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Abnormal vaginal bleeding in women of reproductive age treated with edoxaban or warfarin for venous thromboembolism: a post hoc analysis of the Hokusai-VTE study

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Objective To investigate the characteristics and outcome of abnormal vaginal bleeding in women receiving edoxaban or warfarin for treatment of venous thromboembolism (VTE).

Design and setting Post hoc analysis of the Hokusai-VTE study, a multicentre, randomised, double-blind trial comparing edoxaban with warfarin for acute symptomatic VTE.

Population Women below 50 years receiving edoxaban or warfarin for treatment of VTE.

Methods We collected data on diagnostic measures, treatment, and clinical outcome of abnormal vaginal bleeding events.

Main outcome measures Occurrence of major and clinically relevant nonmajor (CRNM) abnormal vaginal bleeding events.

Results In all, 628 women aged under 50 years were treated with edoxaban and 665 with warfarin. The rate of abnormal vaginal bleeding was 15/100 person-years (py) (95% CI 11–19) in women receiving edoxaban and 9/100 py (95% CI 6–12) in the warfarin group (hazard ratio: 1.7, 95% CI 1.1–2.5). Major abnormal vaginal bleeding occurred in eight (1.3%) women on edoxaban and in three (0.9%) women receiving warfarin [odds ratio (OR) 2.8; 95% CI 0.8–10.8], and CRNM abnormal vaginal bleeding occurred in 53 (8.4%) women treated with edoxaban and in 37 (5.6%) on warfarin therapy (OR 1.6, 95% CI 1.0–2.4). Over 85% of all vaginal bleeds were characterised by heavy menstrual bleeding. Major bleeds frequently required treatment, and in more than 75% of patients anticoagulant therapy was adjusted. The severity of clinical presentation and course of major and CRNM bleeds was mild in most patients.

Conclusions Abnormal vaginal bleeding occurred more frequently in women treated with edoxaban than with warfarin. Reassuringly, most events could be managed conservatively and had a mild outcome.

Keywords Abnormal uterine bleeding, edoxaban, oral anticoagulants, vaginal bleeding, venous thromboembolism, warfarin.

Tweetable abstract Abnormal vaginal bleeding occurred more frequently in women treated with edoxaban than with warfarin.

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Introduction

Direct oral anticoagulants (DOACs) are at least as effective as vitamin K antagonists (VKA) for the treatment of venous thromboembolism (VTE) and cause less overall bleeding.[1,2] In addition, DOACs are user-convenient and can be administered in a fixed-dose regimen without the necessity for regular laboratory monitoring. As a result, DOACs have been rapidly implemented in guidelines and routine clinical practice as the first choice of anticoagulants for the treatment of VTE.[3]

Although the risk of major bleeding, especially intracranial haemorrhage, is lower with DOAC than with VKA therapy,[1] several studies have reported an increased incidence of abnormal vaginal bleeding events in women of reproductive age treated with rivaroxaban and apixaban, compared with warfarin.[4–9] The most frequently reported symptoms were heavy and prolonged menstrual bleeding.[5,8,9] The severity of the bleeds varied widely, from mild discomfort to distinct anaemia to life-threatening bleeding requiring immediate intervention to stop the bleeding.[5,7–9]

In the previously published Hokusai-VTE study, a randomised double-blind placebo controlled trial, edoxaban was compared with warfarin in patients with symptomatic VTE.[10] Whether edoxaban is also associated with increased risks of abnormal vaginal bleeding is unknown, as only a few cases have been described.[7,8] Therefore, we aimed to investigate the occurrence, characteristics, diagnostic measures, treatment, and clinical outcome of abnormal vaginal bleeding events in women of reproductive age receiving treatment with edoxaban or warfarin for VTE in the Hokusai-VTE study.[10]

