Thrombosis Update 13 (2023) 100148

Contents lists available at ScienceDirect

Thrombosis Update

journal homepage: www.sciencedirect.com/journal/thrombosis-update

A prognostic score to identify women at increased risk for abnormal uterine bleeding during anticoagulation for venous thromboembolism

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ARTICLE INFO

Keywords:
Anticoagulants
Venous thromboembolism
Uterine bleeding
Prognostic score

ABSTRACT

Introduction: Little is known about the clinical characteristics of women at increased risk for abnormal uterine bleeding (UB) during anticoagulation for venous thromboembolism (VTE).
Methods: We used the RIETE registry to identify the baseline characteristics of women developing abnormal UB during anticoagulation. We used logistic regression analysis to identify independent predictors for abnormal UB. Then, we built a prognostic score to identify at-risk women.
Results: From March 2001 through October 2022, there were 54,372 women with VTE. During anticoagulation (median, 181 days), 318 (0.6%) developed abnormal UB (major bleeding = 88, clinically relevant non-major (CRNM) = 230). On multivariable analysis, women aged <50 years, weighing >70 kg, with uterine cancer, recent UB, anemia, estrogen-related VTE, or receiving rivaroxaban or apixaban were at increased risk for abnormal UB. Using the prognostic score, 42,273 women (78%) were at low-risk, 8,828 (16%) intermediate-, and 3,271 (6.1%) at high-risk for abnormal UB. Their rates of abnormal UB were: 0.28 (95%CI: 0.23–0.35), 1.32 (95%CI: 1.07–1.61) and 7.12 (95%CI: 5.98–8.41) bleeds per 100 patient-years, respectively. The c-statistic was 0.80 (95%CI: 0.77–0.83). The rates of major UB were: 0.06 (95%CI: 0.04–0.09), 0.43 (95%CI: 0.30–0.60) and 1.85 (95%CI: 1.31–2.53) per 100 patient-years, respectively (c-statistic: 0.84; 95%CI: 0.80–0.89). The rates of CRNM uterine bleeding were: 0.21 (95%CI: 0.17–0.26), 0.85 (95%CI: 0.65–1.08), and 5.02 (95%CI: 4.09–6.10) bleeds per 100 patient-years, respectively (c-statistic: 0.78; 95%CI: 0.75–0.82).
Conclusions: Using 7 variables easily available at admission, we built a prognostic score that reliably identified women with VTE at increased risk for abnormal UB during anticoagulation.

1. Introduction

Major uterine bleeding (UB) is a relatively uncommon complication in women receiving anticoagulant therapy for venous thromboembolism (VTE) [1–6]. The incidence in randomized trials of anticoagulant therapy has been likely underestimated because the standard definitions of

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https://doi.org/10.1016/j.tru.2023.100148
Received 27 April 2023; Received in revised form 30 August 2023; Accepted 4 September 2023
Available online 6 October 2023

major bleeding used in most trials fail to account for the chronic and recurrent nature of abnormal UB [7,8]. The incidence and significance of clinically relevant non-major (CRNM) uterine bleeding is even less known, since women often hesitate to seek needed medical attention, but also due to the wide range of definitions of CRNM bleeding used in clinical trials [9]. However, although these women rarely require transfusions, they often develop iron deficiency, have an increased need for medical interventions, decreased quality of life, and miss school/-work [1].

Early identification of at-risk women may help to better individualize the management of VTE in order to decrease the risk of abnormal UB, and to prevent it earlier. Measures could include close monitoring of patients, education, use of alternative anticoagulant drugs and avoidance of unnecessary concomitant drugs that may increase the risk of bleeding. However, variables that may influence the risk for abnormal UB include demographics (age, body weight), concomitant diseases (endometriosis, cancer, anaemia, renal insufficiency) or drugs (corticosteroids, antiplatelet agents), among others. Prior studies in women with VTE did not specifically focus on the risk for UB, most likely because they were underpowered to evaluate the influence of these variables, because of small patient populations or because of the absence of information on some of them.

The RIETE (Registro Informatizado Enfermedad TromboEmbólica) database is an ongoing, multicenter, international, prospective registry of patients with objectively confirmed, acute VTE. Data from this registry have been used to evaluate outcomes after VTE, such as the frequency of recurrent VTE, major bleeding or mortality, and risk factors for such outcomes [10]. In the current study, we aimed to identify the baseline characteristics of women developing abnormal (either major or CRNM) UB during anticoagulation to build a prognostic score. Moreover, we aimed to evaluate the clinical relevance of abnormal UB assessing their 30-day outcomes (VTE recurrences, re-bleeding or death) after UB.

2. Methods

2.1. Data source

We used the data from the RIETE registry, which prospectively collects information on patients with symptomatic, objectively confirmed acute VTE (ClinicalTrials.gov identifier, NCT02832245). The design and conduct of the RIETE registry have been described previously [10]. All patients (or their relatives) provided written or oral informed consent for participation in the registry, in accordance with the local ethics committee requirements.

2.2. Inclusion criteria

Consecutive women with acute, symptomatic VTE confirmed by objective tests (ventilation-perfusion lung scan, helical CT-scan or contrast angiography for patients with clinically suspected pulmonary embolism [PE]; compression ultrasonography or contrast venography for those with suspected deep vein thrombosis [DVT]) were considered for this analysis. Women were excluded if they were currently participating in a blind therapeutic clinical trial.

2.3. Study design

First, we compared the baseline characteristics and 30-day outcomes (death, re-bleeding or VTE recurrences) after bleeding in women developing abnormal UB (major- or CRNM) during anticoagulation vs. those who bled (major- or CRNM) in other sites. To present a point of clinical reference, we also reported the baseline characteristics of women without bleeding events. Bleeding was classified as major if it was overt and required transfusion $\geq$2 units of blood, or was retroperitoneal, spinal or intracranial, or fatal [10]. This definition has been used since inception of the registry in 2001. Although the RIETE bleeding definition preceded the definition of the International Society on Thrombosis and Haemostasis (ISTH) for major bleeding [11], these two closely resemble each other. CRNM bleeding was defined as any overt bleeding not meeting criteria for major bleeding but requiring medical assistance. All episodes of clinically suspected VTE recurrences were investigated by repeat compression ultrasonography, helical CT scan, ventilation–perfusion lung scintigraphy or angiography.

