Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin

Marjolein P. A. Brekelmans[1*]; Luuk J. J. Scheres[1,2*]; Suzanne M. Bleker[1]; Barbara A. Hutten[3]; Anne Timmermans[4]; Harry R. Büller[1]; Saskia Middeldorp[1]

[1]Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; [2]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands; [3]Department of Clinical Epidemiology, Academic Medical Center, Amsterdam, the Netherlands; [4]Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, the Netherlands

Summary

Abnormal vaginal bleeding can complicate direct oral anticoagulant (DOAC) treatment. We aimed to investigate the characteristics of abnormal vaginal bleeding in patients with venous thromboembolism (VTE) receiving apixaban or enoxaparin/warfarin. Data were derived from the AMPLIFY trial. We compared the incidence of abnormal vaginal bleeding between patients in both treatment arms and collected information on clinical presentation, diagnostic procedures, management and outcomes. In the AMPLIFY trial, 1122 women were treated with apixaban and 1106 received enoxaparin/warfarin. A clinically relevant non-major (CRNM) vaginal bleeding occurred in 28 (2.5 %) apixaban and 24 (2.1 %) enoxaparin/warfarin recipients (odds ratio [OR] 1.2, 95 % confidence interval [CI] 0.67–2.0). Of all CRNM bleeds, 28 of 62 (45 %) and 24 of 120 (20 %) were of vaginal origin in the apixaban and enoxaparin/warfarin group, respectively (OR 3.4; 95 % CI 1.8–6.7). Premenopausal vaginal bleeds on apixaban were characterised by more prolonged bleeding (OR 2.3; 95 %CI 0.5–11). In both pre- and postmenopausal vaginal bleeds, diagnostic tests were performed in six (21 %) and in seven (29 %) apixaban and enoxaparin/warfarin treated patients, respectively. Medical treatment was deemed not necessary in 16 (57 %) apixaban and 16 (67 %) enoxaparin/warfarin recipients. The severity of clinical presentation and course of the bleeds was mild in 75 % of the cases in both groups. In conclusion, although the absolute number of vaginal bleeding events is comparable between apixaban and enoxaparin/warfarin recipients, the relative occurrence of vaginal bleeds is higher in apixaban-treated women. The characteristics and severity of bleeding episodes were comparable in both treatment arms.

Keywords

Anticoagulants, apixaban, warfarin, venous thromboembolism, abnormal vaginal bleeding

Correspondence to:
Marjolein P. A. Brekelmans
Department of Vascular Medicine, Academic Medical Center
Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands
Tel.: +31 20 5668791, Fax: +31 20 5669343
E-mail: m.p.brekelmans@amc.nl

*Both authors contributed equally to this manuscript.

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Introduction

Women of reproductive age have a higher risk of venous thromboembolism (VTE) than men of the same age, which can likely be explained by the use of hormonal contraceptives and pregnancy in this phase of life (1–3). Direct oral anticoagulants (DOACs) have been introduced as an alternative for vitamin K antagonists (VKA) for the treatment of VTE, and were found to be safer and at least as efficacious (4).

Little is known on sex-specific complications of anticoagulant treatment with DOACs. In a meta-analysis of patients receiving rivaroxaban, apixaban and ximelagatran, women more often experience clinically relevant bleeding (the composite of major and clinically relevant non major [CRNM]) compared to men (5). In addition, recent studies have shown that abnormal vaginal bleeding is a frequent complication in women receiving DOACs, affecting 20 % to 40 % of all treated women (6–10). Furthermore, DOAC use has been associated with a higher frequency of heavy menstrual bleeding, and required more medical interventions and adaptations of anticoagulant treatment for abnormal uterine blood loss in comparison to treatment with VKA (7, 8).

Most published data are limited to women using rivaroxaban. Therefore, for the present study, we compared the incidence of abnormal vaginal bleeding in a cohort of female VTE patients who received apixaban or enoxaparin followed by warfarin. In addition, we evaluated the characteristics, applied diagnostic procedures, treatment and subsequent clinical outcome of all vaginal bleeding events and explored the association of these characteristics with the received treatment.