Methods

Study population

The Hokusai-VTE study

Data for the present analyses were obtained from an in-depth analysis of the Hokusai-VTE study, a multicentre, randomised, double-blind, double-dummy trial comparing edoxaban with warfarin in patients with acute, symptomatic VTE (ClinicalTrials.gov identifier: NCT00986154).[10] Patients from both groups received initial treatment with enoxaparin or unfractionated heparin for a minimum of 5 days. After discontinuation of heparin treatment, edoxaban 60 mg (and placebo) was started. A reduced dose of edoxaban 30 mg was prescribed in patients with a decreased creatinine clearance of 30–50 ml/min, a bodyweight of 60 kg or less, or concomitant use of verapamil or quinidine (P-glycoprotein inhibitors). Warfarin (and placebo) was started simultaneously with enoxaparin or unfractionated heparin, with a target INR of 2.0–3.0. The minimal treatment duration was 3 months with a maximum of 12 months at the discretion of the treating physician. Patients were excluded from the study if they had any of the following: any contraindications for treatment with edoxaban or warfarin, active cancer with long-term treatment with heparin anticipated, continued treatment with aspirin in a daily dose of 100 mg or higher or dual antiplatelet therapy, a creatinine clearance below 30 ml/min. Full information on inclusion and exclusion criteria is detailed in the original publication of the Hokusai-VTE study.[10]

The principal safety outcome was the occurrence of clinically relevant bleeding events [a combination of major and clinically relevant nonmajor (CRNM) bleeding]. All bleeding events were recorded in standardised case report forms. The protocol did not specify the treatment options for bleeding events, but appropriate diagnostic and laboratory work-up was required.[10] Suspected outcomes were adjudicated by an independent committee whose members were unaware of study treatment allocation. The study protocol was reviewed and approved by the institutional medical ethical review board at each participating centre and all patients provided written informed consent.[10]

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Current study population and design

For the current analysis, we included all women aged under the age of 50 years. Two independent investigators (M.P.B. and L.J.S.) who were unaware of treatment allocation, collected the following data for all abnormal vaginal bleeding events that occurred during the study period: characteristics of the vaginal bleeding event [duration, severity (major or CRNM bleeding), frequency, relation to menstrual cycle], applied diagnostic tests, medical interventions, procedures or treatment to control the bleeding, and severity of clinical presentation and clinical course of the event. Data were obtained from case report forms, bleeding narratives, and patient profiles. Bleeding events were included if they occurred during the treatment period (when patients were receiving the study drug or within 3 days after discontinuation or interruption of the study drug).

Classification abnormal uterine bleeding

We used the definitions of the International Federation of Gynaecology and Obstetrics (FIGO)[11] further to categorise abnormal vaginal bleeding as: prolonged, intermenstrual or

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heavy menstrual bleeding, or menstrual bleeding leading to anaemia or an unscheduled evaluation by a physician, the need for a medical or surgical intervention, or temporary or permanent interruption of the study drug.

Classification of clinical presentation and clinical course

The clinical presentation and course of all major and CRNM abnormal vaginal bleeding events were classified by two independent clinicians (M.P.B. and L.J.S.) using predefined criteria (Supporting Information Table S1), as previously described.[12–14] In short, the first classification assessed the severity of the abnormal vaginal bleeding event at the moment of presentation. In the second classification, the course and outcome of the bleeding event were evaluated. If the assessors were in doubt between two categories of the classification scheme, the more severe outcome was chosen.

Statistical analysis

We used the independent sample *t*-test and Mann–Whitney U test to compare normally distributed and not normally distributed continuous variables, respectively, and the chi-square test to compare categorical variables.

A Cox proportional hazard regression analysis was performed to compare abnormal vaginal bleeding rates between the women treated with edoxaban and warfarin. The outcome was defined as major or CRNM vaginal bleeding. Observation time started at the time of randomisation and ended at the time of a first abnormal vaginal bleed. If a vaginal bleed did not occur, participants were censored at the last day of study drug use plus 3 days, or at the end of follow up. The absolute incidence of vaginal bleeds was calculated by dividing the number of events by observation time, with Poisson-based 95% confidence intervals (95% CI). The Cox model was adjusted for dose adjustments, site of VTE (deep vein thrombosis versus pulmonary embolism with or without deep vein thrombosis), and provoked versus unprovoked VTE.

