Management of Heavy Menstrual Bleeding for Patients on Anticoagulation

Thrombosis Canada
Thrombose Canada

Objective

To guide clinicians in the assessment and management of heavy menstrual bleeding in patients receiving anticoagulation therapy.

Background

Heavy menstrual bleeding (HMB), defined as excessive menstrual blood loss that interferes with an individual's physical, emotional, social, and material quality of life, is a distinct and often underrecognized complication of anticoagulation therapy in individuals who menstruate. Approximately one-third of menstruating individuals experience HMB during their reproductive years. Among those individuals who require anticoagulation for venous thromboembolism (VTE) or other indications, the rate of HMB increases up to 70%. Heavy menstrual bleeding can result in significant complications, including:

- Iron deficiency (with or without anemia)
- Need for medical or surgical interventions
- Hospitalizations
- Interruptions in anticoagulation therapy
- Increased risk of recurrent VTE
- Negative impact on multiple dimensions of an individual's quality of life

Given the high rates of anticoagulation-associated HMB and its consequences, it is essential that clinicians adopt a systematic approach to its assessment and management.

Evaluation For Heavy Menstrual Bleeding While Receiving Anticoagulation

When initiating anticoagulation therapy, a comprehensive assessment of the patient's menses should be conducted, including review of the following:

- **Menstrual history**: Past and current pattern of menstrual bleeding including cycle length and regularity, duration of menstrual bleeding, heaviness of flow, associated symptoms, and any previous or current treatments for menstruation-associated symptoms (e.g., hormonal contraception, tranexamic acid, anti-inflammatory medications).
- **Screening for HMB:** Helpful screening questions for HMB consist of the **"7-2-1"** signs of HMB: **periods lasting more than 7 days**, needing to **change menstrual product every 2 hours** or less and passing **clots larger than 1 inch**.
- **Contraception:** Methods used (if any) for prevention of pregnancy.

- **Iron deficiency**: Past or current history of iron deficiency with or without anemia. Common symptoms of iron deficiency include fatigue, shortness of breath, decreased exercise tolerance, inability to concentrate, headaches, hair loss and restless legs (see section on Iron Deficiency Anemia, below).
- **Medications**: Screen for medications that increase the risk of bleeding (e.g., antiplatelet therapies, non-steroidal anti-inflammatories, selective serotonin reuptake inhibitors, herbal supplements). Counsel on risks of bleeding and consider deprescribing when appropriate.

For patients who report other bleeding symptoms in addition to HMB, a standardized bleeding assessment tool such as the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT) can be done to better characterize the bleeding symptoms, and a workup for an underlying bleeding disorder should be considered. Another key component of the initial evaluation for patients who menstruate and require anticoagulation is assessing whether they are using hormonal therapies, either for contraception or to manage menstrual symptoms. Abrupt discontinuation of these therapies can lead to new or worsened HMB. Although there is an increased risk of VTE with certain hormonal therapies, specifically the combined hormonal contraceptive therapies (CHCs) and depot medroxyprogesterone acetate (DMPA), post hoc data from registry trials of apixaban and rivaroxaban suggest that CHCs and DMPA can be used safely in patients on therapeutic anticoagulation. Shared decision-making is essential when deciding whether to continue hormonal therapy during anticoagulation treatment (see section on Hormonal Therapies, below). All patients should be counselled around the potential changes in menstrual bleeding following the initiation of anticoagulation therapy. They should be encouraged to monitor for signs and symptoms of HMB and to report any concerns to their healthcare provider.

Follow Up for Patients with Heavy Menstrual Bleeding While Receiving Anticoagulation

A follow up assessment for HBM after one or two menstrual cycles on anticoagulation is recommended as anticoagulation-related HMB often starts within the first few menstrual cycles. Ongoing assessment for HMB should continue at every follow-up visit and, at a minimum, on an annual basis for patients receiving long-term anticoagulation. Periodic monitoring of complete blood count (CBC) and ferritin is recommended, and frequency should be guided by clinical context. Clinicians should also be aware that HMB can develop at any point during anticoagulation therapy, especially in adolescence or perimenopause, when ovulation and bleeding can be most irregular.