Materials and methods

Study population and design

The AMPLIFY study

Data for the present analysis were derived from the database of the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) trial, of which the full study design has been previously published (11). Briefly, in the AMPLIFY study, patients with VTE were randomised in a double-blind fashion to either apixaban or enoxaparin followed by warfarin for a duration of six months. Patients were eligible for inclusion in the study if they were 18 years of age or older and had objectively confirmed, symptomatic proximal deep-vein thrombosis (DVT) or pulmonary embolism (PE; with or without DVT). Patients were excluded if they had 1) active bleeding, 2) a high risk of bleeding, 3) other contraindications for treatment with enoxaparin and warfarin, 4) cancer and an indication for long-term treatment with low-molecular-weight heparin, 5) another indication for long-term anticoagulation therapy, or 6) dual antiplatelet therapy or treatment with aspirin at a dose of more than 165 mg daily.

The primary safety outcome was major bleeding, and the secondary safety outcome was the composite of major and CRNM bleeding. Major bleeding was, according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH), defined as clinically overt bleeding, either 1) associated with a fall in haemoglobin level ≥2 g/dl, 2) requiring transfusion ≥2 units of erythrocytes, 3) occurring in a critical site, or 4) contributing to death (12). CRNM bleeding was defined as clinically overt bleeding not meeting the criteria for major bleeding, but associated with 1) a medical intervention, 2) unscheduled contact with a physician, 3) interruption of study drug or 4) discomfort or impairment in carrying out activities of daily life. Bleeding events were prospectively reported and recorded during conduct of the AMPLIFY trial using standardised case report forms (CRFs). The protocol specified potential treatment strategies for bleeding events, but the decision to use these strategies was left at the discretion of the treating physician. Overall bleeding rates in the AMPLIFY study were censored at two days after the last intake of apixaban.

The protocol was reviewed and approved by each participating site's Institutional Review Board, and written informed consent was obtained from participants. The trial was registered with clinicaltrials.gov (NCT00643201). The AMPLIFY study was sponsored by Pfizer Inc. and Bristol Myers Squibb Company.

Table 1: Classification of clinically relevant non-major bleeding events.

Category	Description
1	Bleeding events which were • Self-controlled, and/or • Retrospective in nature, and/or • Required no emergency room/medical visit, stop of study medication, procedures or treatment
2	Bleeding events that could not be classified to any of the other three categories (i. e. only requiring temporary interruption of study medication, bleeding events only requiring contact)
3	Bleeding events requiring an emergency room/medical visit and procedures or treatment to control the bleeding, but no hospitalisation
4	Bleeding events requiring hospitalisation and procedures or treatment to control the bleeding

Current study

For the present study we included all women who participated in the AMPLIFY trial. In case a vaginal bleeding event occurred during the study period, the following data were collected by three independent investigators (MB, LS, SB) blinded for treatment allocation: characteristics of the vaginal bleed (duration, severity, frequency), pre- or postmenopausal status, performed diagnostic tests, applied medical interventions or treatments to stop the bleed, and the severity of clinical presentation and subsequent outcome of the bleed. All data were retrieved from CRFs, bleeding narratives and patient profiles. Only bleeding events that occurred during the on-treatment period (period in which patients received the study drug or within two days after the study drug was stopped or interrupted) were eligible.

Definition of abnormal uterine bleeding

Abnormal uterine bleeding (AUB) was, according to the International Federation of Gynecology and Obstetrics (FIGO), defined as prolonged menstrual bleeding, intermenstrual bleeding, heavy menstrual bleeding or menstrual blood loss causing anaemia or requiring an unscheduled contact with a physician, a medical or surgical intervention, or adaptation of anticoagulant therapy. Since the definition of AUB is only applicable to premenopausal vaginal bleeding events, we described the characteristics of vaginal bleeds separately for pre- and postmenopausal women. The results regarding diagnostics and applied treatment strategies in both pre- and postmenopausal women were combined due to small numbers in both groups.

Classification of clinical presentation and course

Previously, all CRNM bleeding events from the AMPLIFY study were blindly classified using predefined criteria for the severity of clinical presentation and course (13). This classification scheme included four different categories; category one representing the mildest and category four the most severe presentation or course (▶Table 1). For the current analysis, we extracted the adjudicated categories for all CRNM vaginal bleeds. As there was only one major vaginal bleeding event in the AMPLIFY study, we did not classify this event for clinical presentation and clinical course.

