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Uterine bleeding during anticoagulation in women with venous thromboembolism

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ABSTRACT

Background: Women presenting with uterine bleeding during the course of anticoagulant therapy for venous thromboembolism (VTE) present a difficult therapeutic dilemma due to the absence of evidence-based recommendations.
Methods: We used the RIETE (Registro Informatizado Enfermedad TromboEmbólica) database to assess the clinical characteristics of women presenting with uterine bleeding during anticoagulation for VTE, its frequency, time course, management and 30-day outcomes.
Results: As of October 2016, 31,951 women with VTE were recruited in RIETE. During the course of anticoagulant therapy, 53 (0.17%) developed major uterine bleeding, 118 (0.37%) non-major uterine bleeding and 948 (2.97%) had major bleeding in other sites. Median time elapsed from VTE to bleeding was: 32, 71 and 22 days, respectively. Mean age was: 56 ± 17, 52 ± 20 and 75 ± 14 years, respectively. Women with major uterine bleeding more likely had cancer (51%), anemia (72%), raised platelet count (19%) or recent major bleeding (11%) at VTE presentation than those in the other subgroups. During the first 30 days after bleeding, 17%, 1.7% and 31% of women died, respectively. Of 11 women with uterine bleeding who died, 9 (82%) had cancer, two (18%) died of bleeding and one (9.1%) died of pulmonary embolism after discontinuing anticoagulation.
Conclusions: Uterine bleeding during the course of anticoagulation for VTE is not uncommon and mostly affects young women. Those with cancer, anaemia, raised platelet count or recent bleeding at baseline are at an increased risk for uterine bleeding during anticoagulation.

1. Introduction

Abnormal uterine bleeding is a relatively common complication in women receiving anticoagulant therapy for venous thromboembolism (VTE) [1–3]. In the literature, there is scarce information on its frequency, the clinical characteristics of these women, the time course and the severity of bleeding [1,4,5]. Most of the published information came from randomized clinical trials with strict inclusion and exclusion criteria, and limited follow-up [6]. Thus, although randomized clinical trials provide high-level evidence on the efficacy and safety of therapeutic interventions, they generally involve well-defined study populations that exclude complex patients and do not provide data on the management of bleeding [1,7,8]. This is important since uterine bleeding in women receiving anticoagulant therapy for VTE presents a dilemma because the potential benefits of anticoagulation must be weighed against the risk of inducing re-bleeding.

RIETE (Registro Informatizado Enfermedad TromboEmbólica) is a multicenter, ongoing, international (Spain, Belgium, Czech Republic, France, Greece, Israel, Italy, Latvia, Republic of Macedonia, Switzerland, United States, Canada, Ecuador and Venezuela enroll patients) observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245). Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes [9–13].

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Using the RIETE database, we retrospectively assessed the clinical characteristics of these women, the frequency and time course of bleeding, its management and the outcome within the first 30 days after bleeding.

2. Methods

2.1. Inclusion criteria

Consecutive patients with acute, symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) 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. To ensure the validity of the information entered into the database, one of the specially trained monitors visited each participating hospital and compared information in 25 to 50 randomly chosen patient records with the information entered into the RIETE database. For data quality assessment, monitors assessed 4,100 random records from all participating hospitals that included 1,230,000 measurements. These data showed a 95% overall agreement between the registered information and patient records. RIETE also used electronic data monitoring to detect inconsistencies or errors and attempted to resolve discrepancies by contacting the local coordinators.

2.2. Study design

We conducted a retrospective study that used prospectively collected data from consecutive patients enrolled in the RIETE registry. Major uterine bleeding was defined as an overt bleed that required a transfusion of two units or more of blood or was fatal. Clinically relevant non major uterine bleeding was defined as any bleeding requiring a medical intervention (hospitalization, surgery or interventional procedure, further diagnostic imaging, laboratory test or specialist evaluation) and/or treatment discontinuation, and not meeting any of the criteria for major bleeding. We compared the clinical characteristics of women with uterine bleeding during anticoagulation for VTE, its frequency, time course, management and 30-day outcomes vs. those in women presenting with major bleeding in other sites. We focused on the management of anticoagulant therapy after bleeding, not on other interventions (like surgery, hormonal therapy, etc.).

