

Bleeding Issues in Women Under Oral Anticoagulation

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Abstract

In premenopausal women treatment with direct oral anticoagulants (DOACs) can be associated with an increased risk of heavy menstrual bleeding (HMB) compared with vitamin K antagonists. These findings come from retrospective or prospective single-center studies and post hoc analysis of regulatory studies in which HMB was not a predefined safety outcome. In most of these publications, there is a lack of information about the use of different contraceptive methods which can influence HMB. Another limitation is the various definitions of HMB, which makes comparison between studies regarding the incidences of HMB difficult.

Therefore, prospective studies are urgently needed to investigate the severity and duration of unaffected menstrual bleeding under oral anticoagulation independently of oral contraceptives or intrauterine devices. An ongoing multicenter German registry is aiming to compare the incidence of unaffected HMB in consecutive women of reproductive age (18–50 years) treated with different DOACs because of venous thromboembolism.

When HMB occurs during oral anticoagulation, management includes interruption or dose reduction of anticoagulation with the danger of recurrent venous thrombosis, switch to another oral anticoagulant, or additional use of the antifibrinolytic agent tranexamic acid with the potential risk of thrombosis. Concomitant use of either oral hormonal contraceptive therapy or hormone-releasing intrauterine systems can also reduce HMB.

Keywords

- ▶ abnormal uterine bleeding
- ▶ heavy menstrual bleeding
- ▶ PBAC score
- ▶ direct oral anticoagulants
- ▶ venous thrombosis

Case Report

A 23-year-old woman experienced a proximal deep vein thrombosis (DVT) of the left popliteal and superficial femoral vein while taking an estrogen-containing pill which she had begun 2 years ago because of heavy menstrual bleeding (HMB). Thrombophilia examination revealed a heterozygous factor V Leiden mutation. She received rivaroxaban from her health care practitioner and was advised to discontinue the hormonal contraception immediately after the diagnosis of thrombosis. An external blood test a month

before the occurrence of the DVT showed a hemoglobin of 11.9 mg/dL. After discontinuation of contraception, she developed HMB lasting more than 7 days. The bleeding was more pronounced while the patient received rivaroxaban 15 mg twice daily (initiation phase of anticoagulation) and continued on her second cycle while she was treated with rivaroxaban 20 mg once daily. Two months after start of anticoagulation, her hemoglobin had dropped to 8.5 mg/dL and her ferritin was 5 µg/L. Severe iron deficiency was diagnosed.

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Introduction

Abnormal uterine bleeding (AUB) encompasses HMB, post-menopausal bleeding, and bleeding which is prolonged or manifested outside the normal menstrual cycle.

HMB is defined as a blood loss of more than 80 mL during the menstrual cycle. However, almost 40% of women who seek medical assistance because of HMB have a blood loss of less than 80 mL. On the other hand, some women with a blood loss of more than 80 mL report their menses as slight or

moderate.^{1,2} The most recognized tool for objective assessment of the severity of menstrual bleeding is the pictorial blood loss assessment chart (PBAC) which was introduced by Higham et al³ (see -Fig. 1). A score >100 points can predict a blood loss of more than 80 mL, whereas a score >150 points, the presence of blood clots, and the duration of the menstrual bleeding longer than 7 days can predict HMB in a multivariate analysis. In addition, the bleeding assessment tool of the International Society of Thrombosis and Hemostasis (ISTH-BAT)^{4,5} can be used to quantify the severity of

Hygiene products: Type of pads or tampons

The absorbency of hygiene products can be identified by the droplet symbol on the package.

- ◆ or ◆◆ Type 1
- ◆◆◆ or ◆◆◆◆ Type 2
- ◆◆◆◆ or ◆◆◆◆◆ Type 3

If you do not find a droplet icon, please refer to the product name to determine if the product is designed for:

- Light bleeding (Type 1)
- Moderate bleeding (Type 2)
- Heavy bleeding (Type 3)

filling quantity of hygiene product: Date from: _____ to: _____

1st day of menstruation / / DD/MM/YY

Tampons	Day1	2	3	4	5	6	7	8	9	10	Factor	Sum
◆ or ◆◆											x1	
◆◆◆ or ◆◆◆◆											x5	
◆◆◆◆ or ◆◆◆◆◆											x10	
Clot/ soaked												
Sum:												

Pads	Day1	2	3	4	5	6	7	8	9	10	Factor	Sum
◆ or ◆◆											x1	
◆◆◆ or ◆◆◆◆											x5	
◆◆◆◆ or ◆◆◆◆◆											x10	
Clot/ soaked												
Sum:												

How it works:
Please document the consumption of your hygiene products on a daily basis using the tables. To do this, enter the daily number of pads or tampons in the matching line for the filling quantity

It is advisable to keep a tally sheet within the table, to which you add one dash each time you have used a hygiene product.

