteristics, risk factors and outcomes during anticoagulation in VTE patients aged 10–24 years. Data were separately analyzed according to initial presentation and gender.

Results: Of 76,719 patients with VTE, 1571 (2.0%) were aged 10–24 years. Of these, 989 (63%) were women and 669 (43%) presented with pulmonary embolism (PE). Most women were using estrogens (680, 69%) or were pregnant (101, 10%), while 59% of men had unprovoked VTE. Women were more likely to present with PE (48% vs. 34%). The majority (87%) of PE patients had Sat O_2 levels ≥90% at baseline. The vast majority (97%) of PE patients were at low risk according to the PESI score, many (90%) at very low risk. During the course of anticoagulation (median, 192 days), 40 patients had VTE recurrences, 17 had major bleeding and 10 died (3 died of PE). Women had as many VTE recurrences as major bleeds (15 vs. 14 events), while men had many more VTE recurrences than major bleeding (25 vs. 3 events).

Conclusions: VTE is associated with low risk of short-term mortality in young adults. Noticeable gender differences exist in the risk factor profile and the risk of VTE recurrences and major bleeding in the course of anticoagulation.

1. Introduction

The incidence of venous thromboembolism (VTE) progressively increases with the patient's age. In the elderly, VTE usually develops in patients with impaired mobility and a number of comorbidities [1–3]. In the young, it often appears in women using estrogens, during pregnancy or in people with thrombophilia [4–7]. The mortality rate is lower in the young than in older patients [8,9], but any preventable death in young patients is catastrophic. Yet, epidemiological data on the initial VTE presentation, risk factors for VTE, underlying diseases, treatment or outcomes during the course of anticoagulant therapy in young adults with VTE are scarce in the literature. A better knowledge of the burden of VTE in these patients could likely help to improve the awareness of patients, practitioners, and policy-makers. A better understanding of their initial VTE presentation might contribute to detect it earlier. Also, more detailed information on their outcomes during anticoagulation, including gender differences, could be of interest to introduce better therapeutic strategies for young adults with VTE.

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RIETE (Registro Informatizado de Enfermedad TromboEmbólica) is an ongoing, multicenter registry of consecutive patients with acute VTE, with 223 collaborating centers in the Americas, Asia and Europe (ClinicalTrials.gov identifier: NCT02832245). The methodology of the registry has been previously described elsewhere [10]. The aim of the current study was to assess the clinical characteristics at baseline, risk factors and outcomes during anticoagulant therapy in patients aged 10–24 years with acute VTE. Patients were separately analyzed according to gender and initial VTE presentation (either deep vein thrombosis [DVT] or pulmonary embolism [PE]).

2. Patients and methods

2.1. Inclusion criteria

The World Health Organization defines '*Adolescents*' as individuals in the 10–19 years *age group* and '*Youth'* as the 15–24 year *age group, w*hile '*Young Adults*' covers the *age range from 10 to 24 years* [11]. For this study, we included all patients aged 10–24 years who presented with acute, symptomatic PE or DVT, confirmed by objective tests (compression ultrasonography or contrast venography for suspected DVT; pulmonary angiography, ventilation-perfusion lung scan or helical computed tomography scan for suspected PE) since March 2001. Patients were excluded if they were not symptomatic, had thrombosis in the splanchnic, cerebral or retinal veins, or were participating in a therapeutic clinical trial taking a blind medication. All patients provided oral or written informed consent to their participation in the registry, according to the requirements of the ethics committees within each hospital.