Then, we performed a multivariable analysis through a logistic regression model trying to identify independent predictors for abnormal UB (major- or CRNM), and built a prognostic score assigning points to each independent variable according to regression coefficients β.

2.4. Study variables

The following variables were recorded in RIETE: patient's characteristics; VTE signs and symptoms at baseline; clinical status including any coexisting or underlying conditions such as chronic heart or lung disease, recent (<30 days before) major bleeding, anemia or renal insufficiency; concomitant disorders (anemia, thrombocytopenia, renal insufficiency); risk factors for VTE, including the use of estrogens; concomitant drugs; the treatment received upon VTE diagnosis (drugs, doses and duration), and the outcomes during the first 30 days after bleeding.

Immobilized patients were defined as non-surgical patients that had been immobilized (i.e., total bed rest with or without bathroom privileges) for $\geq$4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those that had undergone an operation in the 2 months prior to the index VTE. Active cancer was defined as newly diagnosed cancer (<3 months before) or when receiving anti-neoplastic treatment of any type (i.e., chemotherapy, radiotherapy, surgery, hormonal, support therapy or combined therapies). Anemia was defined as hemoglobin levels <12 g/dL. Creatinine clearance (CrCl) levels at baseline were calculated using the Cockcroft and Gault formula. The RIETE registry restricted all values of these variables to the nearest recorded to the time of VTE diagnosis.

2.5. Treatment and follow-up

There was no standardized treatment for patients in RIETE. Patients were managed according to the recommendations from individual clinicians in the participating hospitals. All (100%) patients in RIETE had follow-up for at least 90 days or death. Longer follow-up was available for most patients. For patients who developed UB after the first 90 days of enrollment in RIETE, a minimum follow-up of 30 days (or until death) occurred in all (100%) of study participants after the bleeding event, irrespective of when it happened. During each visit, the occurrence of VTE recurrences or major bleeding was assessed.

2.6. Statistical analysis

Categorical variables were reported as frequency counts (percentages) and compared using the chi-square test (two-sided) and Fisher's Exact Test (two-sided). Continuous variables were reported as mean and standard deviation (or median with interquartile range, if not normally distributed), and compared using Student *t*-test. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. The incidence rate of major- or CRNM bleeding was expressed as events per 100 person-years with 95%CI. The risk for abnormal UB (either major- or CRNM) was assessed using logistic regression models. Covariates entering into 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. The doses of anticoagulant drugs were not included because its choice might have been influenced by the physician's assessment of a patient's risk of bleeding or recurrent VTE.

We built a prognostic score assigning points to each independent

Table 1
Incidence rates of uterine- and non-uterine bleeding during anticoagulation in 54,372 women with VTE, according to the severity of bleeding and patient's age.

	All women		Aged <50 years		Aged ≥50 years	
	N	N per 100 patient -years (95% CI)	N	N per 100 patient -years (95% CI)	N	N per 100 patient -years (95% CI)
Patients, N	***54,372***		***10,571***		***43,801***	
Duration of therapy,						
Median days (IQR)	181 (101–319)		184 (107–300)		179 (100–324)	
Uterine bleeding,						
Any abnormal	318	0.76 (0.68–0.84)	178	2.19 (1.88–2.53)	140	0.41 (0.35–0.49)‡
Major bleeding	88	0.20 (0.16–0.25)	40	0.47 (0.34–0.64)	48	0.14 (0.10–0.18)‡
CRNMB	230	0.53 (0.46–0.60)	138	1.65 (1.39–1.95)	92	0.26 (0.21–0.32)‡
Non-uterine bleeding,						
Any	3,265	7.77 (7.51–8.04)	264	3.24 (2.87–3.65)	3,001	8.86 (8.55–9.18)‡
Major bleeding	1,495	3.45 (3.28–3.63)	98	1.17 (0.95–1.42)	1,397	4.00 (3.79–4.21)‡
CRNMB	1,770	4.13 (3.95–4.33)	166	1.99 (1.70–2.31)	1,604	4.66 (4.43–4.89)‡

Differences between patients aged <50 vs. ≥ 50 years: *$p < 0.05$; ‡$p < 0.001$.
Abbreviations: CI, confidence intervals; IQR, inter-quartile range; CRNMB, clinically-relevant, non-major bleeding.

variable according to regression coefficients β. We assigned a risk score to each woman by adding up points for each independent variable. Then, we tried to identify women at low-, intermediate- or high risk for abnormal UB during anticoagulation. Discrimination was quantified calculating the area under the receiver operating characteristic curve. Sensitivity, specificity, and positive and negative predictive values were determined. Finally, we performed an internal validation of the final model's performance by bootstrapping methods. Bootstrap sampling was performed 1,000 times from the original sample, sampling the same number of patients as in the original sample with replacement. Statistical analyses were conducted with IBM SPSS Statistics (version 25).

3. Results

From March 2001 through October 2022 there were 54,372 women in RIETE. Of these, 318 (0.6%) developed abnormal UB (major bleeding 88; CRNM bleeding 230) during anticoagulation (median, 181 days), and 3,265 (6.0%) bled in other sites (major bleeding 1,495; CRNM bleeding 1,770). The incidence rate of major UB was: 0.20 bleeds per 100 patient-years (95%CI: 0.16–0.25), and the incidence rate of CRNM uterine bleeding was: 0.53 (95%CI: 0.46–0.60) bleeds per 100 patient-years. The incidence rate of abnormal (major- or CRNM) UB was over 5-fold higher in women aged <50 years than in those aged ≥50 years (Table 1). Among 10,573 women aged <50 years, the incidence rate of CRNM uterine bleeding (1.65 bleeds per 100 patient-years, 95%CI: 1.39–1.95) was similar to the incidence rate of CRNM non-uterine (any other site) bleeding (1.99 bleeds per 100 patient-years, 95%CI: 1.70–2.31).

3.1. Uterine versus non-uterine bleeding

Women developing abnormal UB (major- or CRNM) were younger and more likely to have active cancer (mostly, uterine cancer), recent major bleeding (mostly, uterine bleeding), to have estrogen-related VTE, or to be receiving direct oral anticoagulants (DOACs) compared with those who bled in other sites, or those who did not bleed, but were less likely to have renal insufficiency (Table 2). Median time elapsed from VTE to bleeding was longer in women with UB than in those with non-uterine bleeding (median days: 43 vs. 24 days respectively for major bleeds; 77 vs. 55 days respectively for CRNM bleeds).