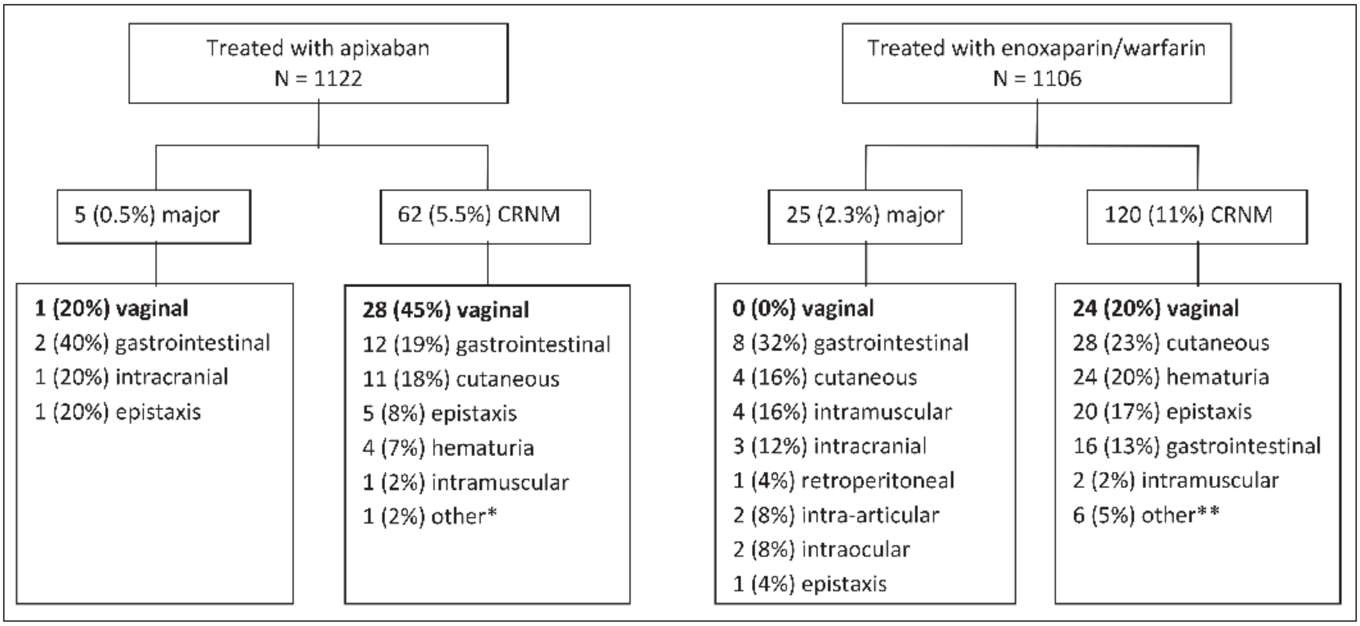

Figure 1: Bleeding events of women in the AMPLIFY trial. CRNM: clinically relevant non-major. *Blood in a hepatic cyst; **Including: 1 gingival bleeding, 1 haemorrhagic Baker's cyst, 1 mild haemoptysis, 2 subconjunctival bleeds, 1 patient with multiple haematomas after a motorised vehicle accident.

Statistical analysis

Differences in normally distributed continuous variables between groups were compared by means of the independent sample-t-test. The Chi-square test was applied for group comparisons of categorical variables.

A logistic regression model was applied to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between bleeding characteristics and the different treatment groups (apixaban versus enoxaparin/warfarin). ORs were adjusted for non-steroidal anti-inflammatory drugs (NSAID) use at randomisation. For the analysis of the severity of clinical presentation and course of the bleeding, ORs for classifying as category 3 or 4 between apixaban and enoxaparin/warfarin associated bleeds were computed.

A p-value of less than 0.05 was considered to indicate a significant difference. Analyses were carried out using SPSS 20 for Windows (IBM Software, Armonk, NY, USA).

Results

Study population

In the AMPLIFY trial, 1122 women were treated with apixaban and 1106 received enoxaparin followed by warfarin. There were no differences in baseline characteristics between apixaban and enoxaparin/warfarin treated women (11). ►Figure 1 provides insight in the incidence and type of bleeding events in the AMPLIFY trial for both treatment arms.

Major vaginal bleed

Major vaginal bleeding occurred in one of 1122 (<0.1%) woman during the use of apixaban, and in none of those receiving enoxaparin/warfarin. The only observed major vaginal bleeding occurred in a 45-year-old women who had an index DVT and a history of endometriosis. She presented with heavy and intermenstrual bleeding on day 51 of the study, accompanied by a haemoglobin drop from 11.2 g/dl at baseline to 6.5 g/dl at the day of presentation. Diagnostics revealed uterine fibroids. Study medication was interrupted and three units of red blood cells were administered. Two weeks after the event a hysterectomy was performed for which a temporary inferior vena cava (IVC) filter was placed. A week after surgery the haemoglobin level reached 10.8 g/dl; three weeks later the IVC filter could be removed.