2.2. Variables and definitions

The following parameters were recorded in RIETE: patient's characteristics at baseline; clinical status including any coexisting or underlying conditions such as chronic heart or lung disease, recent major bleeding, anemia or renal insufficiency; risk factors for VTE; the treatment received upon VTE diagnosis 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 or without bathroom privileges) for ≥ 4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE. Active cancer was defined as newly diagnosed cancer or when receiving anti-neoplastic treatment of any type (i.e., surgery, chemotherapy, radiotherapy, hormonal, support or combined therapies). Unprovoked VTE was considered in the absence of active cancer, recent immobility, surgery, estrogen use, pregnancy, postpartum, or long-term travel. Recent bleeding was considered in patients having suffered major bleeding < 30 days prior to VTE. Anemia was defined as hemoglobin levels < 13 g/dL for men and < 12 g/dL for women. Creatinine clearance levels were measured using the Cockroft-Gault formula. Patients initially presenting with PE were evaluated according to the Pulmonary Embolism Severity Index (PESI) and its simplified version, sPESI [12,13].

2.3. Population and follow up

All patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. During follow-up, special attention was paid to any signs or symptoms suggesting recurrent VTE or bleeding complications. Each episode of clinically suspected recurrent DVT or PE was documented by repeat objective imaging. 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 [10]. Non-major bleeding was defined as any overt bleeding episode that required medical assistance but did not meet the definition for major bleeding. Fatal bleeding was defined as any death occurring < 10 days after a major bleeding episode, in the absence of any alternative cause of death. Fatal PE, in the absence of autopsy, was defined as any death appearing < 10 days after PE diagnosis, in the absence of any alternative cause of death.

2.4. Statistical analyses

Categorical variables were compared using the chi-square test (two-sided) and Fisher's exact test (two-sided). Continuous variables were compared using Student *t*-test. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratios and 95%CI. Cox proportional hazard models were used to assess the risk for recurrent VTE or major bleeding appearing during anticoagulant therapy. Crude and adjusted HR as well as their 95% CI were estimated. Covariates included in the adjusted model were those for which a statistically significant difference (a threshold *p*-value of 0.1 was set to assess significance of differences) was found, and a backward selection was used for the covariate selection in the multivariable model. Statistical analyses were conducted with the Statistical Package for Social Sciences (SPSS) program (version 21.0. for Windows, 2004 SPSS Inc. Chicago, Illinois, USA).

3. Results

3.1. Clinical characteristics

Of 76,719 patients enrolled in RIETE from March 2001 to January 2018, 1571 (2.0%) were aged 10–24 years. Of these, 989 (63%) were women and 669 (43%) presented with PE (with or without concomitant DVT). Most women (69%) were using estrogens, 10% were pregnant (or postpartum) and 12% had unprovoked VTE. Besides, most (59%) men had unprovoked VTE (Table 1). Few patients had cancer or other comorbidities, without gender differences. Half of the patients (women 51%, men 49%) underwent thrombophilia testing, the most frequent findings being Factor V Leiden in 18%, prothrombin mutation in 11% and antiphospholipid syndrome in 11%. There were no relevant gender differences, but Factor V Leiden mutation was less frequently found in patients initially presenting with PE than in those with DVT (odds ratio [OR]: 0.46; 95%CI: 0.31–069).

3.2. Initial VTE presentation

Nearly one in every two women (48%) and one in every three men (34%) initially presented with PE (as compared to DVT). Among patients with acute PE, women were more likely to complain of dyspnea (odds ratio [OR]: 1.58; 95% CI: 1.11–2.25), to present with syncope (OR: 1.78; 95% CI: 1.03–3.20), and to have tachycardia (OR: 2.01; 95% CI: 1.313.16) or hypotension (OR: 1.87; 95% CI: 1.04–3.55) compared with men (Table 2). Overall, the majority (87%) of patients with PE had oxygen saturation levels ≥ 90% at baseline, most (68%) had levels ≥ 95%. The vast majority (97%) of PE patients in both subgroups were at low risk according to the PESI score, many (90%) at very low risk. However, the proportion of patients at low risk according to sPESI was lower in women (59% vs. 72%; OR: 0.54; 95% CI: 0.38–0.78). Among patients initially presenting with DVT, women were less likely to have upper-extremity DVT (OR: 0.44; 95% CI: 0.32–0.62), right-sided DVT (OR: 0.66; 95% CI: 0.51–0.870) or bilateral DVT (OR: 0.31; 95% CI: 0.14–0.66) than men.