Calculation of Score:

- Multiply the number of dashes by the respective factor.
- Every fully soaked tampon or pad is scored an additional 5 points; for a „Clot“ with a length of 2,5cm 5 additional points should be added for a „Clot“ smaller than 2,5cm one additional point should be added.
- Add both sums to get the score. If the score is above 100 further assessment is recommended.

Score:
(sum tampons + sum pads)

Fig. 1 Modified PBAC score to evaluate menstrual bleeding. PBAC, pictorial blood loss assessment chart.

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bleeding according to the necessity for medical or surgical interventions.

To define and recognize AUB and HMB, many aspects should be taken into consideration: age, patient-related characteristics, use of oral contraception, anatomical lesions such as endometriosis, myoma, adenomyosis, and uterine fibrinoids. Furthermore, HMB may be the first manifestation of an inherited bleeding disorder like von Willebrand disease in women of reproductive age. Standard major bleeding (MB) and clinically relevant nonmajor bleeding (CRNMB) definitions, used almost exclusively in large clinical trials of direct oral anticoagulants (DOACs), are problematic because they fail to account for the chronic and recurrent nature of HMB.⁶ Although patients with HMB rarely require transfusions, they often develop iron deficiency but may hesitate to seek needed medical attention. It can therefore be assumed that HMB is underestimated not only in prospective registration studies for oral anticoagulants (OACs), but also in everyday clinical practice.

AUB/HMB under Vitamin K Antagonists or Direct Oral Anticoagulants

Women receiving oral anticoagulation for the treatment of venous thrombosis or atrial fibrillation have a significantly increased risk of developing HMB and/or AUB.

An increase of AUB up to 70% has been reported in premenopausal women using therapeutic doses of OACs.^{7,8}

Vitamin K Antagonists

Huq et al⁸ prospectively analyzed menstrual bleeding and contraception in 53 women aged 14 to 55 years who were treated with warfarin between July 2006 and July 2008. They described HMB (a PBAC score >100) in 66% of women using warfarin. Twenty-nine women (54.7%) were advised to change the contraception method. Most of them (24 of 29 women) had used combined oral contraception (COC) before the initiation of anticoagulation and they changed to barrier contraception, no contraception, or were sterilized. The remaining five had a copper intrauterine device (Cu-IUD) or used a depot medroxyprogesterone acetate.

This is one of the few publications where the use of hormonal contraception prior and after initiation of OAC is reported, suggesting that a higher rate of HMB after beginning OAC can be caused by the interruption of the hormonal contraception.

It can be assumed that most women are not appropriately advised on the options of contraception when oral anticoagulation is started. COC may be immediately stopped after diagnosis of venous thromboembolism (VTE) as they are known to cause venous thrombosis.

A Swedish study also reported an increase of HMB ranging from 44% before initiation of anticoagulation to 70% after initiation of vitamin K antagonist (VKA) treatment⁹ (see ▶Table 1 for more details).

DOAC

Most data on the bleeding profile under DOAC derive from post-hoc analyses of licensing studies for the anticoagulation

of venous thrombosis^{10–13} and some single-center analysis^{14–17} (see ▶Tables 1 and 2 for details).

Rivaroxaban (Direct Factor Xa Inhibitor)

In a single-center prospective study on women aged 18 to 55 years treated with rivaroxaban or VKA for VTE, a two-fold increased risk of HMB was observed in women treated with rivaroxaban: 31 out of 76 women (41%) had HMB in comparison to 8 out of 45 women (18%) treated with warfarin.¹⁵

A second single-center retrospective study evaluated AUB in women with VTE treated with rivaroxaban or VKA¹⁴. The study showed that 73% of patients on rivaroxaban and 67% of patients treated with VKA experienced AUB. However, women receiving rivaroxaban had a significant prolongation of the menstrual bleeding and required more frequently medical or surgical intervention or adaptation of the anticoagulation.¹⁴ Hormonal contraception was assessed, but preexisting anemia or AUB before the initiation of anticoagulation was not analyzed in this study (see ▶Table 1).

In the SELECT-D study, a randomized trial in patients with cancer-associated thrombosis,¹⁸ uterine CRNMB was reported in 1 out of 87 women treated with rivaroxaban in comparison to none out of 105 women treated with dalteparin 150 IU/kg. Uterine CRNMB was defined as major nonfatal bleeding with a decrease of Hb <2 g/dL not requiring transfusion or intervention but requiring medical intervention or affecting daily activities. No major uterine bleeding was reported. The mean age of all cancer patients including men was 67 years. Vaginal bleeding was very low in the study, probably because of the low number of premenopausal women.