Logistic regression models were constructed to estimate odds ratios (OR) and 95% CI for the occurrence of major and/or CRNM abnormal vaginal bleeding events in the different treatment groups (edoxaban versus warfarin). Analyses were carried out using SPSS 24 for Windows (IBM Software, Armonk, NY, USA).

Results

Study population

Among the 8292 patients who participated in the Hokusai-VTE study, 1293 were women and aged below 50 years. Of these, 628 (49%) were treated with edoxaban and 665 (51%) with warfarin. There were no differences in baseline characteristics between these two groups (Supporting Information Table S2).

Supporting Information Figure S1 provides an overview of all major and CRNM bleeding events that occurred in this subgroup of the Hokusai-VTE study. The overall incidence rate of abnormal vaginal bleeding was 15/100 py (95% CI 11–19) with edoxaban and 9/100 py (95% CI 6–12) with warfarin (hazard ratio 1.7, 95% CI 1.1–2.5; see Figure 1 for the Kaplan–Meier curve).

The baseline characteristics of all women aged under 50 years with a major or CRNM abnormal vaginal bleeding in the Hokusai-VTE study are depicted in Table 1. There were no apparent differences in the baseline characteristics between the edoxaban and warfarin groups. The time from randomisation to the bleeding event was similar in both groups with a median of 42 days [interquartile range (IQR) 24–96] for women treated with edoxaban and 36 days (IQR 20–117) for women receiving warfarin. Approximately 10% of women in both groups had a prior gynaecological disorder. One-third of the women receiving edoxaban or warfarin used hormonal contraceptives at the moment of randomisation.

Major bleeds

Major abnormal vaginal bleeding occurred in eight (1.3%) of 628 women on edoxaban and in three (0.9%) of 665 women in the warfarin arm (OR 2.8, 95% CI 0.8–10.8).

Characteristics

All major abnormal vaginal bleeding events were classified as abnormal uterine bleeding according to the FIGO

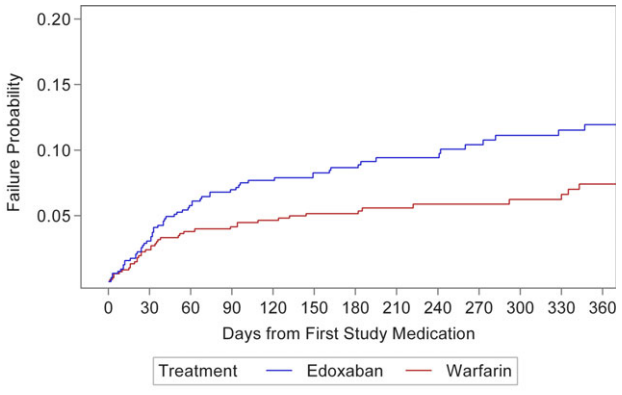

Figure 1. Kaplan–Meier curve for on-treatment abnormal vaginal bleeding in women aged under 50 years in the Hokusai-VTE trial treated with edoxaban or warfarin. The outcome includes both major abnormal vaginal bleeding and clinically relevant nonmajor abnormal vaginal bleeding. The blue line indicates treatment with edoxaban and the red line treatment with warfarin. Numbers in blue and red indicate women at risk during the study for edoxaban and warfarin, respectively.