3.3. Treatment and outcomes

There were no gender differences in prescribed drugs, doses or duration of anticoagulant therapy (Table 2). During the course of

Table 1
Clinical characteristics and thrombophilia testing, according to gender and initial VTE presentation.

	Acute PE Women	Acute PE Men	Acute DVT Women	Acute DVT Men
Patients, N	474	195	515	387
Clinical characteristics,				
Mean age (years ± SD)	21.1 ± 2.3	20.8 ± 2.6	20.9 ± 2.7	20.8 ± 2.8
Median age (years, IQR)	21 (19–23)	21 (19–23)	22 (19–23)	21 (19–23)
Adolescents (age 10–19 years)	128 (27%)	58 (30%)	139 (27%)	126 (33%)
Body weight (mean kg ± SD)	69 ± 17	83 ± 21‡	65 ± 15	78 ± 18‡
Risk factors,				
Active cancer	6 (1.3%)	7 (3.6%)	16 (3.1%)	17 (4.4%)
Immobility ≥4 days	46 (9.7%)	38 (19%)‡	77 (15%)	80 (21%)*
Surgery	44 (9.3%)	40 (21%)‡	56 (11%)	44 (11%)
Estrogen use	363 (77%)	4 (2.1%)‡	317 (62%)	2 (0.52%)‡
Pregnancy or postpartum	34 (7.2%)	0	67 (13%)	0
Prolonged travel	17 (3.6%)	9 (4.6%)	13 (2.5%)	11 (2.8%)
None of the above (unprovoked)	47 (9.9%)	101 (52%)‡	75 (15%)	240 (62%)‡
Prior VTE	22 (4.6%)	15 (7.7%)	15 (2.9%)	39 (10%)‡
Co-morbidities,				
Chronic lung disease	11 (2.3%)	3 (1.5%)	9 (1.7%)	7 (1.8%)
Chronic heart failure	0	4 (2.1%)†	1 (0.19%)	1 (0.26%)
Recent major bleeding	7 (1.5%)	2 (1.0%)	6 (1.2%)	3 (0.78%)
Diabetes	2 (0.59%)	1 (0.75%)	5 (1.6%)	1 (0.41%)
Hypertension	7 (2.1%)	5 (3.7%)	5 (1.6%)	6 (2.5%)
Blood tests at baseline,				
Anemia	139 (29%)	45 (23%)	161 (31%)	89 (23%)†
Platelet count < 100,000/μL	6 (1.3%)	2 (1.0%)	9 (1.8%)	7 (1.8%)
CrCl levels (mL/min)	120 ± 41	145 ± 52‡	112 ± 38	140 ± 43‡
Thrombophilia testing,				
Patients tested, N	240	89	263	194
Factor V Leiden	30 (13%)	8 (9.0%)	61 (23%)	40 (21%)
Prothrombin mutation	36 (15%)	8 (9.0%)	22 (8.4%)	21 (11%)
Protein C deficiency	6 (2.5%)	2 (2.2%)	2 (0.76%)	4 (2.1%)
Protein S deficiency	9 (3.8%)	5 (5.6%)	10 (3.8%)	8 (4.1%)
Antithrombin deficiency	3 (1.3%)	2 (2.2%)	2 (0.76%)	10 (5.2%)†
Antiphospholipid syndrome	18 (7.5%)	15 (17%)*	26 (9.9%)	27 (14%)

Gender differences: *$p < .05$; †$p < .01$; ‡p < .001.
Abbreviations: SD, standard deviation; IQR, inter-quartile range; VTE, venous thromboembolism; CrCl, creatinine clearance; PE, pulmonary embolism; DVT, deep vein thrombosis.