A prospective analysis comparing AUB in 139 women aged 55 years or less taking rivaroxaban or apixaban showed HMB in 24 of 96 women (25%) on rivaroxaban and in 4 of 43 (9.3%) women on apixaban¹⁷ (see ▶Table 1 for more details).

In a post-hoc analysis of the EINSTEIN DVT and EINSTEIN PE trials,¹⁰ 1,888 women with VTE aged <60 years who had been randomized to treatment with rivaroxaban or warfarin were analyzed for uterine bleeding and the use of hormonal therapy (see ▶Table 2). Uterine bleeding leading to transfusion occurred more frequently in women receiving rivaroxaban (2.1%; 19/925 women) in comparison to VKA (0.3%; 3/963 women). In addition, AUB occurred more often during treatment with rivaroxaban in comparison to VKA and led to discontinuation of anticoagulation. More than one-third of women ($n = 705$) had received hormonal therapy before initiation of anticoagulation and 305 women stopped hormonal treatment after the start of anticoagulation, while 475 women restarted or continued hormonal treatment.

In a second post-hoc analysis of the Einstein Choice study which compared therapeutic treatment with rivaroxaban (20 mg once daily) with prophylactic rivaroxaban treatment (10 mg once daily) or aspirin (100 mg daily) for prolonged secondary prevention of VTE, HMB was more frequently observed under therapeutic rivaroxaban treatment compared with prophylactic rivaroxaban treatment or aspirin¹⁹ (see ▶Table 2 for more details).

Table 1 Retrospective and prospective cohorts of women treated with oral anticoagulants

Study and indication of anticoagulation	Number of women on medication ^a	Age (y), range	Assessment of hormonal contraception before and after starting oral anticoagulation	Definition of HMB	AUB/HMB or CRNMB	Assessment of menstrual history, anemia, or gynecologic disorders
Huq et al, 2011 ⁸ Single center prospective study Medication: warfarin Indication: various diseases	Warfarin n = 53	14–55 Mean age: 36	29 (54.7%) changed the contraception method after beginning warfarin. 24/29 had COC prior to warfarin treatment and stopped COC after treatment with warfarin. 3 had Cu-IUD and switched to LNG-IUS or POP. 2 had DMPA and switched to POP or had no contraception.	According to the PBAC score, duration of menstruation	50% of women had an increase of duration of menstruation. 66% had a PBAC score > 100. 9/53 women had anemia prior to and 18/53 women presented with anemia after start of anticoagulation	Menstrual pattern and presence of anemia before OACs were assessed
Själänder et al, 2007 ⁹ Single center prospective study Medication: warfarin Indication: various diseases	Warfarin n = 90	15–49	Before: 69/90 had taken oral contraceptives at any time before the anticoagulation, of which 16 due to menorrhagia After: NA	Menorrhagia	44% had menorrhagia before warfarin and 70.8% while treated with warfarin	NA
De Grem et al, 2015 ¹⁴ Single center retrospective study Medication: rivaroxaban and/or warfarin Indication: VTE and PE	Rivaroxaban n = 52 ^b Warfarin n = 52 ^b Both n = 35 ^b Switched groups n = 8 ^b	23–49	Before 63% of women on rivaroxaban and 85% of women on VKA received estrogen therapy when the VTE was diagnosed. After beginning OA: 23% on rivaroxaban and 7.7% on VKA changed contraceptive method	AUB was defined according to the FIGO criteria ^c	73% had AUB on rivaroxaban and 67% had AUB on VKA. During treatment with rivaroxaban a significant prolongation of the menstrual bleeding was observed	1/52 women (1.9%) on rivaroxaban and VKA had endometrial ablation or embolization. 1/52 women on rivaroxaban and none on VKA had a hysterectomy
Ferreira et al, 2016 ³² Prospective study Medication: rivaroxaban Indication: VTE and PE	Rivaroxaban n = 128	16–55 Mean age: 37.8	NA	HMB	HMB in 26/128 women (20%) 1 episode of MB	NA
Beyer-Westendorf et al, 2016 ¹⁶ Prospective German registry Medication: DOAC Indication: VTE and AF	All women n = 178 Rivaroxaban 20 mg n = NA Apixaban 5 mg n = NA Edoxaban 60 mg n = NA	27–48	5 of 57 women changed hormonal contraception to treat HMB. Out of 9 women with anatomical causes of bleeding, one woman on rivaroxaban had hormone therapy before	Vaginal bleeding complications and HMB (prolongation or increased intensity). Bleeding intensity was assessed according to the ISTH definition	57 of 178 women (32%) on Factor Xa inhibitors had HMB in total 72 bleeding events occurred, 39 (54%) were minor and 6 (8%) were MB events: one on apixaban, one	Bleeding history and NSAID use were assessed. Eight (14%) events required interventional treatment. Nine patients (6 on rivaroxaban, 1 on