If anticoagulation is planned to be discontinued, CHC should be stopped at least four weeks in advance to account for the sustained elevated risk of thrombosis after discontinuation. Although the duration of increased thrombotic risk with DMPA is not well defined, it is similarly recommended to stop DMPA at least four weeks before discontinuing anticoagulation. If CHCs or DMPA are discontinued, prompt transition to an alternative progestin-based therapy should be considered. Conversely, if an individual chooses to continue a CHC or DMPA, anticoagulation should be continued at the full therapeutic dose as reduced-dose regimens (e.g., apixaban 2.5 mg oral twice daily or rivaroxaban 10 mg once daily) have not been studied in this specific clinical context.

Table 1. Evaluation, investigations and counselling around of heavy menstrual bleeding while on anticoagulation treatment

	Ask about	Check	Counsel
At diagnosis	Menstrual history History of HMB: "7, 2, 1" signs • **7 Days:** menses duration ≥ 7 days • **2 Hours:** changing menstrual product every ≤ 2 hours • **1 Inch:** Passing clots larger than 1 inch (size of a quarter) Contraception History of iron deficiency +/- anemia Evaluation for possible underlying bleeding disorder Medication review	CBC Ferritin Pregnancy test	Signs and symptoms of HMB and indications for urgent & emergent evaluation of HMB Options for safe and effective contraception **Remember:** **Combined hormonal contraceptives do not need to be stopped in individuals on therapeutic anticoagulation**
Follow up	Changes in menses Symptoms of iron deficiency +/- anemia	+/- CBC +/- Ferritin +/- Pregnancy test	Signs and symptoms of HMB Options for safe and effective contraception
Near end of treatment	Changes in menses Symptoms of iron deficiency +/- anemia	+/- CBC +/- Ferritin +/- Pregnancy test	Plan for stopping anticoagulation • CHC and DMPA therapies should be discontinued 1 month in advance • Offer effective, estrogen-free contraception

CBC, complete blood count; COC, combined hormonal contraceptive; DMPA, depot medroxyprogesterone acetate; HMB, heavy menstrual bleeding

Management of Heavy Menstrual Bleeding While Receiving Anticoagulation

Anticoagulation agent

Post hoc analyses from large registry trials of oral factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) and the direct thrombin inhibitor dabigatran have reported on HMB rates. Cross-trial comparisons are limited due to differences in the study populations (variations in age and menopause status). Furthermore, these registry trials likely underestimate the true incidence of HMB as the definitions used to capture major or clinically relevant non-major bleeding events do not adequately reflect the chronic and often less acute nature of HMB.

In their respective registry trials, apixaban and edoxaban showed similar relative risks of HMB compared to warfarin (**Table 2**). Dabigatran was the only DOAC associated with a lower risk of HMB; however, the incidence of HMB in the warfarin arms of the dabigatran trials was notably higher than in other thrombosis trial comparing DOAC to VKA (**Table 2)**.

Rivaroxaban was reported to have a two-fold increased risk of HMB compared to warfarin (**Table 2**). Observational studies looking specifically at oral anticoagulants and rates of HMB have also reported that HMB was most likely to occur with rivaroxaban compared to other DOACs or warfarin. Some experts avoid rivaroxaban in menstruating women for this reason.

Table 2. Incidence of heavy menstrual bleeding and relative risk by choice of anticoagulant

Oral anticoagulation agent	Incidence of uterine CRNMB/MB	HR/OR
Vitamin K antagonist (e.g. warfarin)	4.5% - 9.6%	Reference
Apixaban	5.4 %	1.26
Dabigatran	5.9%	**0.59***
Edoxaban	9.0%	1.26
Rivaroxaban	9.5%	**2.13***

CRNMB, clinically relevant non-major bleeding; HR, hazard ratio; MB, major bleeding; OR, odds ratio
*Statistically significant, $P < 0.01$.

The rates of HMB with unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are challenging to evaluate given that these agents are usually only used for a short duration in the treatment of VTE. While UFH and LMWH likely have an effect on menstrual bleeding, their shorter half-lives compared to DOAC, and available reversal agent make these anticoagulants appealing choices in high bleeding risk scenarios.

Hormonal therapies

Hormonal therapies are considered first-line treatment for managing HMB in individuals on anticoagulation. They are effective in reducing menstrual blood loss and can also alleviate other menstruation-related symptoms. Additionally, hormonal therapies provide contraception, which is important as: (1) oral anticoagulants are teratogenic and/or cross the placenta, and (2) pregnancy should be avoided in individuals with a recent history of venous thromboembolism (VTE) due to the elevated risk of recurrence.