anticoagulation (median, 192 days), 20 patients had recurrent PE, 22 had recurrent DVT, 17 had major bleeding (including 4 cases of retroperitoneal bleeding and 3 of, menorrhagia) and 10 patients died (3 died of the PE). Women had a significantly higher rate of major bleeding (hazard ratio [HR]: 3.31; 95%CI: 1.03–14.4), a similar rate of PE recurrences (HR: 0.70; 95% CI: 0.28–1.72), non-major bleeding (HR: 1.42; 95%CI: 0.67–3.16) or mortality (HR: 1.65; 95%CI: 0.43–7.87) and lower rate of DVT recurrences (HR: 0.25; 95%CI: 0.09–0.63) than men (Table 3). The rate of VTE recurrences (combining both DVT and PE events) was also lower in women (HR: 0.40; 95%CI: 0.21–0.76). During anticoagulation, women had as many VTE recurrences as major bleeding events (15 vs. 14 events), but men had many more VTE recurrences than major bleeds (25 vs. 3 events), as shown in Fig. 1. On multivariable analysis, the influence of gender on the risk for recurrent VTE (HR: 1.41; 95% CI: 0.63–3.12) or major bleeding (HR: 0.50; 95%CI: 0.14–1.82) was no longer statistically significant (Table 4).

Ten patients aged 10–24 years (0.64%) died during anticoagulation. Six of them (60%) had initially presented with PE and four with DVT alone. Most frequent causes of death were: fatality of the initial PE event ($n = 3$), disseminated cancer (n = 3) and respiratory insufficiency due to causes other than PE ($n = 2$). No patient died of bleeding. Two patients with fatal PE died on the same day of diagnosis, one died 5 days later. They scored 66, 44 and 89 points on PESI. All three patients with fatal PE were using hormonal therapy.

4. Discussion

Our data, obtained from a large registry of consecutive patients with VTE, reveal that one in every 50 such patients (2.0%) was aged 10–24 years. These patients had few co-morbidities and a low mortality rate. Of the 10 patients who died, three died of PE. Two of them died in < 24 h. Thus, the clinical relevance of PE in patients aged 10–24 years should not be underestimated. Most patients with PE in our cohort (71%) were women, and most (88%) had Sat O_2 levels ≥90% at baseline (as also reported in other series) [14–17]. Since 77% of women with PE were using estrogens (most of them without additional risk factors for VTE), we suggest that doctors working in Emergency wards should improve their awareness of the risk of PE when attending women with dyspnea (even if blood gases are normal), particularly if they are using estrogens. This should also apply to young men, since 52% of those with PE had no risk factors for VTE and most (87%) also had Sat O_2 levels ≥90%. Certainly, imaging for PE involves radiation exposure and substantial financial cost [18], and this concern is particularly acute in women and young adults who are more susceptible to radiation-induced carcinogenesis [19,20]. Thus, accurate identification of what young adults with suspected PE should undergo imaging studies is urgently needed. We also found that men had more often a proximal DVT while women a PE or a distal DVT as first clinical presentation of VTE, as previously reported [21].

Once the diagnosis of PE is established, the next important step is risk stratification. In or cohort, the vast majority (97%) of patients with acute PE scored at low risk according to PESI, including the 3 patients who died of PE. This may be likely explained because increasing age is one of the items included in the PESI score, as are some co-morbidities (infrequent in young adults). Our findings reveal that current prediction rules do not perform accurately in the young, and suggest that a prognostic score specifically designed for them might be welcome. In the meantime, since the proportion of patients at low risk according to sPESI was lower, our findings support to prefer sPESI over PESI to stratify young patients with acute PE.

Table 2
Signs and symptoms of VTE and treatment, according to gender and initial VTE presentation.