Table 1 (Continued)

Study and indication of anticoagulation	Number of women on medication ^a	Age (y), range	Assessment of hormonal contraception before and after starting oral anticoagulation	Definition of HMB	AUB/HMB or CRNMB	Assessment of menstrual history, anemia, or gynecologic disorders
Myers et al, 2017 ¹⁷ Prospective registry Medication: rivaroxaban or apixaban Indication: VTE and PE	Rivaroxaban n = 96 Apixaban n = 43	18–53 for rivaroxaban 14–53 for apixaban Mean age: 40	and after the event, the rest received none.	HMB	HMB in 24 of 96 women (25%) on rivaroxaban HMB in 4 of 43 women (9.3%) on apixaban	apixaban, and 1 on edoxaban and four on rivaroxaban. 2/96 women on rivaroxaban and 1/43 patients on apixaban had local uterine abnormalities
Bryk et al, 2016 ¹⁵ Single-center retrospective study Medication: rivaroxaban or warfarin Indication: VTE	Rivaroxaban n = 76 VKA n = 45	18–55	NA	HMB	A twice-fold increased risk of HMB was observed in women treated with rivaroxaban: 31/76 women (41%) had HMB on rivaroxaban compared with 8/45 women (18%) treated with VKA.	Interruption of anticoagulation was assessed: 18/76 (24%) of women interrupted rivaroxaban and 4/45 (9%) patients interrupted VKA.

Abbreviations: AF, atrial fibrillation; AUB, abnormal uterine bleeding; COC, combined oral contraceptive; CRNMB, clinically relevant nonmajor bleeding; Cu-IUD, copper intrauterine device; DMPA, depot medroxyprogesterone acetate; DOAC, direct oral anticoagulant; FIGO, International Federation of Gynecology and Obstetrics; HMB, heavy menstrual bleeding; ISTH, International Society of Thrombosis and Hemostasis; LNG-IUS, levonorgestrel intrauterine system; MB, major bleeding; n, number; NA, not accessed; NSAID, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; PBAC, pictorial blood loss assessment chart; PE, pulmonary embolism; POP, progesterone only pill; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aDOACs were used in therapeutic doses; under VKA treatment INR was within the therapeutic range.

^bNumber of patients who gave informed consent.

^cMenstrual bleeding >8 days, intermenstrual blood loss causing anemia or requiring medical or surgical intervention.

In the randomized open-label phase III pediatric study (EINSTEIN-Junior phase III) comparing rivaroxaban with VKA and low-molecular-weight heparin (LMWH) in children with VTE, girls up to 17 years had higher rates of HMB with rivaroxaban treatment compared with LMWH or VKA.²⁰ Menorrhagia occurred in 23 out of 121 (19%) patients on rivaroxaban versus 5 out of 70 (7.1%) patients on LMWH or VKA. No uterine MB or CRNMB occurred. In total, 53 of 97 (55%) girls received hormonal contraception when VTE was diagnosed. The number of girls who stopped hormonal therapy after the initiation of anticoagulation was not assessed.

Edoxaban (Direct Factor Xa Inhibitor)

In women <50 years with VTE receiving therapeutic dose edoxaban or warfarin (Hokusai-VTE study),¹³ a post-hoc analysis showed that major AUB occurred more frequently in women treated with edoxaban (13%; 8/61 women) compared with warfarin (7.5%; 3/40 women). In total, 53/61 patients (87%) on edoxaban and 37/40 patients (93%) on warfarin experienced CRNM AUB. The authors reported that one-third of women either on edoxaban or on warfarin used hormonal contraceptives at the time of randomization (see ▶Table 2 for more details).

In this study, the definitions of the International Federation of Gynecology and Obstetrics were used to define AUB, which include the following: prolonged, intermenstrual bleeding, or HMB, or menstrual bleeding causing anemia or an unscheduled evaluation.

Apixaban (Direct Factor Xa Inhibitor)

As already mentioned, a prospective study analyzing AUB in 139 women aged 55 years or less taking rivaroxaban or apixaban showed less HMB in women on apixaban compared with women on rivaroxaban¹⁷ (see ▶Table 1).

