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.

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.
Introduction

Abnormal uterine bleeding (AUB) encompasses HMB, postmenopausal 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 al\(^3\) (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

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**Hygiene products:** Type of pads or tampons

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

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>1</td>
</tr>
<tr>
<td>Type 2</td>
<td>5</td>
</tr>
<tr>
<td>Type 3</td>
<td>10</td>
</tr>
</tbody>
</table>

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: [ ]

<table>
<thead>
<tr>
<th>Day 1 of menstruation</th>
<th>DD/MM/YY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tampons</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Clot soaked</td>
<td></td>
</tr>
</tbody>
</table>

**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:**

1. Multiply the number of dashes by the respective factor.
2. Every fully soaked tampon or pad is scored an additional 5 points; for a ‘Clot’ with a length of 2.5 cm 5 additional points should be added for a ‘Clot’ smaller than 2.5 cm one additional point should be added.
3. Add both sums to get the score. If the score is above 100 further assessment is recommended.

**Score:**

(sum tampons + sum pads)

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*Fig. 1* Modified PBAC score to evaluate menstrual bleeding. PBAC, pictorial blood loss assessment chart.
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 fibroids. 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 al13 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 thrombosis10–13 and some single-center analyses (see Table 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 VKA. 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 out of 96 women (25%) on rivaroxaban and in 4 out 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>
<thead>
<tr>
<th>Study and indication of anticoagulation</th>
<th>Number of women on medication</th>
<th>Age (y), range</th>
<th>Assessment of hormonal contraception before and after starting oral anticoagulation</th>
<th>Definition of HMB</th>
<th>AUB/HMB or CRNMB</th>
<th>Assessment of menstrual history, anemia, or gynecologic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huq et al, 2011*</td>
<td>Warfarin n = 53</td>
<td>14–55 Mean age: 36</td>
<td>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.</td>
<td>According to the PBAC score, duration of menstruation</td>
<td>50% of women had an increase of duration of menstruation. 66% had a PBAC score &gt; 100. 9/53 women had anemia prior to and 18/53 women presented with anemia after start of anticoagulation</td>
<td>Menstrual pattern and presence of anemia before OACs were assessed</td>
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<td>Själander et al, 2007^</td>
<td>Warfarin n = 90</td>
<td>15–49</td>
<td>Before: 69/90 had taken oral contraceptives at any time before the anticoagulation, of which 16 due to menorrhagia After: NA</td>
<td>Menorrhagia</td>
<td>44% had menorrhagia before warfarin and 70.8% while treated with warfarin</td>
<td>NA</td>
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<td>De Crem et al, 2015^</td>
<td>Rivaroxaban n = 52^</td>
<td>23–49</td>
<td>Before 63% of women on rivaroxaban and 85% of women on VKA received estrogen therapy when the VTE was diagnosed. After beginning OAC: 23% on rivaroxaban and 7.7% on VKA changed contraceptive method</td>
<td>AUB was defined according to the FIGO criteria^c</td>
<td>73% had AUB on rivaroxaban and 67% had AUB on VKA. During treatment with rivaroxaban a significant prolongation of the menstrual bleeding was observed</td>
<td>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</td>
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<td>Ferreira et al, 2016^</td>
<td>Rivaroxaban n = 128</td>
<td>16–55 Mean age: 37.8</td>
<td>NA</td>
<td>HMB</td>
<td>HMB in 26/128 women (20%) 1 episode of MB</td>
<td>NA</td>
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<tr>
<td>Beyer-Westendorf et al, 2016^</td>
<td>All women n = 178</td>
<td>27–48</td>
<td>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</td>
<td>Vaginal bleeding complications and HMB (prolongation or increased intensity). Bleeding intensity was assessed according to the ISTH definition</td>
<td>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</td>
<td>Bleeding history and NSAID use were assessed. Eight (14%) events required interventional treatment. Nine patients (6 on rivaroxaban, 1 on...</td>
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<tr>
<td>Study and indication of anticoagulation</td>
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<td>Myers et al, 201717</td>
<td>Rivaroxaban n = 96 Apixaban n = 43</td>
<td>18–53 for rivaroxaban 14–53 for apixaban Mean age: 40</td>
<td>and after the event, the rest received none.</td>
<td>HMB</td>
<td>HMB in 24 of 96 women (25%) on rivaroxaban HMB in 4 of 43 women (9.3%) on apixaban</td>
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<td></td>
<td>Rivaroxaban n = 76 VKA n = 45</td>
<td>18–55</td>
<td>NA</td>
<td>HMB</td>
<td>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.</td>
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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 IIII) 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. 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), 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 rivaroxaban (see Table 1).