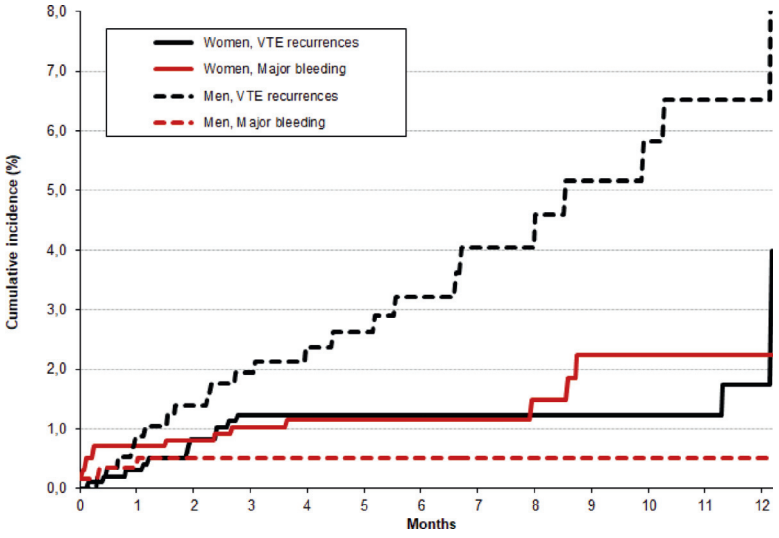
	Acute PE Women	Acute PE Men	Acute DVT Women	Acute DVT Men
Patients, N	474	195	515	387
Clinical characteristics,				
For patients with PE,				
Dyspnea	344 (73%)	122 (63%)*	–	–
Chest pain	333 (70%)	136 (70%)	–	–
Syncope	69 (15%)	17 (8.7%)*	–	–
Hemoptysis	53 (11%)	32 (16%)	–	–
SBP levels < 100 mmHg	60 (13%)	14 (7.2%)*		
Heart rate > 110 bpm	127 (28%)	30 (16%)†	–	–
Sat O_2 levels < 95% (N = 301)	69 (33%)	31 (35%)		
Sat O_2 levels < 90% (N = 301)	26 (12%)	12 (13%)	–	–
PESI ≤85 points	459 (97%)	189 (97%)	–	–
PESI ≤65 points	423 (89%)	175 (90%)	–	–
sPESI < 1 points	278 (59%)	141 (72%)‡	–	–
Diagnostic tests,				
V/Q lung scan	90 (19%)	34 (17%)	–	–
CT-scan	406 (86%)	175 (90%)	–	–
For patients with DVT,				
Upper-limb DVT	–	–	72 (14%)	104 (27%)‡
Proximal lower limb DVT			361 (70%)	241 (62%)*
Right sided DVT	–	–	176 (34%)	170 (44%)†
Bilateral DVT	–	–	10 (1.9%)	23 (5.9%)†
Duration of anticoagulant therapy,				
Mean days (± SD)	284 ± 353	357 ± 461*	243 ± 264	296 ± 484
Median days (IQR)	191 (126–294)	207 (127–378)	177 (105–257)	175 (104–265)
Initial therapy,				
Low-molecular-weight heparin	372 (78%)	145 (74%)	460 (89%)	331 (86%)
Unfractionated heparin	49 (10%)	25 (13%)	18 (3.5%)	15 (3.9%)
Thrombolytics	27 (5.7%)	9 (4.6%)	5 (0.97%)	9 (2.3%)
Fondaparinux	12 (2.5%)	6 (3.1%)	13 (2.5%)	20 (5.2%)*
Direct oral anticoagulants	9 (1.9%)	9 (4.6%)	18 (3.5%)	9 (2.3%)
Inferior vena cava filter	11 (2.3%)	11 (5.6%)	11 (2.1%)	6 (1.6%)
Long-term therapy,				
Vitamin K antagonists	354 (75%)	152 (78%)	362 (70%)	267 (69%)
Low-molecular-weight heparin	56 (12%)	15 (7.7%)	103 (20%)	87 (22%)
Direct oral anticoagulants	53 (11%)	25 (13%)	46 (8.9%)	27 (7.0%)

Gender differences: *$p < .05$; †$p < .01$; ‡$p < .001$.
Abbreviations: PE, pulmonary embolism; PESI, pulmonary embolism severity index; sPESI, simplified PESI; SBP, systolic blood pressure; bpm, beats per minute; DVT, deep vein thrombosis; SD, standard deviation; IQR, interquartile range; LMWH, low-molecular-weight heparin; IU, international units.