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Table 1. Baseline characteristics of women les than 50 years of age with a major or CRNM abnormal vaginal bleeding in the Hokusai-VTE trial

	Edoxaban *n* = 61	Warfarin *n* = 40
Age (years), median (IQR)	42 (35–46)	42 (35–45)
BMI (kg/m²), median (IQR)	29 (25–34)	28 (24–32)
Randomisation to bleeding (days), median (IQR)	42 (24–102)	36 (20–117)
Index event, *n* (%)		
DVT	35 (57)	24 (60)
PE	22 (36)	12 (30)
Both	4 (7)	4 (10)
Risk factors for VTE, *n* (%)*		
Active cancer	1 (2)	0
Known thrombophilia	4 (7)	0
Previous VTE	11 (18)	3 (8)
Immobilisation	15 (25)	8 (20)
Use of estrogen-containing drugs	20 (33)	13 (33)
Other	8 (13)	7 (18)
None	20 (33)	16 (40)
History of anaemia, *n* (%)	26 (43)	18 (45)
Prior gynaecological disorder, *n* (%)	5 (8)	4 (10)
Antiplatelet use at randomisation, *n* (%)	6 (10)	4 (10)
NSAID use at randomisation, *n* (%)	19 (31)	13 (33)
Hormonal contraceptives, *n* (%)**	20 (33)	11 (28)

BMI, body mass index; DVT, deep vein thrombosis; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; SD, standard deviation.
*Multiple risk factors may be present.
**Excluding intrauterine devices and vaginal rings.

Table 2. Characteristics, diagnostic measures, treatment and outcomes of major abnormal vaginal bleeding events in the Hokusai-VTE trial

	Edoxaban	Warfarin
Number of women with major abnormal vaginal bleeding	8	3
Classifying for FIGO criteria AUB, *n* (%)	8 (100)	3 (100)
Prolonged menstrual bleeding	2	0
Intermenstrual bleeding	2	0
Heavy menstrual bleeding	8	3
Anaemia	5	2
Unscheduled contact	8	3
Diagnostic tests applied*, *n* (%)	4 (50)	1 (33)
Ultrasonography	2	1
Biopsy	2	1
Hysteroscopy	1	0
Unknown	0	0
Diagnosis, *n* (%)	2 (25)	3 (100)
Uterine myoma	2	1
Endometriosis	0	1
Cervical cancer	0	1
Haematoma	0	0
Hospital admission, *n* (%)	7 (88)	3 (100)
Treatment, *n* (%)		
Transfusion of packed cells	3 (38)	2 (67)
Iron supplements	2 (25)	0
Hormone therapy		
Estrogen containing	0	0
Progestagen containing	0	0
IUD	0	0
Tranexamic acid	2 (25)	0
Unknown	2 (25)	1 (33)
No treatment	2 (25)	0
Radiologic or surgical interventions, *n* (%)		
Hysterectomy	2 (25)	2 (67)
Endometrial ablation or curettage	1 (12)	0
No interventions	5 (63)	1 (33)
Other	0	0
Unknown	0	0
Change in anticoagulant, *n* (%)		
Unchanged	2 (25)	0
Temporary interruption	3 (38)	3 (100)
Permanent stop	1 (12)	0
Switch to another anticoagulant	1 (12)	0
Adjusted treatment dose	1 (12)	0
Unknown	0	0
Life-threatening bleeding – *n* (%)	0	1 (33)
Fatal bleeding – *n* (%)	0	0
Repetitive bleeding, *n* (%)	1 (13)	0
Recurrent VTE, *n* (%)	2 (25)	0
Classification of presentation of major vaginal bleed, *n* (%)		
Category 1	3 (38)	0
Category 2	4 (50)	2 (67)
Category 3	1 (12)	1 (33)
Category 4	0	0

criteria (Table 2); all bleeds in both groups were characterised as heavy menstrual bleeding and required an unscheduled contact with a physician. Anaemia was common in both groups. Prolonged and intermenstrual bleeding seemed to occur more frequently in women receiving edoxaban, although these differences did not reach statistical significance.