Progesterone-only options include the levonorgestrel intrauterine device (LNG-IUD), etonogestrel subdermal implant and progesterone-only pill (POP) (**Table 3**). These progesterone-only hormonal therapies are not associated with increased risk of VTE, lead to a significant reduction in menstrual blood loss and are effective for contraception (**Table 3**). The LNG-IUD is often cited as the preferred option for the management of HMB while on anticoagulation as it can reduce median menstrual blood loss by 80% after 4 months and the rates of amenorrhea are 44% and 50% at 6 months and 1 year, respectively. The etonogestrel subdermal implant and POP are also effective at reducing menstrual blood loss but disadvantages of these options include breakthrough bleeding or spotting as well as at the need to take the POP at the same time every day to ensure optimal contraceptive efficacy. Depot medroxyprogesterone acetate is another a progesterone-only contraceptive option for the management of HMB and has one of the highest rates of amenorrhea. However, as mentioned earlier, it is associated with an increased risk of VTE. Therapeutic anticoagulation should be in place prior to starting DMPA in the context of recent or remote VTE and should be discontinued at least 1 month before anticoagulation is stopped (see section Follow Up for Patients with Heavy Menstrual Bleeding While Receiving Anticoagulation).

Combined hormonal contraceptives, which have both an estrogen and a progesterone component, are available as pills, patches or vaginal rings (**Table 3**). The advantage of CHCs is that they can be taken with or without scheduled interruptions, allowing for the possibility of inducing amenorrhea. As mentioned earlier,

CHCs are associated with increased risk of VTE, and so therapeutic anticoagulation should be in place prior to starting CHC in the context of recent or remote VTE and should be discontinued at least 4 weeks before if anticoagulation is stopped (see section Follow Up for Patients with Heavy Menstrual Bleeding While Receiving Anticoagulation).

Table 3. Hormonal therapy options for the management of anticoagulant-related heavy menstrual bleeding

	Hormone	Effectiveness for HMB	Contraception efficacy, %	VTE risk
Levonorgestrel intrauterine system	Progesterone	Reduction in MBL 80% after 4 months Amenorrhea in 44% at 6 months and 50% at 1 year	> 99	No
Subdermal implant	Progesterone	Amenorrhea in 20% May result in irregular spotting or bleeding	> 99	No
DMPA	Progesterone	Amenorrhea in up to 68%	> 99	Yes
Progesterone-only pill	Progesterone	Amenorrhea in 5-10% May result in irregular spotting or bleeding	90 (typical use) 99 (perfect use)	No
Combined hormonal contraceptive	Estrogen and progesterone	Variable – can induce amenorrhea with continuous use	90 (typical use) > 99 (perfect use)	Yes

Adapted from: Deloughery E and Bannow B. Hematology AM Soc Hematol Educ Program 2022;1:467-473.
DMPA, Depot medroxyprogesterone acetate; MBL, menstrual blood loss; VTE, venous thromboembolism

Antifibrinolytics

Antifibrinolytics such as tranexamic acid (TXA) are effective in reducing HMB. Studies in non-anticoagulated individuals have shown a 40–50% reduction in menstrual blood loss when TXA is taken three times daily during the heaviest days of the menstrual cycle. Clinicians are often hesitant to use TXA in patients on anticoagulation due to a perceived risk of inducing thrombosis. Randomized trials in high-risk populations, including postpartum, trauma, and perioperative settings, have not demonstrated an increased incidence of thrombotic events with TXA use. Although prospective studies evaluating TXA for the management of HMB in anticoagulated patients are lacking, thrombosis expert consensus support its temporary use in patients with HMB. Antifibrinolytics should generally be avoided at the beginning of VTE treatment, typically the first month, to allow for adequate fibrinolysis of the index thrombus.

Gynecology consultation

Individuals with a history of HMB or those who develop HMB while on anticoagulation may benefit from referral to a gynecologist to assess for underlying structural causes. This is particularly important in cases of abnormal uterine bleeding, a broader category that includes HMB, intermenstrual bleeding, post-coital bleeding, irregular cycles, and postmenopausal bleeding. In addition to hormonal therapies, gynecologists can offer procedural or surgical interventions, such as endometrial ablation, uterine artery embolization, or hysterectomy.