Clinically relevant non-major vaginal bleeds

CRNM vaginal bleeding was observed in 28 of 1122 (2.5%) women receiving apixaban and in 24 of 1106 (2.1%) women receiving enoxaparin/warfarin (OR 1.2, 95%CI 0.67–2.0). In total, 62 women receiving apixaban and in 120 women receiving enoxaparin/warfarin experienced any type of CRNM bleeding; hence vaginal bleeds represents 45% (24 of 62) of all CRNM bleeds in the apixaban and 20% (28 of 120) of all CRNM bleeds in the enoxaparin/warfarin group (OR 3.4, 95%CI 1.8–6.7; ►Figure 1). ►Figure 1 shows the bleeding locations in patients treated with apixaban and enoxaparin/warfarin; in both groups, vaginal and gastro-intestinal bleeds were relatively common, and in the enoxaparin/warfarin group cutaneous bleeds, haematuria, and epistaxis were also frequently observed.

Table 2: Baseline characteristics of women in the AMPLIFY trial with a CRNM vaginal bleeding.

	Apixaban	Enoxaparin/ Warfarin	P-value
Number	28	24	N. A.
Age (years) – mean (SD)	46 (11)	44 (14)	0.77
BMI (kg/m²) – mean (SD)	30 (6)	30 (8)	0.40
Randomisation to bleeding (days) – median (IQR)	27 (8–85)	32 (9–80)	0.78
Index event – n (%)			0.23
DVT	20 (71)	14 (58)	
PE	5 (18)	9 (38)	
Both	3 (11)	1 (4)	
Risk factors for VTE – n (%)			0.43
Active cancer	1 (4)	1 (4)	
Known thrombophilia	0	2 (8)	
Previous VTE	7 (25)	3 (13)	
Immobilisation	0	1 (4)	
Use of hormones	5 (18)	4 (17)	
None	18 (64)	15 (63)	
Unknown	1 (4)	0	
History of anaemia – n (%)	12 (43)	9 (38)	0.46
Prior gynaecological disorder*- n (%)	10 (36)	6 (25)	0.30
Antiplatelet use at randomisation – n (%)	4 (14)	5 (21)	0.40
NSAID use at randomisation – n (%)	8 (29)	2 (8)	0.07

*This includes the following gynaecological disorders, that are associated with vaginal bleeding: uterine myoma, menorrhagia, ovarian cancer, endometrial hyperplasia, and active termination of pregnancy 5 days before the bleeding event. NA: not applicable; CRNM: clinically relevant non-major; SD: standard deviation; IQR: interquartile range; VTE: venous thromboembolism; NSAID: non-steroidal anti-inflammatory drugs.

►Table 2 details the baseline characteristics of all women who had a CRNM vaginal bleed during the AMPLIFY trial. The time from randomisation to first episode of vaginal bleeding was a median 27 days (interquartile range [IQR] 8–85) in the apixaban and 32 days (IQR 9–80) in the enoxaparin/VKA group. No statistically significant differences were detected between women using apixaban and those using enoxaparin/warfarin. Although confidence intervals crossed unity, a trend was observed towards more frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) at randomisation in apixaban recipients compared to women in the enoxaparin/VKA group (8 [29%] vs 2 [8%], p=0.07). Therefore, subsequent ORs were adjusted for NSAID use at randomisation.

Table 3: Characteristics of clinically relevant non-major vaginal bleeds.

	Apixaban	Enoxaparin/ warfarin
Number of women with vaginal CRNM bleeding events	28*	24
Premenopausal bleeding – n (%)	22 (79)	18 (75)
Prolonged menstrual bleeding	8 (35)	3 (17)
Intermenstrual bleeding	4 (18)	3 (17)
Heavy menstrual bleeding	18 (82)	15 (83)
Anaemia**	13 (59)	7 (39)
Unscheduled contact	13 (59)	12 (67)
Classifying for AUB	All	All
Postmenopausal bleeding – n (%)	5 (21)	6 (25)
Anaemia**	1 (20)	0
Unscheduled contact	4 (80)	4 (67)

**In one patient the pre- or postmenopausal status was unknown; **Anaemia during study participation. CRNM: clinically relevant non-major; AUB: abnormal uterine blood loss.