2.3. Baseline variables and definitions

The following parameters are routinely recorded in RIETE: patient's baseline characteristics; clinical status including any co-existing or underlying conditions; risk factors for VTE; diagnostics tools used for diagnosis; laboratory data; the treatment received upon VTE diagnosis (drugs, doses, regimen and duration); and the outcome during the course of anticoagulation. Age was divided in three categories (less than 35 years, 35 to 50 years and more than 50 years). Active cancer was defined as newly diagnosed cancer, metastatic cancer, or cancer that was being treated (i.e. surgery, chemotherapy, radiotherapy, support therapy). Anemia was defined as a hemoglobin content <13 g/dL for men and <12 g/dL for women.

2.4. Treatment and follow-up

Patients were managed according to the clinical practice of each participating centre (i.e., there was no standardization of treatment). Patients were followed-up during the course of therapy in the outpatient clinic or physician's office. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent VTE was investigated by repeat compression ultrasonography, lung scanning, helical-CT scan or 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. Statistical analysis

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, and a p-value <0.05 was considered to be statistically significant. Statistical analyses were conducted with SPSS for Windows Release 17.0 (SPSS, Inc).

2.6. Role of the funding source

The sponsors of the RIETE registry (Sanofi and Bayer) had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

As of October 2016, 31,951 women with VTE were recruited in RIETE. During the course of anticoagulant therapy, 53 (0.17%; 95% CI: 0.13–0.21) developed major uterine bleeding, 118 (0.37%; 95% CI: 0.31–0.44) had clinically relevant non major uterine bleeding and 948 (2.97%; 95% CI: 2.79–3.16) suffered major bleeding in other

Table 1
Clinical characteristics of the patients, according to severity and site of bleeding during the course of anticoagulant therapy.

	Major uterine bleeding	Non-major uterine bleeding	Major bleeding in other sites	No major bleeding in other sites
Patients, *N*	53	118	948	30,832
Clinical characteristics				
Mean age (years ± SD)	56 ± 17‡	52 ± 20‡	75 ± 14‡	67 ± 19
Age <35 years	4 (7.5%)	23 (19%)‡	27 (2.8%)‡	2,736 (8.9%)
Age 35–50 years	17 (32%)‡	44 (37%)‡	35 (3.7%)‡	3,672 (12%)
Age >50 years	32 (60%)†	51 (43%)‡	886 (93%)‡	24,424 (79%)
Body weight (kg ± SD)	77 ± 20*	78 ± 21‡	69 ± 15†	71 ± 15
Associated conditions				
Cancer	27 (51%)‡	27 (23%)	272 (29%)‡	6,145 (20%)
Uterine	19 (36%)‡	15 (13%)‡	26 (2.7%)*	515 (1.7%)
Metastatic cancer	15 (56%)	9 (33%)	127 (47%)	2,606 (42%)
Pregnancy/puerperium	3 (5.7%)	4 (3.4%)	3 (0.32%)‡	820 (2.7%)
Anemia	38 (72%)‡	51 (43%)	479 (51%)‡	10,980 (36%)
PlC <100,000/μL	0	3 (2.5%)	34 (3.6%)‡	600 (1.9%)
PlC >450,000/μL	10 (19%)‡	6 (5.1%)	62 (6.5%)‡	1,160 (3.8%)
CrCl levels <60 ml/min	13 (25%)‡	26 (22%)‡	638 (67%)‡	14,616 (47%)
Recent major bleeding	6 (11%)‡	7 (5.9%)*	47 (5.0%)‡	645 (2.1%)
Initial VTE presentation				
Pulmonary embolism	30 (57%)	72 (61%)	595 (63%)‡	16,421 (53%)

Comparisons between women who bled vs. those that did not bleed: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: SD, standard therapy; PlC, platelet count; CrCl, creatinine clearance; VTE, venous thromboembolism.

Table 2
Time course and 30-day outcomes according to site and severity of bleeding.