Diagnostic measures and treatment

Diagnostic tests were performed in four major bleeds on edoxaban and one of those on warfarin (Table 2). Uterine myomas were the underlying cause in two women on edoxaban and and one woman on warfarin.

Of the abnormal vaginal bleeds in both treatment arms, 10 of 11 women required hospital admission. Packed cell transfusions were given to three edoxaban users and two warfarin recipients. None of the women received treatment with oral or intrauterine contraceptives. Radiological or surgical interventions were performed in three major bleeds

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Table 2. (Continued)

	Edoxaban	Warfarin
Classification of course of major vaginal bleed, *n* (%)		
Category 1	2 (25)	1 (33)
Category 2	6 (75)	2 (67)
Category 3	0	0
Category 4	0	0

AUB, abnormal uterine bleeding; FIGO, International Federation of Gynaecology and Obstetrics; IUD, intrauterine device; VTE, venous thromboembolism.
*Patients may have undergone multiple diagnostic tests.

with edoxaban and in two with warfarin; four of these concerned a hysterectomy. In two major vaginal bleedings with edoxaban, treatment was not deemed necessary (Table 2).

Anticoagulant treatment was unchanged in only two major abnormal vaginal bleedings in edoxaban recipients and in none receiving warfarin. Temporary interruption was deemed necessary in three women on edoxaban and and three women on warfarin. Other changes included permanent discontinuation ($n = 1$), switch to another anticoagulant ($n = 1$), and dose adjustment ($n = 3$) (Table 2).

Clinical presentation, course, and clinical outcome

In the women with a major abnormal vaginal bleed, repetitive bleeding was uncommon, with only one observation in the edoxaban arm. With respect to the severity of the vaginal bleeds, most bleeding events presented as category 1 or 2 and were mild (seven in the edoxaban and two in the warfarin arm). One woman using edoxaban and one woman using warfarin had a category 3 clinical presentation of the major abnormal vaginal bleed. Reassuringly, none of the major bleeds in either group was classified as having a category 3 or 4 clinical course (i.e. severe clinical course).

Clinically relevant nonmajor bleeds

CRNM abnormal vaginal bleeding occurred in 53 (8.4%) of 628 women treated with edoxaban and in 37 (5.6%) of 665 women receiving warfarin (OR 1.6, 95% CI 1.0–2.4). Of the total 80 CRNM bleeds in the edoxaban arm, 53 (66%) were of vaginal origin, whereas of the 68 bleeds in the warfarin arm, this was 37 (55%) (OR 1.6, 95% CI 0.8–3.2; Figure S1).

Characteristics

All but one CRNM bleed in the warfarin arm was classified as abnormal uterine bleeding according to the FIGO criteria (consequently, this bleeding event was not included in further analyses). Most CRNM abnormal vaginal bleeds, 45 (85%) in the edoxaban arm and 32 (89%) in the warfarin arm, were characterised as heavy menstrual bleeding. More CRNM abnormal vaginal bleeds in women treated with edoxaban were associated with anaemia [11 (21%)] compared with in women using warfarin in [6 (2%); Table 3].

Diagnostic measures and treatment

In women receiving edoxaban, diagnostic tests were applied in 10 (19%) patients versus three (8%) women treated with warfarin. In four (40%) edoxaban and in two (67%) warfarin recipients, a cause of the vaginal bleeding could be detected (Table 3). Approximately 10% of patients in both groups required hospital admission for the bleeding event.

Medical treatment was not initiated in 31 (58%) edoxaban recipients and in 24 (66%) women on warfarin. The majority of women [51 women (96%) in the edoxaban arm and 34 (94%) in the warfarin arm] did not undergo any radiological or surgical interventions.

The anticoagulation remained unchanged in most women: it was temporarily suspended in 12 (22%) edoxaban and in eight (22%) warfarin recipients, and permanently discontinued in two (4%) and one (3%) patients.