Table 3
Clinical outcomes during the course of anticoagulant therapy, according to initial VTE presentation and gender.

	Women		Men		Hazard ratio for women compared with men (95% CI)
	N	Events per 100 patient-years	N	Events per 100 patient-years	
Patients, N	989		582		
Recurrent PE	10	1.43 (0.72–2.54)	10	2.04 (1.04–3.63)	0.70 (0.28–1.72)
Recurrent DVT	6	0.85 (0.35–1.77)	16	3.35 (1.98–5.32)	0.25 (0.09–0.63)
Recurrent VTE	15	2.16 (1.26–3.49)	25	5.36 (3.54–7.79)	0.40 (0.21–0.76)
Major bleeding	14	1.98 (1.13–3.24)	3	0.60 (0.15–1.63)	3.31 (1.03–14.4)
Sites of bleeding					
Retroperitoneal	3	0.42 (0.11–1.15)	1	0.20 (0.01–0.98)	2.12 (0.23–55.9)
Menorrhagia	3	0.42 (0.11–1.15)	0	–	–
Haematoma	1	0.14 (0.01–0.69)	1	0.20 (0.01–0.98)	0.71 (0.02–27.6)
Gastrointestinal	2	0.28 (0.05–0.93)	0	–	–
Intracranial	1	0.14 (0.01–0.69)	0	–	–
Non-major bleeding	20	2.87 (1.80–4.35)	10	2.02 (1.03–3.61)	1.42 (0.67–3.16)
Sites of bleeding					
Menorrhagia	13	1.86 (1.04–3.10)	0	–	–
Haematoma	0	–	3	0.60 (0.15–1.63)	–
Haemoptysis	0	–	3	0.59 (0.15–1.62)	–
Gastrointestinal	2	0.28 (0.05–0.93)	0	–	–
Death	7	0.98 (0.43–1.95)	3	0.59 (0.15–1.62)	1.65 (0.43–7.87)
Causes of death					
Pulmonary embolism	2	0.28 (0.05–0.93)	1	0.20 (0.01–0.98)	1.42 (0.11–41.8)
Disseminated cancer	2	0.28 (0.05–0.93)	1	0.20 (0.01–0.98)	1.42 (0.11–41.8)
Respiratory insufficiency	2	0.28 (0.05–0.93)	0	–	–

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



Days		30	90	180	240	360
Women	***VTE recurrences***	3 (0.31%)	12 (1.24%)	12 (1.24%)	12 (1.24%)	13 (1.75%)
	Major bleeding	7 (0.71%)	10 (1.02%)	11 (1.15%)	12 (1.48%)	14 (2.23%)
Men	***VTE recurrences***	5 (0.87%)	11 (1.94%)	16 (3.21%)	19 (4.59%)	22 (6.53%)
	Major bleeding	3 (0.52%)	3 (0.52%)	3 (0.52%)	3 (0.52%)	3 (0.52%)

Fig. 1. Cumulative rates of VTE recurrences and major bleeding during the of course of anticoagulant therapy, according to gender.

Table 4
Uni- and multivariable analyses for VTE recurrences and for major bleeding during anticoagulation. Results expressed as hazard ratio and 95% confidence intervals (in brackets).