Among 1,583 women developing major bleeding, those with UB had a lower 30-day mortality rate than those who bled in other sites (13% vs. 29%, respectively), and similar rates of major re-bleeding (4.5% vs. 4.7%) or VTE recurrences (2.3% vs. 3.5%) (Table 2). Among 2,000 women with CRNM bleeding, those with UB also had a lower mortality rate than those who bled in other sites (2.2% vs. 8.4%), and similar rates of major re-bleeding (0.9% vs. 1.1%) or VTE recurrences (0.9% vs. 1.2%).

3.2. Abnormal uterine bleeding

Among 318 women developing abnormal UB, 178 (56%) were aged <50 years, 79 (25%) had active cancer (uterine cancer, 38), 95 (30%) had estrogen-related VTE, and 105 (33%) were receiving DOACs at the time of bleeding (Table 3). Among 178 women with abnormal UB aged <50 years, 76 (43%) had estrogen-related VTE, 17 (9.6%) had active cancer, and 86 (48%) were using DOACs (rivaroxaban n= 67, apixaban n=16) at the time of the bleed. Among 140 women with abnormal UB aged ≥50 years, 30 (21%) had estrogen-related VTE, 62 (44%) had cancer (uterine cancer, 33) and 19 (14%) were using DOACs (rivaroxaban 11, apixaban 5) at the time of the bleed.

Anticoagulant therapy was immediately discontinued (transiently or permanently) in all 88 women with major bleeding and in 13 (5.7%) with CRNM bleeding. Most women with CRNM uterine bleeding (149 of 204, 73%) continued with the same drug, many (109 of 149, 73%) at lower doses than before the bleed. All women suffering major UB, and 37 of 230 women with uterine CRNMB (16%) required hospitalization. No women aged <50 years died within the first 30 days after abnormal UB (neither major- or CRNMB). Among 16 women aged ≥50 years who died within the first 30 days after abnormal UB, 13 (81%) had cancer. There were no significant differences in the 30-day rates of VTE recurrences or re-bleeding between women aged more or less than 50 years (Table 3).

3.3. Identification of at-risk women

On multivariable analysis, women aged <50 years (odds ratio [OR]: 3.59; 95%CI: 2.68–4.82), weighing >70 kg (OR: 1.56; 95%CI: 1.23–1.97), with uterine cancer (OR: 10.6; 95%CI: 7.24–15.6), recent uterine bleeding (OR: 5.03; 95%CI: 2.96–8.55), anemia (OR: 2.18; 95% CI: 1.73–2.76), estrogen-related VTE (OR: 1.79; 95%CI: 1.35–2.36), or receiving rivaroxaban (OR: 3.77; 95%CI: 2.64–5.37) or apixaban (OR: 2.27; 95%CI: 1.36–3.79) were at increased risk for abnormal UB (Table 4). Interestingly, there were no missing data in any of these variables.

These variables were used to build a prognostic score assigning different points according to the β coefficients. There were 42,273 women (78%) at low risk (≤1.5 points), 8,828 (16%) at intermediate risk (2.0–2.5 points), and 3,271 (6.1%) at high risk (≥3 points). Their rates of abnormal (major or non-major) UB were: 0.28 (95%CI: 0.23–0.35), 1.32 (95%CI: 1.07–1.61) and 7.12 (95%CI: 5.98–8.41) bleeds per 100 patient-years, respectively. The c-statistic was 0.80 (95% CI: 0.77–0.83). The rates of major UB were: 0.06 (95%CI: 0.04–0.09), 0.43 (95%CI: 0.30–0.60) and 1.85 (95%CI: 1.31–2.53) events per 100 patient-years, respectively (c-statistic: 0.84; 95%CI: 0.80–0.89). The rates of CRNM uterine bleeding were: 0.21 (95%CI: 0.17–0.26), 0.85 (95%CI: 0.65–1.08), and 5.02 (95%CI: 4.09–6.10) events per 100

Table 2
Baseline characteristics, treatment and 30-day outcomes after bleeding in 54,372 women with VTE, according to the presence or absence of bleeding during anticoagulation.