Clinical presentation, course, and clinical outcome

In these women with an abnormal vaginal CRMN bleed, repetitive bleeding was frequently observed [28 (53%) edoxaban and 18 (50%) warfarin recipients; Table 3]. The clinical presentation and course of CRNM vaginal bleeds were classified as mild (i.e. category 1 or 2) in 28 (54%) of edoxaban recipients and in 23 (64%) of warfarin recipients.

Discussion

Main findings

Edoxaban is the most recently approved DOAC for the treatment and secondary prevention of VTE.[15] As the uptake of edoxaban in clinical practice will likely increase over the following years, there is a need for information on the occurrence, clinical impact, and management of abnormal vaginal bleeding complications related to the use of edoxaban.

In this analysis, abnormal vaginal bleeding occurred frequently (9–15/100 py) and significantly more often in women of reproductive age receiving edoxaban compared with women receiving warfarin. In addition, the risk of major abnormal vaginal bleeding also appeared greater with edoxaban than warfarin, albeit with 95% CI crossing unity. All major bleeds were characterised by heavy menstrual bleeding, and most cases required a treatment or intervention to control the bleeding and resulted in modifications of the anticoagulant treatment. The severity of clinical presentation and course of the major abnormal vaginal bleeds

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Table 3. Characteristics, diagnostics, treatment and outcomes of CRNM abnormal vaginal bleeding events in the Hokusai-VTE trial

	Edoxaban	Warfarin
Number of women with CRNM abnormal vaginal bleeding	53	37
Classifying for FIGO criteria AUB, *n* (%)	53 (100)	36 (97)
Prolonged menstrual bleeding	8	5
Intermenstrual bleeding	8	2
Heavy menstrual bleeding	45	32
Anaemia	11	2
Unscheduled contact	29	14
Diagnostic tests applied*, *n* (%)	10 (19)	3 (8)
Ultrasonography	6	3
Biopsy	0	0
Hysteroscopy	1	0
Unknown	3	1
Diagnosis, *n* (%)	4 (8)	2 (5)
Uterine myoma	2	1
Endometriosis	0	0
Cervical cancer	2	0
Haematoma	0	1
Hospital admission, *n* (%)	7 (13)	4 (11)
Treatment, *n* (%)		
Transfusion of packed cells	2 (4)	1 (3)
Iron supplements	5 (9)	1 (3)
Hormone therapy		
Estrogen-containing	1 (2)	1 (3)
Progestagen-containing	1 (2)	0
IUD	0	1 (3)
Tranexamic acid	3 (6)	0
Unknown	10 (19)	8 (22)
No treatment	31 (58)	24 (66)
Radiologic or surgical interventions, *n* (%)		
Hysterectomy	0	1 (3)
Endometrial ablation or curettage	1 (2)	0
No interventions	51 (96)	34 (94)
Other	0	1 (3)
Unknown	1 (2)	0
Change in anticoagulant, *n* (%)		
Unchanged	38 (72)	25 (69)
Temporary interruption	12 (22)	8 (22)
Permanent stop	2 (4)	1 (3)
Switch to another anticoagulant	0	0
Adjusted treatment dose	0	0
Unknown	1 (2)	2 (6)
Repetitive bleeding, *n* (%)	28 (53)	18 (50)
Recurrent VTE, *n* (%)	0	0
Classification of CRNM vaginal bleed, *n* (%)		
Category 1	18 (34)	18 (50)
Category 2	10 (19)	5 (14)
Category 3	17 (32)	10 (28)
Category 4	7 (13)	3 (8)
Unknown	1 (2)	0

AUB, abnormal uterine bleeding; CRNM, clinically relevant nonmajor; FIGO, International Federation of Gynaecology and Obstetrics; IUD, intrauterine device; VTE, venous thromboembolism. *Patients may have undergone multiple diagnostic tests.

was mild in most patients and no fatal events were observed. However, hysterectomies were performed in four of 11 women with a major abnormal vaginal bleeding, underlining the potentially serious consequences of these events. Regarding the CRNM bleeds, diagnostic tests and interventions were needed in a minority of the patients, and most women remained on their usual anticoagulant treatment. The severity of clinical presentation and course did not differ between the treatment groups and was mild in more than half of the patients.