Vaginal bleeding characteristics

Premenopausal women

The majority of women with CRNM vaginal bleeds were premenopausal (►Table 3). Premenopausal vaginal bleeding events in women on apixaban were characterised by more prolonged bleeding (i.e. >7 days; OR 2.3, 95%CI 0.5–11) compared to those using enoxaparin/warfarin, albeit this difference did not reach statistical significance. The occurrence of intermenstrual bleeding, heavy menstrual bleeding and anaemia (i.e. haemoglobin <11.9 g/dL) were comparable between both treatment groups (OR 1.3, 95%CI 0.2–7.3; OR 0.7, 95%CI 0.1–4.4; and OR 1.3 95%CI 0.3–5.5, respectively). In 13 of 22 (59%) of the apixaban associated and in 12 of 18 (67%) of the enoxaparin/warfarin associated premenopausal vaginal bleeds there was an unscheduled contact with a physician (OR 0.7, 95%CI 0.2–2.9).

Postmenopausal women

Eleven patients with a vaginal bleeding event were postmenopausal; five of those were using apixaban, and six were on enoxaparin/warfarin (►Table 3). Six of 11 (55%) women had a known gynaecological disorder associated with bleeding prior to randomisation; three had a uterine myoma, one had ovarian cancer, one had a history of endometrial hyperplasia, and one had uterine cancer.

Diagnostics and treatment

For both pre- and postmenopausal vaginal bleeding events, additional diagnostic tests were performed in 6 of 28 (21%) and 7 of 24 (29%) of apixaban and enoxaparin/warfarin recipients, respectively. In 8 of 28 (29%) of the apixaban treated women (5 premenopausal, 3 postmenopausal) a cause for the vaginal bleed could be detected compared to 9 of 24 (38%) of the women using enoxaparin/warfarin (7 premenopausal, 2 postmenopausal; ▶Table 4). A uterine myoma was the underlying cause in 2 of 8 (25%) of the apixaban and 6 of 9 (67%) of the enoxaparin/warfarin recipients.

Medical treatment was deemed not necessary in 16 of 28 (57%) of the apixaban recipients and in 16 of 24 (67%) of those receiving enoxaparin/warfarin. Iron supplements only were given in 8 of 28 (29%) of apixaban and in 1 of 24 (4%) of enoxaparin/warfarin associated vaginal bleeds. Hormone therapy was started in 1 of 28 (4%) woman in the apixaban versus 3 of 28 (13%) women in the enoxaparin/warfarin group. In 5 of 28 (18%) and 3 of 24 (13%) women treated with apixaban and enoxaparin/warfarin, a radiological or surgical intervention was indicated to stop the bleeding. Anticoagulant treatment was temporarily stopped in 8 of 28 (29%) apixaban and 8 of 24 (33%) enoxaparin/warfarin recipients, whereas 2 of 28 (7%) and 3 of 24 (13%) patients, respectively, stopped anticoagulants permanently.

Table 4: Applied diagnostic tests and treatment of vaginal bleeding in both pre- and postmenopausal women.

	Apixaban	Enoxaparin/ warfarin
Number of women with vaginal CRNM bleeding events	28	24
Diagnostic tests applied – n (%)	6 (21)	7 (29)
Ultrasonography	2	4
Hysteroscopy	0	1
Biopsy	3	2
Diagnostic endometrial ablation	1	0
Diagnosis – n (%)	8 (29)	9 (38)
Uterine myoma	2	6
Uterine leiomyoma	1	0
Endometriosis	0	1
Endometrial hyperplasia	1	0
Ovarian cancer	0	1
Uterine cancer	1	0
Other	3*	1**
Hospital admission – n (%)	2 (7)	3 (13)
Treatment – n (%)		
Iron suppletion	8 (29)	1 (4)
Hormone therapy	1 (4)	3 (13)
Estrogen containing	0	1
Progestagen containing	1	2
IUD	1 (4)	0
Tranexamic acid	1 (4)	2 (8)
Combination	1 (4)	2 (8)
No treatment	16 (57)	16 (67)
Radiologic or surgical interventions – n (%)		
Hysterectomy	2 (7)	1 (4)
Endometrial ablation or curettage	2 (7)	2 (8)
Removal of Nuva-ring	1 (4)	0
No interventions	23 (82)	20 (84)
Unknown	0	1 (4)
Change in anticoagulant – n (%)		
Unchanged	18 (64)	13 (54)
Temporary interruption	8 (29)	8 (33)
Permanent stop	2 (7)	3 (13)

*These included bleeding after biopsy, bleeding due to a contraceptive vaginal ring, and a blood clot in the uterus with uncertain etiology; **Cervical polyp in combination with endometriosis. CRNM: clinically relevant non-major; IUD: intra-uterine device.