	Uterine bleeding		Non-uterine bleeding		No bleeding
	Major	Non-major	Major	Non-major	
Patients, N	**88**	**230**	**1,495**	**1,770**	**50,789**
Age (mean years ±SD)	56 ± 16‡	51 ± 20‡	74 ± 14‡	72 ± 16‡	67 ± 19
Weight (mean kg ±SD)	77 ± 20†	77 ± 20‡	70 ± 15‡	71 ± 16	71 ± 16
Initial presentation as PE	47 (53%)	140 (61%)*	918 (61%)‡	1,072 (61%)‡	26,610 (52%)
Risk factors for VTE,					
Active cancer	22 (25%)‡	44 (19%)	401 (27%)‡	390 (22%)‡	8,970 (18%)
Uterine cancer	35 (40%)‡	16 (7.0%)‡	34 (2.3%)†	28 (1.6%)	712 (1.4%)
Recent surgery	10 (11%)	21 (9.1%)	172 (12%)	209 (12%)	5,622 (11%)
Recent immobility ≥4 days	10 (11%)†	37 (16%)†	507 (34%)‡	503 (28%)‡	11,988 (24%)
Pregnancy or puerperium	4 (4.5%)	5 (2.2%)	7 (0.5%)‡	19 (1.1%)‡	1,218 (2.4%)
Estrogen use	20 (23%)‡	75 (33%)‡	47 (3.1%)‡	98 (5.5%)‡	5,272 (10%)
Risk factors for bleeding,					
Recent major bleeding (any)	9 (10%)‡	11 (4.8%)*	97 (6.5%)‡	70 (4.0%)‡	1,120 (2.2%)
Recent uterine bleeding	9 (10%)‡	8 (3.5%)‡	6 (0.4%)	7 (0.4%)	179 (0.35%)
Anemia	65 (74%)‡	101 (44%)*	780 (52%)‡	730 (41%)‡	18,263 (36%)
Platelet count <100,000/μL	1 (1.1%)	5 (2.2%)	54 (3.6%)‡	57 (3.2%)†	1,068 (2.1%)
CrCl levels <60 mL/min	15 (17%)‡	43 (19%)‡	912 (61%)‡	948 (54%)‡	21,040 (41%)
Initial therapy (first 10 days),					
Low-molecular-weight heparin	69 (78%)*	166 (72%)‡	1,282 (86%)	1,528 (86%)	43,869 (86%)
Unfractionated heparin	12 (14%)†	14 (6.1%)	109 (7.3%)†	122 (6.9%)†	2,727 (5.4%)
Direct oral anticoagulants	3 (3.4%)	31 (13%)‡	11 (0.7%)‡	41 (2.3%)*	1,742 (3.4%)
Rivaroxaban, any	3 (3.4%)	24 (10%)‡	5 (0.3%)‡	32 (1.8%)	1,136 (2.3%)
Rivaroxaban, low doses	0	1 (0.4%)	1 (0.1%)	1 (0.1%)	122 (0.2%)
Apixaban, any	0	4 (1.7%)	5 (0.3%)*	6 (0.3%)*	457 (0.9%)
Aixaban, low doses	0	2 (0.9%)	1 (0.1%)	2 (0.1%)	95 (0.2%)
Thrombolytic drugs	3 (3.4%)	6 (2.6%)	53 (3.5%)‡	43 (2.4%)‡	598 (1.2%)
Long-term therapy (beyond Day 10),					
Vitamin K antagonists	28 (32%)‡	96 (42%)†	586 (39%)‡	838 (47%)‡	26,493 (52%)
Low-molecular-weight heparin	38 (43%)*	51 (22%)†	570 (38%)‡	641 (36%)‡	15,471 (30%)
Direct oral anticoagulants	16 (18%)	78 (34%)‡	64 (4.3%)‡	215 (12%)	6,575 (13%)
Among those <50 years	11 (13%)‡	67 (29%)‡	4 (0.3%)‡	23 (1.3%)‡	1,577 (3.1%)
Rivaroxaban, any	11 (13%)*	56 (25%)‡	25 (2.0%)‡	116 (6.7%)	3,213 (6.5%)
Rivaroxaban, low doses	2 (2.3%)	2 (0.9%)	3 (0.2%)	12 (0.7%)	220 (0.4%)
Apixaban, any	3 (3.4%)	18 (7.8%)†	25 (1.7%)‡	52 (2.9%)*	2,049 (4.0%)
Aixaban, low doses	0	1 (0.4%)	3 (0.2%)	11 (0.6%)	252 (0.5%)
Edoxaban, any	1 (1.1%)	3 (1.3%)	9 (0.6%)*	25 (1.4%)	644 (1.3%)
Edoxaban, 30 mg	0	0	0	3 (0.2%)	207 (0.4%)
Dabigatran	1 (1.2%)	0	2 (0.2%)	8 (0.5%)	209 (0.4%)
Time elapsed since VTE,					
Median days (IQR)	43 (13–154)	77 (23–145)	24 (8–113)	55 (14–148)	–
>90 days	36 (41%)‡	101 (44%)‡	429 (29%)‡	647 (37%)‡	–
30-day outcomes after bleeding,					
Death	11 (13%)	5 (2.2%)	427 (29%)	149 (8.4%)	–
Major re-bleeding	4 (4.5%)	2 (0.9%)	70 (4.7%)	20 (1.1%)	–
Non-major re-bleeding	0	5 (2.2%)	18 (1.2%)	66 (3.7%)	–
Recurrent VTE	2 (2.3%)	2 (0.9%)	53 (3.5%)	20 (1.1%)	–

Comparisons between patients with bleeding events vs. those that did not bleed: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: SD, standard deviation; VTE, venous thromboembolism; PE, pulmonary embolism; CrCl, creatinine clearance; IQR, inter-quartile range.

patient-years, respectively (c-statistic: 0.78; 95%CI: 0.75–0.82). Using bootstrap sampling, the rate of abnormal UB was 0.29 (95%CI, 0.24–0.33), 1.31 (95%CI: 1.11–1.54), and 7.14 (95%CI, 6.08–8.15) events per 100 person-years, respectively.

Finally, we analyzed how the prognostic score performed separately in women aged <50 or ≥50 years. Among women aged <50 years, the prognostic score performed better to identify non-major UB (c-statistic: 0.75; 95%CI: 0.71–0.79) than major UB (c-statistics: 0.69; 95%CI: 0.61–0.77), as shown in Table 5 and in Fig. 1. On the contrary, among women aged >50 years, it was the opposite: the c-statistic was 0.64 (95%CI: 0.58–0.70) for non-major UB and 0.83 (95%CI: 0.76–0.91) for major UB (Fig. 2).

4. Discussion

Our findings, obtained from a large cohort of women with VTE, reveal that the incidence rate of abnormal (including major- and CRNM) uterine bleeding during anticoagulation was of 0.76 (95%CI: 0.68–0.84) bleeds per 100 patient-years. Of these, there were 0.20 (95%CI: 0.16–0.25) major bleeds and 0.53 (95%CI: 0.46–0.60) CRNM bleeds. The rate was particularly high in young women, those with uterine cancer, recent vaginal bleeding and in those receiving DOACs. Our rate of 0.20 major uterine bleeds per 100 patient-years was higher than the rate in large randomized trials of oral anticoagulants: no major UB was reported in any of the 10 studies included in a recent review [8,11–14]. This may be explained by the fact that most trials excluded women perceived to be at increased risk for bleeding. Our rate of 0.53 CRNM uterine bleeds per 100 patient-years was also slightly higher than the rates in randomized trials [7,8]. Interestingly, one in every 6 women with CRNMB in our cohort (37 of 230, 16%) required hospitalization. Unfortunately, RIETE does not gather information on bleeds not requiring medical assistance. We can only hypothesize that the incidence of less severe forms of UB in our cohort may have been much higher. In recent years, new data have become available from extension trials, cancer-associated VTE trials, pediatric trials, and some observational studies specifically examining UB as an outcome [15–19]. Rates of abnormal UB not meeting major- or CRNM bleeding were much higher, affecting up to 50% of women receiving DOACs.

We built a prognostic score that reliably identifies which women at baseline were at increased risk for abnormal UB during anticoagulation. These women might benefit from education, close monitoring of early

Table 3
Clinical characteristics, management of bleeding and 30-day outcomes in 281 women with abnormal uterine bleeding.