	VTE recurrences		Major bleeding	
	Univariable	Multivariable	Univariable	Multivariable
Clinical characteristics,				
Male gender	2.69 (1.41–5.12)†	1.41 (0.63–3.12)	0.36 (0.10–1.25)	0.50 (0.14–1.82)
Age 10–19 years	0.83 (0.41–1.70)	–	0.75 (0.25–2.31)	–
Body weight < 60 kg	0.89 (0.42–1.88)	–	0.87 (0.28–2.68)	–
Initial VTE presentation,				
Pulmonary embolism	0.66 (0.34–1.26)	–	3.09 (1.09–8.77)*	3.60 (1.24–10.4)*
Risk factors,				
Estrogen use	0.23 (0.10–0.55)‡	–	1.15 (0.44–2.98)	–
Immobility ≥ 4 days	0.15 (0.02–1.09)	–	0.76 (0.17–3.34)	–
Postoperative	1.63 (0.68–3.90)	–	1.72 (0.49–5.99)	–
Pregnancy or postpartum	1.22 (0.38–3.96)	–	3.21 (0.92–11.2)	3.00 (0.87–10.1)
Active cancer	3.91 (1.36–11.2)*	4.06 (0.96–17.2)	0.05 (0.00–466)	–
Unprovoked	3.96 (2.06–7.61)‡	3.39 (1.09–10.5)*	0.70 (0.23–2.14)	–
Prior VTE	2.64 (1.17–5.93)*	–	0.87 (0.11–6.59)	–
Co-morbidities,				
Chronic lung disease	0.05 (0.00–495)	–	3.13 (0.41–23.6)	–
Recent major bleeding	0.05 (0.00–27,504)	–	5.50 (0.73–41.4)	–
Blood tests at baseline,				
Anemia	2.17 (1.16–4.05)*	2.54 (1.30–4.95)†	2.95 (1.14–7.64)*	–
Platelet count < 100,000/μL	2.11 (0.29–15.4)	–	9.81 (2.24–42.9)†	10.1 (2.19–46.3)†
CrCl levels < 60 mL/min	3.53 (0.48–25.8)	–	7.43 (0.98–56.4)	–

Abbreviations: PE, pulmonary embolism; SBP, systolic blood pressure; bpm, beats per minute; PESI, pulmonary embolism severity index; sPESI, simplified PESI; VTE, venous thromboembolism; CrCl, creatinine clearance; OR, odds ratio; CI, confidence intervals.

* $p < .05$
† $p < .01$
‡ $p < .001$.

During the course of anticoagulation, women had fewer VTE recurrences (particularly fewer DVT recurrences) than men, as previously reported in other studies [22,23]. We can only hypothesize that many women using hormonal therapy may have discontinued its use after VTE, and this may have influenced the rate of VTE recurrences. At the same time, the rate of major bleeding was higher in women than in men. In fact, women had as many VTE recurrences as major bleed (15 vs. 14 events), but men had many more VTE recurrences than major bleeds (25 vs. 3 events). Hence, efficacy seems to be the most important issue (over safety) during anticoagulation in men aged 10–24 years with VTE. From a theoretical point of view, the higher rate of VTE recurrences than major bleeding in men might suggest the need for a different therapeutic approach (that is, a shorter duration and/or intensity of anticoagulant therapy in women). Further studies are needed to confirm these hypotheses.

The present study has a number of limitations. First, data from registries are susceptible to selection bias if a non-representative sample of patients is selected for analysis. However, RIETE registry captures a broad range of consecutive patients with symptomatic VTE from multiple medical centers, countries, and treatment settings, making it less likely that the study cohort is made up of a skewed population. Second, we studied only the outcomes during the course of anticoagulation. The gender differences in the rate of VTE recurrences or bleeding may not apply after discontinuing therapy and warrant further investigation. Third, even in our large registry, the number of events is small, limiting the possibility of additional investigations; such as consideration of a specific risk-stratification tool in this age subgroup. Fourth, the use of estrogens in some women may be necessary as treatment of heavy menstrual bleeding. Unfortunately, we do not gather information in RIETE on how many of these women had lesions predisposing to vaginal bleeding. Finally, our data are hypothesis generating and must be validated by properly designed trials. Although these concerns are valid, our data probably represent the largest available pool of prospectively collected information in this patient population. Although facing some limitations, our data could inform practice, until larger high-quality data emerge.

In summary, our study reveals that the clinical characteristics (including blood gases and scoring systems) at baseline in most young patients with PE may hinder early diagnosis and stratification of PE. During anticoagulation, women had similar rates of VTE recurrences and major bleeding, but in men the risk for VTE recurrences far outweighed the risk for bleeding. These differences were likely not due gender itself since they disappeared after adjusting for potential confounders.

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Appendix A

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