In the AMPLIFY VTE treatment study, which compared apixaban treatment with VKA/enoxaparin treatment in patients with acute venous thrombosis, similar rates of clinically relevant nonmajor vaginal bleeding in patients treated with apixaban in comparison to those treated with VKA/enoxaparin were observed: clinically relevant nonmajor vaginal bleeding occurred in 28 out of 1,125 (2.5%) women receiving apixaban and in 24 out of 1,106 (2.1%) women receiving warfarin/enoxaparin. In total, 22 of 24 women under apixaban and 18 of 24 women under VKA/enoxaparin had premenopausal bleeding. Major vaginal bleeding occurred in none on warfarin and in 1 of 1,122 (<0.1%) women on apixaban.²¹ This was a 45-year old woman who had a history of endometriosis and was diagnosed with uterine fibroids.

However, the duration of menstrual bleeding seemed to be prolonged with apixaban. In this study, pre- and postmenopausal women were included.

In the Caravaggio study, a randomized trial on cancer-associated venous thrombosis comparing treatment with apixaban to LMWH treatment, similarly low rates of uterine CRNMB were reported in patients on apixaban compared with LMWH.¹¹ However, the mean age of the patient popu-

lation was 67 years, indicating that most women were postmenopausal (see ▶Table 2).

Dabigatran (Direct Thrombin Inhibitor)

Dabigatran, an oral direct thrombin inhibitor, seems to show a favorable profile regarding HMB unlike rivaroxaban. In a post-hoc analysis of the RE-MEDY and RE-COVER VTE trials on AUB (MB or CRNMB), 634 women aged 18 to 50 years treated with dabigatran and 637 women treated with warfarin were analyzed. Dabigatran-treated women had an approximately 41% lower risk of AUB in comparison to the warfarin-treated women.¹² The rate of AUB was 5.9% for women treated with dabigatran and 9.6% for women treated with warfarin. In the dabigatran-treated patients, 3 out of 634 (0.5%) suffered from MB compared with 5 out of 637 (0.8%) warfarin-treated patients. In both groups, two severe AUB events were reported, whereas the rest were mild or moderate (see ▶Table 2).

Limitations and Discussion of the Available Data

Reviews by Godin et al²² and by Jacobson-Kelly and Samuelson Bannow² summarizing some of the above-mentioned studies suggest that AUB is increased during treatment with rivaroxaban compared with treatment with apixaban.

A recent report using real-world data from an U.S. health care database compared severe uterine bleeding in women aged 18 to 89 years with atrial fibrillation or VTE newly exposed to apixaban, rivaroxaban, dabigatran, or warfarin. The rate of severe uterine bleeding was higher in patients with VTE who were younger in age. They found that patients with VTE on rivaroxaban had a higher rate of uterine bleeding compared with apixaban and warfarin.²³

Beyer-Westendorf et al analyzed vaginal bleeding, HMB, and underlying gynecological conditions in 178 women on DOAC, predominantly rivaroxaban. Fifty-seven of included women presented with vaginal bleeding events (50 received rivaroxaban, 6 received apixaban, and 1 received edoxaban)¹⁶ (see ▶Table 1). According to these data, women with anatomical lesions can present with a higher bleeding pattern during treatment with direct factor Xa inhibitors. This information is often not available or unknown when anticoagulation is started. Another limitation is the various definitions of HMB which makes a comparison between the different studies regarding the incidences of HMB difficult.

Concluding, DOACs differ in their menstrual bleeding profile with rivaroxaban and edoxaban showing a rather unfavorable profile, whereas apixaban and dabigatran seem to have a more favorable profile regarding HMB. So far, VKA-treated women seem to present with a better menstrual bleeding profile compared with rivaroxaban- or edoxaban-treated women. However, randomized prospective studies comparing the risk of HMB caused by different anticoagulants are missing and the available data derived from randomized studies so far are not very meaningful, as they are post hoc analyses.

The estimation of AUB/HMB during treatment with OACs depending on these retrospective and prospective single-

Table 2 Analyses and post hoc analyses of the multicenter, randomized, double-blind trials comparing DOAC with warfarin, NMH, or acetylsalicylic acid in patients with symptomatic VTE