	<50 years		≥50 years	
	Major bleeding	Non-major bleeding	Major bleeding	Non-major bleeding
Patients, N	***40***	***138***	***48***	***92***
Demographics,				
Mean age (years ±SD)	43 ± 7	37 ± 9‡	66 ± 13	71 ± 13*
Body weight (mean kg±SD)	80 ± 21	75 ± 19	74 ± 19	79 ± 22
Time elapsed since VTE,				
Median days (IQR)	45 (10–228)	79 (29–141)	43 (13–127)	65 (16–166)
Over 90 days (n)	23 (57%)	77 (56%)	29 (60%)	52 (57%)
Risk factors for VTE,				
Active cancer	7 (18%)	10 (7.2%)	28 (58%)	34 (37%)*
Uterine cancer	3 (7.5%)	2 (1.4%)	19 (40%)	14 (15%)†
Recent surgery	4 (10%)	14 (10%)	6 (13%)	7 (7.6%)
Recent immobility >4 days	3 (7.5%)	14 (10%)	7 (15%)	23 (25%)
Estrogen use	11 (28%)	65 (47%)*	9 (19%)	10 (11%)
Pregnancy or puerperium	4 (10%)	5 (3.6%)	0	0
Concomitant disorders,				
Anemia	27 (68%)	61 (44%)*	38 (79%)	40 (43%)‡
CrCl levels <60 mL/min	1 (2.5%)	3 (2.2%)	14 (29%)	40 (43%)
Current therapy at bleeding,				
Thrombolytics	2 (5.0%)	0	0	1 (1.1%)
Low-molecular-weight heparin	11 (28%)	17 (12%)*	21 (44%)	31 (34%)
Unfractionated heparin	1 (2.5%)	1 (0.72%)	6 (13%)	1 (1.1%)†
Fondaparinux	0	2 (1.7%)	0	1 (1.1%)
Vitamin K antagonists	13 (33%)	45 (33%)	14 (29%)	45 (49%)*
Direct oral anticoagulants	13 (33%)	73 (53%)*	6 (13%)	13 (14%)
Rivaroxaban	9 (22%)	58 (42%)‡	4 (8.3%)	7 (7.6%)
Apixaban	3 (7.5%)	13 (9.4%)	1 (2.1%)	4 (4.3%)
Edoxaban	0	2 (1.4%)	1 (2.1%)	2 (2.2%)
Dabigatran	1 (2.5%)	0	0	0
Changes in anticoagulant therapy,				
Discontinuation	40 (100%)	5 (4.1%)‡	48 (100%)	8 (8.7%)‡
Switch to other drugs	0	29 (21%)‡	0	28 (30%)‡
Same drug	0	93 (67%)‡	0	56 (61%)‡
Inferior vena cava filter	4 (10%)	4 (2.9%)	5 (10%)	6 (6.5%)
30-day outcomes after bleeding,				
Death	0	0	11 (23%)	5 (5.4%)†
Major re-bleeding	2 (5.0%)	0	2 (4.2%)	2 (2.2%)
Non-major re-bleeding	0	3 (2.2%)	0	2 (2.2%)
Recurrent VTE	1 (2.5%)	1 (0.7%)	2 (4.2%)	0

Comparisons between patients with major-vs. non-major uterine bleeding: *$p < 0.05$; †$p < 0.01$.

Abbreviations: CI, confidence intervals; SD, standard deviation; IQR, interquartile range; VTE, venous thromboembolism; CrCl, creatinine clearance.

signs of UB and use of a personalized approach to anticoagulation prescription. We found 7 variables easily available at baseline (age <50 years, weight >70 kg, uterine cancer, estrogen-related VTE, recent vaginal bleeding, anemia and long-term therapy with rivaroxaban or apixaban) that were significantrisk factors for the n subsequent development of abnormal UB. Using our prognostic score, there were 38,923 women (78.9%) at low risk, 8,255 (16.7%) at intermediate risk, and 2,157 (4.4%) at high risk. The c-statistic was 0.83 (95%CI: 0.79–0.88) for major UB, and 0.78 (95%CI: 0.75–0.82) for CRNM uterine bleeding. Thus, our score was reasonably good at identifying women at increased risk for abnormal UB. It consistently identified women at increased risk for major- and for CRNM uterine bleeding.

Table 4
Uni- and multivariable analyses for abnormal uterine bleeding (major or non-major) in 54,372 women with VTE.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Demographics,				
Age 50–75 years	Ref.	–	Ref.	–
Age <50 years	4.38 (3.37–5.66)	<0.001	3.59 (2.68–4.82)	<0.001
Age >75 years	0.70 (0.50–0.98)	0.04	0.99 (0.67–1.44)	0.940
Body weight >70 kg	1.45 (1.14–1.85)	0.002	1.56 (1.23–1.97)	<0.001
Initial VTE presentation,				
Symptomatic PE	1.17 (0.94–1.46)	0.169	–	–
Risk factors for VTE,				
Uterine cancer	10.8 (7.63–15.0)	<0.001	10.6 (7.24–15.6)	<0.001
Non-uterine cancer	0.86 (0.62–1.19)	0.371	–	–
Recent surgery	0.91 (0.63–1.32)	0.627	–	–
Recent immobility ≥4 days	0.63 (0.46–0.85)	0.003	0.89 (0.65–1.22)	0.471
Pregnancy or puerperium	1.23 (0.63–2.38)	0.544	–	–
Estrogen use	3.57 (2.81–4.54)	<0.001	1.79 (1.35–2.36)	<0.001
Risk factors for bleeding,				
Recent uterine bleeding	22.7 (13.9–37.0)	<0.001	5.03 (2.96–8.55)	<0.001
Anemia	2.15 (1.73–2.68)	<0.001	2.18 (1.73–2.76)	<0.001
Platelet count <100,000/μL	1.05 (0.47–2.36)	0.902	–	–
CrCl levels <60 mL/min	0.33 (0.25–0.44)	<0.001	0.86 (0.59–1.25)	0.428
Initial therapy (first 7–10 days),[a]				
LMWH	Ref.	–	Ref.	–
Unfractionated heparin	1.89 (1.26–2.84)	0.002	1.49 (0.98–2.25)	0.061
Rivaroxaban	5.14 (3.45–7.66)	<0.001	1.59 (0.97–2.60)	0.066
Apixaban	2.17 (1.43–5.38)	0.035	1.33 (0.53–3.35)	0.545
Long-term therapy (beyond Day 10),				
Vitamin K antagonists	Ref.	–	Ref.	–
LMWH	1.47 (1.11–1.93)	0.006	1.11 (0.83–1.48)	0.494
Rivaroxaban	5.19 (3.85–6.99)	<0.001	3.77 (2.64–5.37)	<0.001
Apixaban	2.35 (1.49–3.71)	<0.001	2.27 (1.36–3.79)	0.002
Edoxaban	1.15 (0.43–3.12)	0.780	1.19 (0.44–3.23)	0.735
Dabigatran	1.12 (0.16–8.07)	0.904	1.04 (0.15–7.49)	0.966

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism; CrCl, creatinine clearance; LMWH, low-molecular-weight heparin; Ref., reference; HR, hazard ratio; CI, confidence intervals.