Strengths and limitations

Strengths of the present analysis are that the Hokusai-VTE study was a double-blind study in which all bleeding events were adjudicated without knowledge of treatment allocation; information on bleeding was collected prospectively on predefined event forms. Another strength is that patients were actively asked about signs and symptoms of bleeding, and therefore the risk of underreporting is low. Several limitations should also be mentioned. The first is the relatively modest sample size. We were able to analyse the occurrence and outcome of the bleeding events in this high-quality data set. However, we cannot rule out that possible differences in characteristics, treatment or outcome between the two treatment groups may not have been detected due to the limited number of events; however, we believe that the risk of confounding in this subgroup analysis remains low. Furthermore, the diagnostic process and applied treatment options were not standardised and were at the discretion of the treating physician. This might have introduced bias, as local hospital protocols or expert opinions may vary. Additionally, no information was available on hormonal contraceptive use during the study period. It would have been informative to know whether women were treated with hormones, which therapies were used, and how this affected important clinical outcomes, such as recurrences, repetitive bleeding, and severity of the bleeds. Currently, only a few studies have been able to investigate the safety of prescribing hormones during the use of anticoagulants,[6,16] but future studies should confirm these results. Finally, no information was collected on the quality of life of the women with abnormal vaginal bleeding. Data on quality of life are important to assess the impact on the patients' daily activities, and to guide treatment and management decisions.

Interpretation

Several recent studies have shown an increased rate of vaginal bleeding events in women of reproductive age treated with rivaroxaban compared with VKA.[4–6,17] The occurrence of abnormal vaginal bleeding varied between 20 and 32% in women receiving rivaroxaban and between 12 and 15% in VKA-treated women.[4,8,17–20] The data for apixaban are

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less clear; some studies reported a similar risk of heavy vaginal bleeding for apixaban and VKA,[9,18,20] whereas in others, apixaban was associated with an increased risk of excess vaginal bleeding.[7,8] For edoxaban, only a few cases have been described in the literature,[7,8] and in our study, the rate of abnormal vaginal bleeds appeared to be higher with edoxaban than with VKA. To date, data on the occurrence and outcome of abnormal vaginal bleeding events associated with the use of dabigatran etexilate, a direct thrombin inhibitor, are scarce. In a conference abstract reporting on a post hoc analysis of the pooled RE-COVER studies, a lower risk of abnormal uterine bleeding was reported with dabigatran etexilate than with warfarin in women aged up to 50 years with VTE.[21] Further detailed observational data are needed to provide more insight into this.

Abnormal vaginal bleeding associated with anticoagulant use in women of reproductive age is frequently related to the menstrual cycle, and may involve prolonged, heavy or intermenstrual bleeding.[11,22] It decreases quality of life and may impact daily activities.[22] Physicians should be aware of this complication and inform the patients at risk. It is important to encourage patients to seek medical attention in case abnormal vaginal bleeding occurs, to prevent temporary or permanent discontinuation of anticoagulant treatment, leading to an increased risk of recurrent VTE.[19] Several preventive and therapeutic measures are available to manage abnormal vaginal bleeding in women using anticoagulants, although practice patterns are diverse and not in accordance with guideline recommendations.[23] Effective treatment options for excess vaginal bleeding are the placement of an intrauterine device or hormonal contraceptive, and neither are associated with an increased VTE risk during the use of anticoagulants.[6,16] In addition, intrauterine devices also have been found safe in terms of VTE risk outside of anticoagulant use.[24] Another option is the use of tranexamic acid during the menstrual period; however, its safety profile and efficacy are not well documented in this patient group.[25,26] Also, one can switch a woman to another DOAC or to VKA, but the reduction in bleeding symptoms of switching is unclear. All DOAC and VKA therapies carry a risk of abnormal vaginal bleeding and, for VKA, several other disadvantages also apply, such as higher rate of intracranial haemorrhages, interactions with other drugs, and the necessity of frequent laboratory controls and dose adjustments. Referral to a gynaecologist should be considered. An assessment and management strategy for women with abnormal vaginal bleeding associated with anticoagulants were suggested recently by Boonyawat et al.[27]