Modification of anticoagulation therapy

Modification of anticoagulation therapy, such as dose reduction or temporary stopping anticoagulation during menses, is not recommended in the acute VTE treatment period (first three to six months of treatment) as it increases the risk of VTE recurrence. There is also a paucity of data to support dose

modification or temporary interruption of anticoagulation for the management of HMB in patients on long-term anticoagulation.

As noted previously, rivaroxaban is associated with the highest rates of HMB, based on observational data and post hoc analyses. If HMB occurs while on rivaroxaban, switching to an agent with lower HMB rates, such as apixaban or dabigatran, should be considered.

Special considerations

Iron deficiency anemia

Iron deficiency (ID) with or without anemia is common and often underrecognized issue in individuals who have HMB. Similarly to HMB, consequences of ID with or without anemia can significantly affect a patient's health and quality of life. All women who report symptoms of HMB or ID should have CBC and ferritin level assessed and treatment with oral or intravenous iron should be administered if there is iron deficiency with or without anemia.

Other Relevant Thrombosis Canada Clinical Guides

- Apixaban
- Dabigatran
- Deep Vein Thrombosis (DVT): Treatment
- DOACs: Management of Bleeding
- Edoxaban
- Pulmonary Embolism: Treatment
- Rivaroxaban
- Unfractionated Heparin and Low-Molecular-Weight Heparin
- Venous Thromboembolism: Duration of Treatment
- Warfarin

References

Abdulrehman J, et al. TRanEXamic acid to decrease Heavy Menstrual Bleeding in individuals anticoagulated for venous thromboembolism (T-REX HMB): Health care practitioner survey. Thromb Res. 2024;235:11-14.

Boonyawat K, et al. How I treat heavy menstrual bleeding associated with anticoagulants. Blood. 2017;130:2603-2609.

Brekelmans MPA, et al. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. Thromb Haemost. 2017;117:809-815.

Bryk AH, Piróg M, et al. Heavy menstrual bleeding in women treated with rivaroxaban and vitamin K antagonists and the risk of recurrent venous thromboembolism. Vascul Pharmacol. 2016;87:242-247.

Deloughery E, Samuelson Bannow B. Anticoagulant therapy for women: implications for menstruation, pregnancy, and lactation. Hematology AM Soc Hematol Educ Program 2022;1:467-473.

De Crem N, et al. Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. Thromb Res. 2015;136:749-753.

de Jong CMM, et al. Incidence and impact of anticoagulation-associated abnormal menstrual bleeding in women after venous thromboembolism. Blood. 2022;140:1764-1773.

Dhamangaonkar P, et al. Levonorgestrel intrauterine system (Mirena): An emerging tool for conservative treatment of abnormal uterine bleeding. J Midlife Health. 2015;6:26.

Godin R, et al. Abnormal uterine bleeding in women receiving direct oral anticoagulants for the treatment of venous thromboembolism. Vascul Pharmacol. 2017;93-95:1-5.

Hidalgo M, et al. Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. Contraception. 2002;65:129-132.

Hugon-Rodin J, et al. Longitudinal profile of estrogen-related thrombotic biomarkers after cessation of combined hormonal contraceptives. Blood. 2024;143:70-78.

Huisman M V, et al. Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute venous thromboembolism. J Thrombos Haemost. 2018;16:1775-1778.

Martinelli I, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood. 2016;127:1417-1425.

Relke N, et al. Tranexamic acid evidence and controversies: An illustrated review. Res Pract Thromb Haemost. 2021;5.

Samuelson Bannow BT. Management of abnormal uterine bleeding on anticoagulation: the patient–clinician perspective. J Thrombos Haemost. 2024;22:1819-1825.

Scheres LJJ, et al. 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. BJOG. 2018;125:1581-1589.

Tepper NK, et al. Progestin-only contraception and thromboembolism: A systematic review. Contraception. 2016;94:678-700.

Warner PE, et al. Menorrhagia I: Measured blood loss, clinical features, and outcome in women with heavy periods: A survey with follow-up data. Am J Obstet Gynecol. 2004;190:1216-1223.

Date of Version: 29May2025