[a] Neither edoxaban nor dabigatran were prescribed for initial therapy.

The influence of cancer, recent bleeding or anemia on the risk for bleeding in patients with VTE is well known [20–22]. The higher risk for abnormal UB in women receiving DOACs has been also reported previously, particularly in those receiving rivaroxaban [22–29]. However, to our knowledge the higher risk in women weighing >70 kg has not previously been reported. We have no explanation to explain the influence of body weight on the risk for bleeding. These findings must be externally validated in properly designed studies. If proven, women with VTE scoring at high-risk should be advised to avoid the use of DOACs (at least rivaroxaban and apixaban) and to replace them by other anticoagulant drugs.

Table 5
Application of the prognostic score for the risk of uterine bleeding.

Variables:	Patients, N	Points	Any uterine bleeding		Major uterine bleeding		Non-major uterine bleeding	
			N	Events per 100 patient-years	N	Events per 100 patient-years	N	Events per 100 patient-years
All patients	**54,372**	**Any**	**318**	**0.76 (0.68–0.84)**	**88**	**0.20 (0.16–0.25)**	**230**	**0.53 (0.46–0.60)**
Age <50 years	10,534 (19%)	1.28	178	2.19 (1.88–2.53)	40	0.47 (0.34–0.64)	138	1.65 (1.39–1.95)
Body weight >70 kg	26,598 (49%)	0.44	121	0.65 (0.54–0.78)	35	0.18 (0.13–0.25)	86	0.45 (0.36–0.55)
Uterine cancer	812 (1.5%)	2.36	38	8.56 (6.14–11.6)	22	4.66 (2.99–6.94)	16	3.37 (1.99–5.35)
Estrogen use	5,512 (10%)	0.58	95	2.25 (1.83–2.73)	20	0.46 (0.29–0.69)	75	1.73 (1.37–2.16)
Prior uterine bleeding	157 (0.3%)	1.62	17	19.1 (11.5–30.0)	9	9.07 (4.42–16.6)	8	7.76 (3.60–14.7)
Anemia	19,941 (36%)	0.78	166	1.27 (1.09–1.48)	65	0.47 (0.37–0.60)	101	0.74 (0.60–0.89)
Long-term rivaroxaban	3,421 (6.3%)	1.23	67	2.96 (2.31–3.74)	11	0.46 (0.24–0.80)	56	2.37 (1.80–3.05)
Long-term, apixaban	2,414 (4.4%)	0.82	22	1.33 (0.86–1.98)	3	0.18 (0.04–0.48)	19	1.12 (0.70–1.72)
Points:								
Risk of bleeding,								
Low-risk	42,273 (78%)	0–1.5	94	0.28 (0.23–0.35)	21	0.06 (0.04–0.09)	73	0.21 (0.17–0.26)
Intermediate-risk	8,828 (16%)	2.0–2.5	92	1.32 (1.07–1.61)‡	31	0.43 (0.30–0.60)‡	61	0.85 (0.65–1.08)‡
High-risk	3,271 (6.1%)	≥3	132	7.12 (5.98–8.41)‡	36	1.85 (1.31–2.53)‡	96	5.02 (4.09–6.10)‡
Discrimination:								
c-statistics (95%CI)	–	–	0.80 (0.77–0.83)		0.84 (0.80–0.89)		0.78 (0.75–0.82)	
Sensitivity	–	–	58.5 (51.1–66.2)		59.1 (51.6–66.6)		58.3 (50.8–65.8)	
Specificity	–	–	5.3 (4.9–5.5)		5.4 (5.0–5.6)		5.3 (4.9–5.5)	
PPV	–	–	0.36 (0.19–0.41)		0.09 (0.01–0.13)		0.26 (0.12–0.33)	
NPV	–	–	95.6 (95.1–96.3)		98.8 (98.5–99.2)		96.8 (96.4–97.4)	
PLR	–	–	0.62 (0.59–0.65)		0.62 (0.52–0.75)		0.62 (0.57–0.66)	
NLR	–	–	7.86 (6.86–9.01)		7.53 (5.84–9.72)		7.82 (6.68–9.14)	
In patients <50 years,	***11,029***	***Any***	***184***	***2.16 (1.86–2.49)***	***44***	***0.50 (0.37–0.66)***	***32***	***1.60 (1.35–1.88)***
Low-risk	1,998 (18%)	0–1.5	8	0.45 (0.21–0.86)	2	0.11 (0.02–0.36)	6	0.33 (0.13–0.69)
Intermediate-risk	6,663 (60%)	2.0–2.5	76	1.45 (1.15–1.80)‡	25	0.46 (0.30–0.67)*	51	0.94 (0.71–1.23)†
High-risk	2,368 (21%)	≥3	100	6.67 (5.46–8.08)‡	17	1.08 (0.65–1.70)‡	83	5.43 (4.35–6.69)‡
c-statistic	–	–	0.74 (0.70–0.77)		0.69 (0.61–0.77)		0.75 (0.71–0.79)	
In patients >50 years,	***43,345***	***Any***	***134***	***0.40 (0.34–0.47)***	***44***	***0.13 (0.09–0.17)***	***90***	***0.26 (0.21–0.31)***
Low-risk	40,276 (93%)	0–1.5	86	0.27 (0.22–0.34)	19	0.06 (0.04–0.09)	67	0.20 (0.16–0.26)
Intermediate-risk	2,450 (5.6%)	2.0–2.5	16	0.93 (0.55–1.47)‡	6	0.33 (0.13–0.69)†	10	0.55 (0.28–0.99)†
High-risk	619 (1.4%)	≥3	32	8.97 (6.24–12.5)‡	19	5.00 (3.10–7.66)‡	13	3.38 (1.88–5.63)‡
c-statistic	–	–	0.70 (0.65–0.75)		0.83 (0.76–0.91)		0.64 (0.58–0.70)	