	Major uterine bleeding	Non-major uterine bleeding	Major bleeding in other sites
Patients, *N*	53	118	948
Time elapsed from index VTE			
Mean days (± SD)	74 ± 108	130 ± 200	137 ± 358
Median days (IQR)	32 (7–121)	71 (19–143)	22 (7–105)
Day 0 to Day 7	14 (26%)	15 (13%)†	240 (25%)
Day 8 to Day 30	10 (19%)	24 (20%)*	288 (30%)
Day 31 to Day 90	14 (26%)	31 (26%)*	165 (17%)
Beyond Day 90	15 (28%)	48 (41%)†	255 (27%)
30-day outcomes			
Major re-bleeding	4 (7.5%)	2 (1.7%)	44 (4.6%)
Uterine	2 (3.8%)†	1 (0.85%)	0
Non-major re-bleeding	0	3 (2.5%)	11 (1.2%)
Uterine	0	1 (0.85%)	1 (0.11%)
Recurrent VTE	1 (1.9%)	1 (0.85%)	37 (3.9%)
Death	9 (17%)*	2 (1.7%)‡	291 (31%)
Fatal pulmonary embolism	1 (1.9%)	0	12 (1.3%)
Fatal bleeding	2 (3.8%)†	0‡	193 (20%)

Comparisons between women with uterine bleeding vs. those who bled in other sites: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: VTE, venous thromboembolism; SD, standard therapy; IQR, interquartile range.

sites. Their mean age was: 56 ± 17, 52 ± 20 and 75 ± 14 years, respectively (Table 1). Women with uterine bleeding (major or non-major) were over 10 years younger than those that did not bleed, and 20 years younger than those with major bleeding in other sites. Fifty-one percent of women with major uterine bleeding and 23% of those with non-major bleeding had cancer, mostly (63%) in the uterus. Women with major (but not those with non-major) uterine bleeding more likely had anemia (72%), raised platelet count (19%) or recent major bleeding (11%) at VTE presentation than those presenting with major bleeding in other sites or without bleeding.

Among 53 women with major uterine bleeding, 26% bled within the first week of anticoagulant therapy, 19% from Day 8 to Day 30, 26% from Day 31 to day 90 and 28% beyond Day 90 (Table 2). Among 118 women with non-major uterine bleeding the proportions were 13%, 20%, 26% and 41%, respectively. The proportion of women who re-bled within the first 30 days was similar, but the mortality rate was half in women with major uterine bleeding than in those with major bleeding in other sites (17% vs. 31%, odds ratio: 0.46; 95% CI: 0.21–0.93).

Most bleeding episodes appeared during the course of therapy with vitamin K antagonists (VKA) or low-molecular-weight heparin (LMWH), as shown in Table 3. Women with cancer were more likely to be on LMWH than those without cancer (46% vs. 14%, $p < 0.0001$), and less likely to be on VKA (37% vs. 51%, $p = 0.12$) or direct oral anticoagulants (3.7% vs. 27%, $p = 0.0004$). Among women with uterine bleeding, anticoagulant therapy was definitely discontinued in 13 (25%) women with major bleeding and in 10 (8.5%) with non-major bleeding ($p = 0.009$). Anticoagulation was transiently discontinued in 9 (17%) women with major- and in 3 (2.5%) with non-major bleeding ($p = 0.003$). After uterine bleeding, most patients re-started anticoagulation with LMWH, at lower mean doses than before. Nine women with major bleeding (17%) and two (with non-major bleeding 1.7%) died within the first 30 days. Of these, 10 (91%) had cancer. Two women died of bleeding and one died of PE after discontinuing anticoagulant therapy.

Table 3
Treatment at uterine bleeding, after its cessation and 30-day outcomes, according to the severity of bleeding and presence of cancer.