Study/indication of anticoagulation	Number of women on medication ^a	Age (y)	Number of women on contraception before and after starting oral anticoagulation	Definition of HMB	AUB/HMB or CRNNB	Assessment of menstrual history, anemia, or gynecologic disorders
Martinelli et al, 2016 ¹⁰ Post hoc analysis of the Einstein DVT and PE trials Medication: rivaroxaban or warfarin	Rivaroxaban n = 925 vs. Warfarin n = 963	<60 Mean age: 41	705 had hormonal therapy before randomization and 305 of them stopped hormonal therapy after start of anticoagulation. 400 of 705 continued or restarted contraception therapy ^b .	AUB	Uterine bleeding leading to transfusion occurred in 19/925 women on rivaroxaban versus 3/963 patients treated with VKA	101 women in total had gynecologic disorders. 9 of 22 women with AUB had uterine fibrinoids or adenomyosis.
Agnelli et al, 2020 ¹¹ Post hoc analysis of the Caravaggio trial. Apixaban for the treatment of VTE associated with cancer Medication: apixaban or dalteparin	Apixaban n = 293 vs. Dalteparin n = 309	Mean age: 67	NA	CRNMB MB	Vaginal bleeding occurred in 4/293 (1.4%) women on apixaban and 3/309 (1.0%) on dalteparin	NA
Huisman et al, 2018 ¹² Post hoc analysis of the RE-MEDY and RE-COVER VTE trials Medication: dabigatran or warfarin	Dabigatran n = 643 vs. Warfarin n = 635	18–50 Mean age: 37	NA	AUB MB CRNMB	Women on dabigatran had a 41% lower risk of AUB compared with women on warfarin. The rate of AUB was 5.9% on dabigatran and 9.6% for women treated with warfarin.	NA
Scheres et al, 2018 ¹³ Post hoc analysis of the Hokusai-VTE study Medication: edoxaban or warfarin	Edoxaban n = 61 vs. Warfarin n = 40	<50 Mean age: 42	20/61 on edoxaban and 13/40 on warfarin used hormonal contraceptives at the moment of randomization. After randomization none of the women who experienced major AUB received hormonal treatment.	FIGO criteria Major AUB CRNMB	Major AUB 8/61 (13%) women on edoxaban and 3/40 (7.5%) women on warfarin	2 women on edoxaban had uterine myoma. 2 women on warfarin received hysterectomy and one woman had endometrial ablation.
Boonyawat et al, 2021 ¹⁹ EINSTEIN CHOICE trial HMB on women on anti-coagulant treatment for	Rivaroxaban 20 mg n = 134 vs. Rivaroxaban 10 mg ^c	32–45	9/134 (6.7%) women with HMB on rivaroxaban 20 mg, 9/120 (7.5%) of women with HMB on	HMB	Menstrual duration increased in: 12–18% on rivaroxaban 20 mg	History of HMB and NSAID use was assessed. Gynecological disorders: 3/134 on rivaroxaban 20

(Continued)

Table 2 (Continued)

Study/indication of anticoagulation	Number of women on medication ^a	Age (y)	Number of women on contraception before and after starting oral anticoagulation	Definition of HMB	AUB/HMB or CRNMB	Assessment of menstrual history, anemia, or gynecologic disorders
VTE: comparison of high-dose and low-dose rivaroxaban with aspirin. Medication: rivaroxaban or ASS	n = 120 vs. ASS 100 mg ^c n = 108		rivaroxaban 10 mg, and 8/108 (7.4%) of women with HMB on ASS changed their hormonal therapy.		6–12% on rivaroxaban 10 mg 9–12% on ASS 100 mg Menstrual intensity increased in: 14–21% on rivaroxaban 10 mg 19–24% on rivaroxaban 20 mg 13–20% of women on ASS 100 mg	mg 5/120 on rivaroxaban 10 mg 7/108 on ASS 100 mg
Brekelmans et al, 2017 ²¹ AMPLIFY study Abnormal vaginal bleeding in Women with VTE Medication: apixaban or warfarin	Apixaban n = 1,122 Warfarin n = 1,106	Mean age: 44–46	Before: 5/1122 (18%) and 4/1106 (17%) used hormones After: NA	Major bleeding CRNM vaginal bleeding	Major vaginal bleeding occurred in 1/1,122 (<0.1%) of apixaban-treated patients and none of warfarin treated patients. CRNM vaginal bleeding occurred in 28 out of 1,125 (2.5%) women on apixaban and in 24 out of 1,106 (2.1%) women on warfarin.	Baseline characteristics such as anemia and gynecological disorders and menopausal state were assessed. In one patient with major vaginal bleeding and uterine fibroids, a hysterectomy was performed.

Abbreviations: AUB, abnormal uterine bleeding; COC, combined oral contraceptives; CRNMB, clinically relevant nonmajor bleeding; HMB, heavy menstrual bleeding; LMWH, low-molecular-weight heparin; MB, major bleeding; n, number; NA, not assessed; PBAC, pictorial blood loss assessment; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

^aDOACs were used in therapeutic doses; under VKA treatment INR within therapeutic range.