Differences between patients at low-risk vs. other subgroups: ‡$p < 0.001$.
Abbreviations: CI, confidence intervals; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

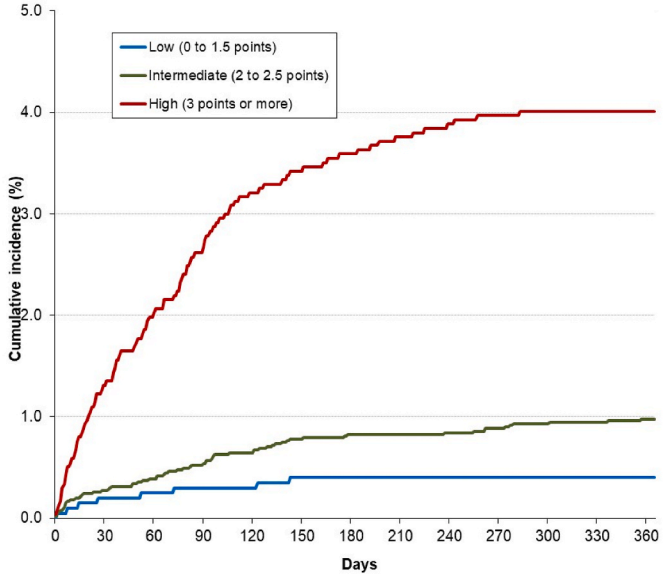

Fig. 1. Cumulative rates of abnormal uterine bleeding (either major- or non-major bleeding) during the first year of anticoagulation, according to the prognostic score for women aged <50 years old.

Our study suffers from a number of limitations that should be reported. First, the analysis was a post-hoc analysis of prospectively collected data, in unselected women with acute VTE. Despite not being a-priori calibrated to gather exhaustive information on abnormal UB, and may be underpowered, the RIETE registry is the largest ongoing database on patients with VTE. Second, the management (for the index VTE and for the bleeding event) of women was decided by investigators and local usual care. Third, there is a relatively small number of women treated with DOACs at the bleeding event. This may be explained by the long period of the RIETE registry which is running since 2001. Fourth, since RIETE does not capture less severe bleeds, we cannot use our score to identify at-risk women for these bleeds. Fifth, unfortunately the RIETE registry does not capture information on additional factors or disorders (such as endometriosis, uterine polyps, polycystic ovary syndrome, or others) that could also have influenced on the risk of bleeding. Finally, we did not externally validate the prognostic score, but hope that other researchers will be able to do it.

We conclude that abnormal UB is a not an uncommon complication in women receiving anticoagulation for VTE. Using 7 variables easily available at baseline, we built a prognostic score that reliably identified those at increased risk for abnormal UB. The score consistently identified at-risk women for major- and for CRNM uterine bleeding.

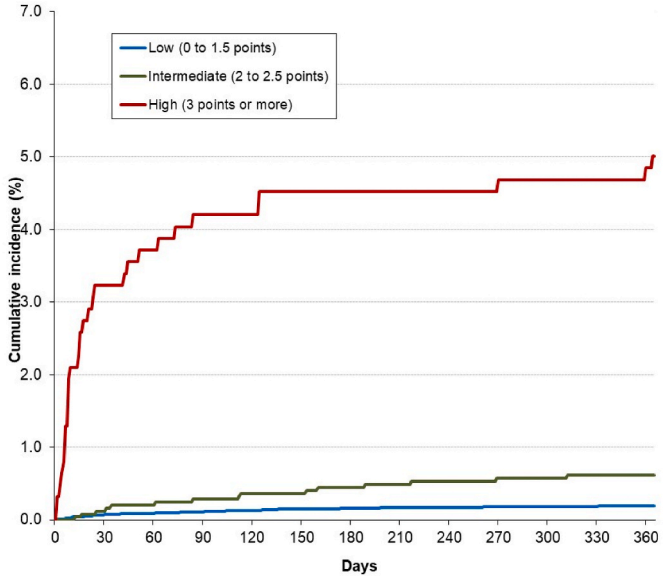

Fig. 2. Cumulative rates of abnormal uterine bleeding (either major- or non-major bleeding) during the first year of anticoagulation, according to the prognostic score in women aged ≥50 years old.

Authors contribution

Conceived and designed the analysis: GSB, MM.
Collected the data: GSB, JC, SM, JAN, MDP, NRG, BB, MM, PDM.
Performed the analysis: MM.
Wrote the paper: GSB, JC, SM, JAN, MDP, NRG, BB, MM, PDM.

Declaration of competing interest

Any of the authors declare no conflicts of interest.

Acknowledgements

We express our gratitude to Sanofi Spain, LEO PHARMA and ROVI for supporting this Registry with an unrestricted educational grant. We also thank the RIETE Registry Coordinating Center, S&H Medical Science Service, for their quality control data, logistic and administrative support.