	Major bleeding		Non-major bleeding	
	cancer	no cancer	cancer	no cancer
Patients, *N*	27	26	27	91
Current therapy at bleeding				
Vitamin K antagonists	7 (26%)	11 (42%)	13 (48%)	49 (54%)
Low-molecular-weight heparin	14 (52%)	6 (23%)*	11 (41%)	10 (11%)†
Mean LMWH dose (IU/kg/day)	161 ± 45	157 ± 34	146 ± 58	157 ± 33
LMWH+VKA	1 (3.7%)	1 (3.8%)	0	0
Direct oral anticoagulants	1 (3.7%)	5 (19%)	1 (3.7%)	27 (30%)†
Unfractionated heparin	4 (15%)	2 (7.7%)	1 (3.7%)	2 (2.2%)
Fondaparinux	0	0	1 (3.7%)	2 (2.2%)
Thrombolytics	0	1 (3.8%)	0	1 (1.1%)
Therapy on bleeding				
Cessation of therapy	5 (18%)	8 (31%)	1 (3.7%)	9 (9.9%)
Transient discontinuation	4 (15%)	5 (19%)	1 (3.7%)	2 (2.2%)
Days without therapy (mean)	5.0 ± 4.1	9.1 ± 13	–	3.9 ± 2.8
Days without therapy (median)	4 (3–8)	4 (2–5)	–	4 (2–6)
Therapy after bleeding				
Low-molecular-weight heparin	17 (63%)	8 (31%)*	14 (52%)	22 (24%)†
Mean LMWH dose (IU/kg/day)	92 ± 55	146 ± 61	108 ± 55	120 ± 47
Vitamin K antagonists	1 (3.7%)	8 (31%)*	10 (37%)	42 (46%)
Direct oral anticoagulants	1 (3.7%)	2 (7.7%)	1 (3.7%)	18 (20%)*
Unfractionated heparin	3 (11%)	0	1 (3.7%)	0
Vena cava filter	4 (15%)	2 (7.7%)	4 (15%)	3 (3.3%)*
30-day outcomes				
Major re-bleeding	4 (15%)	0	1 (3.7%)	1 (1.1%)
Uterine	2 (7.4%)	0	1 (3.7%)	0
Non-major uterine bleeding	0	0	0	3 (3.3%)
Recurrent DVT	0	1 (3.8%)	0	0
Recurrent PE	1 (3.7%)	0	0	1 (1.1%)
Death	8 (30%)	1 (3.8%)*	2 (7.4%)	0
Fatal bleeding	2 (7.4%)	0	0	0
Fatal PE	1 (3.7%)	0	0	0

Comparisons between women with versus without cancer: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Abbreviations: LMWH, low-molecular-weight heparin; IU, international units; VKA, vitamin K antagonists; DVT, deep vein thrombosis; PE, pulmonary embolism.

4. Discussion

Abnormal uterine bleeding in women receiving anticoagulant therapy for VTE may have significant impact on their physical, social and emotional quality of life [2,14,15]. Our data, obtained from a large series of consecutive women receiving anticoagulant therapy for VTE, reveal that uterine bleeding is not that common. Only one in every 603 (0.17%) women presented with major uterine bleeding (accounting for 5.3% of all major bleeds), and one in every 270 (0.37%) presented with non-major uterine bleeding. However, one in every 6 women with major uterine bleeding (17%) died within the first 30 days, and this is important since many (40%) were aged <50 years, two died of the bleeding event and one died of PE appearing shortly after discontinuing anticoagulant therapy. Thus, its clinical relevance should not be underestimated.

Compared with women that did not bleed, women presenting with major uterine bleeding were more likely to have cancer, anaemia or raised platelet count at the index VTE presentation. These three conditions have been associated with an increased risk for bleeding in the literature [16–22], and suggest that early identification of women with VTE at increased risk for uterine bleeding during the course of anticoagulation might be feasible in the future.

Our study also shows that the management of major uterine bleeding in real life is rather heterogeneous, most likely due to the absence of evidence-based recommendations in the literature [23–25]. In our series, anticoagulation was stopped in 20%, transiently discontinued in 15% and modified in most. Besides, it was not modified in most women with non-major bleeding. The 30-day outcome was clearly worse in women with cancer. However, further studies are needed to more precisely identify women at an increased risk for re-bleeding and for VTE recurrences after discontinuing anticoagulant therapy.

The present study has potential limitations. First, RIETE is an observational registry, and our findings are hypothesis-generating. Thus, our data are of no help to decide the best therapeutic strategy

for these women. Moreover, there is no external adjudication of the events (including major bleed), which are reported by the doctors. However, some prior studies showed that adjudicated data usually match well with onsite outcome assessment [26–28]. Second, patients in the RIETE database were selected in several countries. The variability of practices in different countries could potentially affect the study outcomes. For instance, the dosing and regimen can vary according to each individual's country's pattern of practice, underlying disease process, and/or presence or absence of cancer. Furthermore, a variety of practitioners entered data into the registry, which may lend itself to potential inaccuracies in the data being reported. However, the RIETE registry provides insights into the natural history of VTE with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It can, therefore, help to identify factors associated with better or worse outcomes, and provide feedback from real-world clinical situations, which may be valuable when designing new randomized clinical studies.

In summary, this is the first real-life study on the frequency, time course, clinical characteristics and severity of uterine bleeding occurring during the course of anticoagulation for VTE. These events are not common, but clinically relevant because they mostly affect young women. The existence of cancer, anaemia or raised platelet count at baseline should alert the clinician to be aware about an increased risk for bleeding.

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Conflict of interest statement

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

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