^b1,183 had no hormonal therapy before randomization and 75 of 1,183 women started therapy after randomization.

^cOnce daily.

center registries and post-hoc analyses is difficult. Studies such as the SELECT-D trial, the Caravaggio trial, the EIN-STEIN-, and AMPLIFY-studies included pre- and postmenopausal women. In most of these studies, the number of premenopausal women was low, explaining the lower uterine bleeding rates compared with the results of the retrospective and prospective cohort studies focusing on menstrual bleeding. For these reasons, safety endpoints such as MB and CRNMB may not reflect HMB sufficiently.

Additionally, it was not always assessed if women had a history of HMB or AUB prior to the start of oral anticoagulation. In most of these publications, there is also lack of information about the use of hormonal contraceptives and other methods of contraception before and after initiation of anticoagulation, which can influence the severity of menstrual bleeding.

Future Studies to Determine AUB during Treatment with DOAC

The RAMBLE study (NCT02761044)²⁴ is a randomized open-label interventional study aiming to compare AUB in women treated with apixaban or rivaroxaban. Enrollment has started and results are expected in 2026.

The MEDEA study is a randomized open-label trial²⁵ initiated in women with HMB while on factor Xa inhibitor treatment. This study is based on the previous observations that patients under dabigatran had less HMB in comparison to warfarin.¹² Women with HMB under factor Xa inhibitor are randomized either to continue the factor Xa inhibitor, to switch to dabigatran, or to continue with the factor Xa inhibitor with the addition of tranexamic acid.

An international, multicenter, academically sponsored, observational study (NCT04748393) that focused on fertile female patients with proven symptomatic VTE and the incidence and severity of abnormal menstrual bleeding was terminated in February 2021 due to low enrolment. Results have not been published so far.

Rationale and Design of the HEMBLEMED-Registry (HEavy Menstrual BLEEDing in Patients on Direct Oral Anticoagulants, NCT04477837)

The HEMBLEMED-Registry is an ongoing multicenter German registry aiming to compare the incidence of HMB in women of reproductive age (18–50 years) treated with different DOACs because of different types of venous thrombosis including lower extremity-DVT, pulmonary embolism, upper extremity vein thrombosis, or sinus vein thrombosis. This is a prospective noninterventional investigator-initiated registry which includes consecutive female patients who are treated as standard of care. The decision of which DOAC will be given is made before the subject will enter the trial. Patients will be included consecutively without randomization. The dosage of the anticoagulant (DOACs) will be chosen by the treating physicians according to the most recent European Medicines Agency-approved drug information. Subjects are included after the initiation phase when they are treated with therapeutic dosage of 20 mg rivaroxaban once daily, 60 mg edoxaban once daily, 5 mg apixaban twice

daily, or 150 mg dabigatran twice daily. Patients treated with 15 mg rivaroxaban twice daily (first 3 weeks after diagnosis of venous thrombosis) or treated with 10 mg apixaban twice daily (first week after diagnosis of venous thrombosis) are excluded. Furthermore, patients under treatment with 30 mg edoxaban once daily, or 10 mg or 15 mg rivaroxaban once daily, or 2.5 mg apixaban twice daily are also excluded. Subjects have to be on DOAC treatment for at least 7 days and have to stay on the treatment for at least 4 months.

A vaginal ultrasound which is routinely performed when menstrual bleeding is enhanced is offered to the patients to check for the presence of uterine fibroids, endometrial polyps, and/or adenomyosis.

The study includes routine blood draw at baseline and at 4 months after inclusion. Three consecutive menstrual bleeding cycles will be prospectively documented by the participating patients at home using a modified PBAC score (see ▶Fig. 1). One baseline data reporting and one follow-up reporting after 4 months are planned in the participating coagulation centers.

The primary aim is the comparison of the frequency of HMB in female patients of reproductive age anticoagulated with DOACs who do not use hormonal contraceptives or intrauterine devices because these measures influence the intensity and duration of menstrual bleeding.

Secondary aims are the prevalence of von Willebrand disease in young anticoagulated female patients and correlation of HMB with age, ISTH-BAT score at inclusion, blood group, underlying uterine pathologies, i.e., presence of uterine fibroids, endometrial polyps, and/or adenomyosis, occurrence of iron deficiency, hemoglobin level, and intermittent use of non-steroidal anti-inflammatory drugs (NSAID).

Enrolment has started and first results are expected in 2024.