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References

[1] I. Martinelli, A.W.A. Lensing, S. Middeldorp, M. Levi, J. Beyer-Westendorf, B. Van Bellen, et al., Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use, Blood 127 (2016) 1417–1425.
[2] S. Schulman, Less menorrhagia for women with VTE, Blood 127 (2016) 1378–1379.
[3] F.A. Klok, K. Schreiber, K. Stach, W. Ageno, S. Middeldorp, S. Eichinger, et al., Oral contraception and menstrual bleeding during treatment of venous thromboembolism: expert opinion versus current practice: combined results of a systematic review, expert panel opinion and an international survey, Thromb. Res. 153 (2017) 101–107.
[4] O. Beckerath, A.M. Paulitschek, K. Kröger, B. Kowall, F. Santosa, A. Stang, Increasing use of anticoagulants in Germany and its impact on hospitalization rates for genitourinary bleeding, J. Thromb. Thrombolysis 49 (2020) 533–539.
[5] B. Bikdeli, F. Moustafa, J.A. Nieto, A.I. Lee, N. Ruíz-Giménez, A. Lorenzo, et al., Clinical characteristics, time course, and outcomes of major bleeding according to bleeding site in patients with venous thromboembolism, Thromb. Res. 211 (2022) 10–18.
[6] A. Anderson, A. Gassman, L. Hou, T.Y. Huang, E. Eworuke, D. Moeny, et al., Incidence of uterine bleeding following oral anticoagulant use in Food and Drug Administration's Sentinel System, Am. J. Obstet. Gynecol. April (2021) 403–404.
[7] T.Y. Huang, L. Hou, A. Anderson, A. Gassman, S. Spring, D. Moeny, et al., Incidence of severe uterine bleeding outcomes among oral anticoagulant users and nonusers, Am. J. Obstet. Gynecol. (2022) 140–143.
[8] A.E. Jacobson-Kelly, B.T. Samuelson Bannow, Abnormal uterine bleeding in users of rivaroxaban and apixaban, Hematology Am Soc Hematol Educ Program (2020 Dec 4) 538–541.
[9] S. Kaatz, D. Ahmad, A.C. Spyropoulos, S. Schulman, For the Subcommittee of control of anticoagulation, J. Thromb. Haemostasis 13 (2015) 2119–2126.
[10] B. Bikdeli, D. Jiménez, M. Hawkins, S. Ortiz, P. Prandoni, B. Brenner, et al., Rationale, design and methodology of the computerized registry of patients with venous thromboembolism (RIETE), Thromb. Haemostasis 118 (2018) 214–224.
[11] G. Agnelli, H.R. Buller, A. Cohen, M. Curto, A.S. Gallus, M. Johnson, et al., AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism, N. Engl. J. Med. 368 (8) (2013) 699–708.
[12] J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, et al., EINSTEIN-CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism, N. Engl. J. Med. 376 (13) (2017) 1211–1222.

[13] A.M. Young, A. Marshall, J. Thirlwall, O. Chapman, A. Lokare, C. Hill, et al., Comparison of an oral factor Xa inhibitor with low-molecular-weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D), J. Clin. Oncol. 36 (20) (2018) 2017–2023.
[14] G. Agnelli, C. Becattini, G. Meyer, A. Muñoz, M.V. Huisman, J.M. Connors, et al., Caravaggio Investigators. Apixaban for the treatment of venous thromboembolism associated with cancer, N. Engl. J. Med. 382 (17) (2020) 1599–1607.
[15] C.M.M. de Jong, M. Blondon, C. Ay, A. Buchmuller, J. Beyer-Westendorf, J. Biechele, L. Bertoletti, et al., Incidence and impact of anticoagulation-associated abnormal menstrual bleeding in women after venous thromboembolism, Blood (2022) PMID: 35925686. 140(16):1764-1773.
[16] J.P. Patel, O. Nzelu, L.N. Roberts, J. Johns, J. Ross, R. Arya, How do anticoagulants impact menstrual bleeding and quality of life? The PERIOD study, Res Pract Thromb Haemost 7 (2) (2023), 100072.
[17] I. Schastlivtsev, K. Lobastov, S. Tsaplin, I. Kanzafarova, V. Barinov, L. Laberko, et al., Rivaroxaban in the treatment of upper extremity deep vein thrombosis: a single center experience and review of the literature, Thromb. Res. (2019) 24–28.
[18] P. Monagle, A.W.A. Lensing, K. Thelen, I. Martinelli, C. Male, A. Santamaría, et al., EINSTEIN-Jr Phase 2 Investigators. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicenter, single-arm, phase 2 studies, Lancet Haematol 6 (10) (2019) e500–e509.
[19] C. Male, A.W.A. Lensing, J.S. Palumbo, R. Kumar, I. Nurmeev, K. Hege, et al., EINSTEIN-Jr Phase 3 Investigators. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial, Lancet Haematol 7 (1) (2020) e18–e27.
[20] R. Lecumberri, L. Jiménez, P. Ruiz-Artacho, J.A. Nieto, N. Ruiz-Giménez, A. Visonà, et al., Prediction of major bleeding in anticoagulated patients for venous thromboembolism: comparison of the RIETE and the VTE-Bleed scores, TH Open 5 (3) (2021) e319–e328.
[21] J. Catella, L. Bertoletti, F. Moustafa, J.A. Nieto, R. Valle, J.M. Pedrajas, et al., Major gastrointestinal bleeding in patients receiving anticoagulant therapy for venous thromboembolism, Thromb. Res. 214 (2022) 29–36.
[22] J. Weaver, A. Shoaibi, H.Q. Truong, L. Larbi, S. Wu, P. Wildgoose, et al., Comparative risk assessment of severe uterine bleeding following exposure to direct oral anticoagulants: a network study across four observational databases in the USA, Drug Saf. 44 (2021) 479–491, 21.- Ferreira M, Barsam S, Patel JP.
[23] J. Czuprynska, L.N. Roberts, R.K. Patel, R. Arya, Heavy menstrual bleeding on rivaroxaban, Br. J. Haematol. 173 (2016) 314–315.
[24] J. Beyer-Westendorf, F. Michalski, L. Tittl, S. Hauswald-Dörschel, S. Marten, Vaginal bleeding and heavy menstrual bleeding during direct oral anti-Xa inhibitor therapy, Thromb. Haemostasis 115 (2016) 1234–1236.
[25] B. Myers, A. Webster, Heavy menstrual bleeding on rivaroxaban-comparison with apixaban, Br. J. Haematol. 176 (2017) 833–835.
[26] J. Beyer-Westendorf, S. Marten, Reproductive issues in women on direct oral anticoagulants, Res Pract Thromb Haemost 5 (2021), e12512.
[27] V. Speed, J.P. Patel, D. Cooper, S. Miller, L.N. Roberts, R.K. Patel, R. Arya, Rivaroxaban in acute venous thromboembolism: UK prescribing experience, Res Pract Thromb Haemost 5 (2021), e12607.
[28] E. Eworuke, L. Hou, R. Zhang, H.L. Wong, P. Waldron, A. Anderson, et al., Risk of severe abnormal uterine bleeding associated with rivaroxaban compared with apixaban, dabigatran and warfarin, Drug Saf. 44 (7) (2021) 753–763.
[29] S. Bilal, Challenge in managing abnormal uterine bleeding in a patient on novel oral anticoagulant therapy, BMJ Case Rep. 12 (2019), e225727.