In the AMPLIFY VTE treatment study, which compared apixaban treatment with VKA/enoxaparine 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/enoxaparine 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/enoxaparine. In total, 22 of 24 women under apixaban and 18 of 24 women under VKA/enoxaparine had premenopausal bleeding. Major vaginal bleeding occurred in none on warfarin and in 1 of 1,122 (0.1%) women on apixaban. 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 post-menopausal woman 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. However, the mean age of the patient population 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. Dabigatan-treated women had an approximately 41% lower risk of AUB in comparison to the warfarin-treated women. 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 al. and by Jacobson-Kelly and Samuel-Bannow 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.

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) (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 acetylic salicylic acid in patients with symptomatic VTE

<table>
<thead>
<tr>
<th>Study/indication of anticoagulation</th>
<th>Number of women on medication*</th>
<th>Age (y)</th>
<th>Number of women on contraception before and after starting oral anticoagulation</th>
<th>Definition of HMB</th>
<th>AUB/HMB or CRNNB</th>
<th>Assessment of menstrual history, anemia, or gynecologic disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinelli et al, 2016[10]</td>
<td>Rivaroxaban n = 925 vs. Warfarin n = 963</td>
<td>&lt;60 Mean age: 41</td>
<td>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[9].</td>
<td>AUB</td>
<td>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 fibroids or adenomyosis.</td>
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<tr>
<td>Agnelli et al, 2020[11]</td>
<td>Apixaban n = 293 vs. Dalteparin n = 309</td>
<td>Mean age: 67</td>
<td>NA</td>
<td>CRNMB MB</td>
<td>Vaginal bleeding occurred in 4/293 (1.4%) women on apixaban and 3/309 (1.0%) on dalteparin</td>
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<tr>
<td>Huisman et al, 2018[12]</td>
<td>Dabigatran n = 643 vs. Warfarin n = 635</td>
<td>18–50 Mean age: 37</td>
<td>NA</td>
<td>AUB MB CRNMB</td>
<td>Women on dabigatran had a 41% lower risk of AUB compared with women on warfarin. The rate of AUB was 5.9% for women treated with warfarin.</td>
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<tr>
<td>Scheres et al, 2018[13]</td>
<td>Edoxaban n = 61 vs. Warfarin n = 40</td>
<td>&lt;50 Mean age: 42</td>
<td>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.</td>
<td>FIGO criteria Major AUB CRNMB</td>
<td>Major AUB 8/61 (13%) women on edoxaban and 3/40 (7.5%) women on warfarin</td>
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<tr>
<td>Boonyawat et al, 2021[19]</td>
<td>Rivaroxaban 20 mg n = 134 vs. Rivaroxaban 10 mg</td>
<td>32–45</td>
<td>9/134 (6.7%) women with HMB on rivaroxaban 20 mg, 9/120 (7.5%) of women with HMB on rivaroxaban 10 mg</td>
<td>HMB</td>
<td>Menstrual duration increased in: 12–18% on rivaroxaban 20 mg</td>
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</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study/indication of anticoagulation</th>
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</tr>
</thead>
<tbody>
<tr>
<td>VTE: comparison of high-dose and low-dose rivaroxaban with aspirin.</td>
<td>rivaroxaban 10 mg, and 8/108 (7.4%) of women with HMB on ASS changed their hormonal therapy.</td>
<td>6–12% on rivaroxaban 10 mg 9–12% on ASS 100 mg</td>
<td>Menstrual intensity increased in: 14–21% on rivaroxaban 10 mg 19–24% on rivaroxaban 20 mg 13–20% of women on ASS 100 mg</td>
<td>rivaroxaban 10 mg and 8/108 (7.4%) of women with HMB on ASS changed their hormonal therapy.</td>
<td>5/120 on rivaroxaban 10 mg 7/108 on ASS 100 mg</td>
<td>Menstrual intensity increased in: 14–21% on rivaroxaban 10 mg 19–24% on rivaroxaban 20 mg 13–20% of women on ASS 100 mg</td>
</tr>
<tr>
<td>Brekelmans et al, 2017**</td>
<td>Apixaban n = 1,122 Warfarin n = 1,106</td>
<td>Mean age: 44–46</td>
<td>Before: 5/1122 (18%) and 4/1106 (17%) used hormones After: NA</td>
<td>Major bleeding CRNM vaginal bleeding</td>
<td>Major vaginal bleeding occurred in 1/1,122 (&lt;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.</td>
<td>Baseline characteristics such as anemia and gynecological disorders and menopausal state were assessed. In one patient with major vaginal bleeding and uterine fibrinoids, a hysterectomy was performed.</td>
</tr>
</tbody>
</table>

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 accessed; PBAC, pictorial blood loss assessment; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

*DOACs were used in therapeutic doses; under VKA treatment INR within therapeutic range.

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

*Once daily.
Bleeding Issues in Women Under Oral Anticoagulation

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center registries and post-hoc analyses is difficult. Studies such as the SELECT-D trial, the Caravaggio trial, the EINSTEIN-‡, 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) 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 trial 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. 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 enrollment. Results have not been published so far.

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

The HEMBLED-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, 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.

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 anticoagulation, 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.

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

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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.13 When additional factors such as adipsity, 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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