Clinical outcomes of vaginal bleeding events

Reassuringly, in approximately 75% of the women with a CRNM vaginal bleed, the clinical presentation and course were classified as “mild” (i.e. category 1 or 2). The OR for classifying as category 3 or 4 (i.e. a severe clinical course) in patients using apixaban versus those using enoxaparin/warfarin was 0.7 (95%CI 0.2–2.2).

Repetitive bleeding was common (14 of 28 [50%] of apixaban and 10 of 24 [42%] of enoxaparin/warfarin recipients), no difference was observed between the two treatment groups (OR 1.0, 95% CI 0.3–3.3) (▶Table 5).

Discussion

Overall, the occurrence of vaginal bleeding events was comparable between women treated with apixaban and enoxaparin/warfarin. However, if a CRNM bleeding occurred, the bleeding was observed to be more often of vaginal origin in women treated with apixaban compared to women treated with enoxaparin/warfarin. Hence, there is a difference in bleeding sites between patients treated with apixaban and enoxaparin/warfarin. In addition, premenopausal vaginal bleeds in women using apixaban appeared to be more frequently characterised by prolonged menstrual bleeding than in patients receiving enoxaparin/warfarin, although no statistically significant difference was observed between the groups. The severity of clinical presentation and course of the bleeds was mild in the majority of the cases, and was comparable for both treatment groups. Interventions to stop the bleeding were indicated infrequently and iron supplements were deemed sufficient by the treating physicians in a quarter of the apixaban associated bleeds. Overall, vaginal bleeds led to an unscheduled contact with a physician in more than 60% of the cases, to temporary cessation of the study drug in about 30%, and in 10% anticoagulants were permanently ceased, all reflecting the distress caused by these bleeds. No differences were observed between the treatment groups.

To our knowledge, this is the first study evaluating characteristics, diagnostics and treatment of vaginal bleeding events in women receiving apixaban. Previous studies mainly focused on rivaroxaban and the occurrence of vaginal bleeding (5–8, 10). One study applied the same criteria for AUB as the present study, and observed that rivaroxaban was associated with prolonged menstrual bleeding in comparison to VKA (p<0.001), and with more

Table 5: Clinical outcomes of bleeding in women with vaginal CRNM bleeding.

	Apixaban	Enoxaparin/ warfarin
Repetitive bleeding – n (%)	14 (50)	10 (42)
Recurrent VTE – n (%)	0	1(4)
Classification of CRNM vaginal bleed – n (%)		
Category 1	6 (22)	5 (21)
Category 2	14 (50)	10 (42)
Category 3	4 (14)	6 (25)
Category 4	4 (14)	3 (12)

CRNM: clinically relevant non-major; VTE: venous thromboembolism.

medical interventions and adaptation of anticoagulant treatment (7).

In a study including women with inherited bleeding disorders, a situation comparable to women receiving anticoagulants, vaginal bleeds were observed to be associated with a decreased quality of life (14). Hence, physicians should be vigilant of the occurrence of vaginal bleeds in women on anticoagulants, especially in the reproductive phase of life. It is important to inform women of this complication at start of treatment with anticoagulants, and they should be encouraged to seek medical attention when abnormal vaginal bleeding occurs. If this does occur, referral to a gynaecologist should be considered. The gynaecologist is able to determine whether there is an underlying condition and if so, treat this accordingly. However, in most of both pre- and postmenopausal vaginal bleeding events no underlying cause is identified, and therefore general measures should be considered. Potential therapies and preventative measures for vaginal bleeding are placement of a hormone releasing intra-uterine device, use of combined oral contraceptives, or use of tranexamic during menstrual periods, which all are not associated with an increased risk of VTE during the use of anticoagulants (1, 8, 15, 16, 17).