Therapeutic Approaches to Treat AUB and HMB in Women under Oral Anticoagulation

Common therapeutic approaches of HMB are based upon the use of hormonal contraception such as estrogen-containing (COC) or progestin-only contraceptives (POC). COCs are the most frequently prescribed medications in women with HMB without a personal or family history of thrombosis. However, the use of estrogen-containing contraceptives, especially those containing 30 to 35 mg of estrogen in combination with drospirenon, gestoden, or desogestrel can increase the thrombosis risk up to sevenfold.²⁶

Therefore, when COCs are used, use of <35 mg ethinylestradiol and a lower risk progestogen such as levonorgestrel or norethisterone should be preferred. Estrogen-containing oral contraceptives can be used while receiving anticoagulants as an increase in thrombosis has not been observed with simultaneous anticoagulation¹⁰; however, their use should be avoided in patients with severe thrombophilia. Estrogen-containing pills should be discontinued approximately 6 weeks prior to cessation of the anticoagulation in women having experienced at least one thrombotic episode.²⁷

Progestin-only pills can also be used with reports of success in reducing HMB.²⁸ POCs have the advantage that

they can be continued after stop of anticoagulation due to their lower venous thrombotic risk.

The use of levonorgestrel-based intrauterine systems (LNG-IUS) is another recommended approach which does not increase the thrombotic risk²⁶ and therefore can be used in patients with thrombophilia or a history of thrombosis as well as during and after cessation of the anticoagulant treatment. These devices can reduce HMB by 50% and can effectively help treating HMB and dysmenorrhea associated with underlying conditions such as endometriosis.^{29,30}

Antifibrinolytic agents such as oral tranexamic acid may be used in the first days of menstrual bleeding. As this medication inhibits the lysis of fibrin, it might increase the rate of VTE.³¹ An increase of arterial thrombosis has not been observed. It should therefore only be used in the acute management of HMB.

In women with inherited bleeding disorders such as von Willebrand disease or platelet disorders, the use of nasal desmopressin might also be considered. However, the use should be limited to the first 2 to 3 days. Its use beyond 5 days is not recommended due to tachyphylaxis.

A dose interruption of the DOAC for the first 2 days might be considered in women who do not receive combined oral contraceptives and who require prolonged anticoagulation after 3 to 6 months of initial therapy. Estimation of the thrombotic risk however is strongly recommended because patients with HMB who discontinue DOAC may develop recurrent venous thrombosis.¹⁵ When additional factors such as adiposity, active cancer, severe thrombophilia, or antiphospholipid syndrome are present, this option is not suitable.

Finally, switching to a DOAC with a better profile regarding menstrual bleeding such as dabigatran or apixaban may be considered.

In patients with a long-term indication for oral anticoagulation, dose reduction to prophylactic dose anticoagulation might be considered after 6 months of initial anticoagulation and a switch to a DOAC which is licensed for prolonged anticoagulation at a lower dose (apixaban 2.5 mg twice daily or rivaroxaban 10 mg once daily) should be discussed with the patient.

Women who have an indication for anticoagulation with VKA (e.g., antiphospholipid syndrome, recurrent thrombosis while on DOAC, mechanical heart valve) and who perform international normalized ratio (INR) self-measurements can try to keep the INR on the lowest therapeutic range while having their menses or switch to a VKA with a shorter half-life like warfarin.

Rarely procedure-based interventions such as endometrial ablation, myoma removal, or hysterectomy may be necessary if the above-mentioned treatment options are not successful.

Clinical Case Continuation and Comments

Oral iron supplementation was begun. We suggested changing to apixaban 5 mg twice daily as we have observed a less HMB when switching from rivaroxaban to apixaban. After

switching to apixaban, the menstrual bleeding on her following cycle was slightly improved in comparison to the first two cycles under rivaroxaban 15 mg twice daily and 20 mg once daily but remained increased. We prescribed tranexamic acid 500 mg three times daily and advised the patient to check out for gynecological abnormalities and to discuss with her gynecologist the use of a gestagen-only pill or the implantation of a gestagen-releasing IUD.

A levonorgestrel-releasing IUD was inserted which stopped the menstrual bleeding. The gynecological examination and intravaginal ultrasound revealed no abnormalities. As no severe thrombophilia and no concomitant risk factors were present, apixaban was discontinued after 6 months.

Conclusions

In conclusion data on frequency and severity of HMB in anticoagulated women are sparse. Prospective studies in anticoagulated female patients which focus on menstrual bleeding and take the DOAC doses, the premenopausal and postmenopausal status as well as the numerous aspects of the multifactorial development of HMB into account are therefore urgently needed. In addition, uniform international bleeding definitions to better characterize AUB and HMB should be established by the international societies and should be included in future regulatory studies on new OACs when major or minor bleeding is assessed.

Conflicts of Interest

Lida Kalmanti declares no conflicts of interest.

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