The underlying mechanism of the observed increased risk of abnormal vaginal bleeding with fXa inhibitors is unknown. The use of fXa inhibitors may have a direct effect on the uterine wall, similar to the effect of fXa inhibitors on the gastrointestinal wall and the variable amount of active drug present there, which might induce local bleeding tendency.[28,29] Also, fXa inhibitors may influence the apparently tightly regulated process of local haemostasis of the uterine wall.[30]

Conclusion

In conclusion, we found that the incidence of abnormal vaginal bleeding events in women under 50 years of age was higher with edoxaban than with warfarin. Almost all abnormal vaginal bleeding events were characterised by heavy menstrual bleeding, and in most cases remained mild with a limited clinical impact. These findings provide reassurance that although vaginal bleeding events are a frequent complication of anticoagulant treatment in women of reproductive age, most events can be managed conservatively and have a mild outcome. Nevertheless, awareness should be increased among physicians and patients to prevent and recognise vaginal bleeding complications early in order to avoid temporary or permanent cessation of anticoagulant treatment.

Disclosure of interests

LJJS, MPAB, BAH, and KS have nothing to disclose. WA reports grants from Bayer and personal fees from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, Aspen, Portola, Stago, CSL Behring, Sanofi, outside the submitted work. CA reports personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer outside the submitted work. HRB 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. SE reports personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer outside the submitted work. FAK reports research grants from Bayer, research grants from Bristol-Myers Squibb, research grants from Boehringer-Ingelheim, research grants from MSD, Research grants from Actelion, and non-financial research support from Daiichi-Sankyo outside the submitted work. SM reports grants or research support from GSK/Aspen, BMS/Pfizer, Sanquin, Bayer, and Daiichi Sankyo. Consultant fees from Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi Sankyo, Paid Instructor at Bayer, GSK, BMS/Pfizer, Boehringer Ingelheim, Sanofi, and Daiichi Sankyo, outside the submitted work. All fees are paid to her Institution. KS reports grants and personal fees from Daiichi Sankyo, Sanofi, Novartis, Amgen, Berlin Chemie, outside the submitted work. MB reports travelling fees from Daiichi Sankyo, outside the submitted work. AD reports research grants from Bayer, BMS-Pfizer, Boehringer,

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Contribution to authorship

LJJS, MPAB, WA, CA, HRB, SE, BAH, FK, SM, KS, ST, MBl, and AD were involved in the study conception and planning of the study. LJJS, MPAB, BAH, and HRB carried out the analysis and interpretation of data, and drafting of the manuscript. WA, CA, SE, BAH, FK, SM, KS, ST, MBl, and AD revised the manuscript critically for important intellectual content. LJJS, MPAB, WA, CA, HRB, SE, BAH, FK, SM, KS, ST, MBl, and AD provided final approval of the manuscript submitted.

Details of ethics approval

The protocol of the original Hokusai-VTE study (ClinicalTrials.gov number, NCT00986154) was reviewed and approved by the institutional medical ethical review board at each participating centre and all patients provided written informed consent.[10] A full list of the participating centres is available elsewhere.[31]

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 All bleeding events in women aged under 50 years in the hokusai-VTE trial.

Table S1. Classification of clinical presentation and course of major and clinically relevant nonmajor bleeding events

Table S2. Baseline characteristics of all women less than 50 years of age in the Hokusai-VTE study ■

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