The underlying mechanism of differences in bleeding pattern and especially the higher relative number of vaginal bleeds in women using DOACs is unknown. DOACs directly target coagulation factors and a part of the DOAC dose remains in the gastrointestinal tract, due to incomplete absorption. Therefore, DOACs have a local effect on the gastrointestinal wall and mucosa potentially leading to a higher frequency of gastrointestinal bleeding compared to VKA treatment (18, 19). One might speculate that DOACs, as opposed to VKA, also have a direct effect on the uterine wall, thereby increasing local bleeding tendency. Another possibility is that, as menstrual vaginal bleeding is a natural bleeding process, DOACs act synergistically with the natural anticoagulants necessary for menstrual bleeding and the menstrual cycle.

Our study has several strengths. First, the AMPLIFY study was a randomised, double-blind, double-dummy study in which data on bleeding events were prospectively collected on pre-designed forms. Another strength is that the adjudicators were blinded for treatment regimen at time of data collection. Therefore, bias due to misclassification of bleeding events will be minimal.

Some limitations deserve acknowledgement. A first limitation is the relatively small sample size. Although we included 2228 women from the AMPLIFY trial, a vaginal bleeding episode only occurred in 29 apixaban- and 24 enoxaparin/warfarin-treated patients. Therefore, possible existing differences in bleeding characteristics between the treatment groups may not have been detected. For example, the observed difference between apixaban and enoxaparin/warfarin may driven by an imbalance of hormone treatment during anticoagulant treatment. In addition, the balancing property of randomisation is lost which may have increased the potential for confounding. However, to address this, we adjusted the ORs for potential confounding factors by means of multivariate regression models and therefore the impact on the present study results is likely to be limited. Third, although treatment cessation, unscheduled contact or hospital admission seem valid parameters of disease burden, we were not able to assess quality of life objectively. Future studies should provide more insight in the impact of vaginal bleeding on quality of life. Finally, due to the retrospective nature of this study, it was not possible to quantify the amount and composition of vaginal blood loss. In future prospective studies validated blood loss scores such as the pictorial blood assessment chart (PBAC) score could be applied to objectify vaginal bleeding events (20).

In conclusion, although the absolute number of vaginal bleeding events is comparable between apixaban and enoxaparin/warfarin, the relative occurrence of vaginal bleeds is higher in apixaban treated women. Hence, there is a difference in bleeding sites between apixaban and enoxaparin/warfarin. Bleeding characteristics did not differ between both treatment groups and the severity of the bleeds was mild in three-quarter of all women. We would ad-

What is known about this topic?

- Direct oral anticoagulants (DOACs) are a safe, effective and user friendly alternative to vitamin K antagonists in the treatment of venous thromboembolism (VTE).
- Abnormal vaginal bleeding is a frequently observed complication of DOAC treatment.
- Current data on abnormal vaginal bleeding is mostly limited to women treated with rivaroxaban. Little is known on the incidence and characteristics of apixaban associated vaginal bleeding events.

What does this paper add?

- The absolute number of vaginal bleeding events is comparable between apixaban and enoxaparin/warfarin.
- However, if a bleeding event occurred, it was significantly more like to be of vaginal origin in apixaban-treated women.
- No differences were observed in the characteristics and treatment of vaginal bleeds between both treatment groups and the majority of the vaginal bleeds had a mild clinical course.

vise clinicians to actively monitor and inform women on anticoagulants in order to early identify abnormal vaginal bleeding, so preventive and therapeutic measures can be installed timely.

Author contributions

M.P.A. Brekelmans, L.J.J. Scheres, S.M. Bleker and H.R. Buller were responsible for the study conception and design. M.P.A. Brekelmans, L.J.J. Scheres and S.M. Bleker were responsible for analysis and interpretation of data, and drafting of the manuscript. All authors revised the manuscript critically for important intellectual content and provided final approval of the manuscript submitted. All authors had full access to the data in the study.

Conflicts of interest

M.P.A. Brekelmans has nothing to disclose. L.J.J. Scheres has nothing to disclose. S.M. Bleker has nothing to disclose. B.A. Hutten has nothing to disclose. A. Timmermans has nothing to disclose. H.R. Buller reports grants and personal fees from Daiichi Sankyo, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Isis Pharmaceuticals, GSK, Roche, Sanofi, Thrombogenics, outside the submitted work. S. Middeldorp reports grants or research support from GSK/Aspen, BMS/Pfizer, Sanquin and Bayer, Consultant fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo, Paid Instructor at Bayer, GSK BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo, outside the submitted work.

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