How we treat heavy menstrual bleeding associated with anticoagulants

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Abstract

Anticoagulant-associated heavy menstrual bleeding (HMB) is an underrecognized but not uncommon problem in clinical practice. Premenopausal women should be advised of the potential effect of anticoagulant therapy on menstrual bleeding at the time of treatment initiation. Consequences of HMB should be assessed and treated on an ongoing basis. In the acute setting, the decision to withhold anticoagulants is based on an individual patient’s risk of thrombosis and the severity of the bleeding. For women who require long-term
anticoagulation, the use of levonorgestrel intrauterine system, tranexamic acid (during menstrual flow), high dose progestin-only therapy, and combined hormonal contraceptives are effective for controlling HMB; the risk of thrombosis during anticoagulant therapy with these treatments is not well studied, but is likely to be low. Selection of type of hormonal therapy is based on patient preference, other indications for and contraindications to therapy, as well as side effect profile and ongoing thrombotic risk factors. Women who do not respond to medical treatment or who do not wish to retain their fertility should be considered for surgical management.

Case vignette 1

A 22-year-old female with a history of recurrent unprovoked venous thromboembolism (VTE) presented to the Emergency Department with heavy menstrual bleeding (HMB) of 8 days duration. She had been started on rivaroxaban 20 mg orally per day some months prior because of poor INR control on warfarin. Since the initiation of rivaroxaban, she had experienced monthly heavy and prolonged menstrual bleeding, resulting in iron deficiency anemia and a requirement for iron infusions. To reduce HMB, her rivaroxaban was stopped for a few days during menses; during one of these interruptions she developed recurrent pulmonary embolism. Insertion of a levonorgestrel eluting intrauterine system (LNG-IUS) did not improve her HMB. An ultrasound revealed normal anatomy
and there was no personal or family history of bleeding. The patient reported her HMB had a significant negative effect on her quality of life.

**Case vignette 2**

A 44-year-old woman had a history of provoked deep vein thrombosis treated with 3 months of warfarin. Shortly after warfarin discontinuation, she developed recurrent unprovoked pulmonary embolism and was started on therapeutic doses of rivaroxaban. Coincident with initiating rivaroxaban, she reported HMB. She described passing blood clots associated with abdominal cramps. A pelvic ultrasound prior had revealed no structural abnormality. On one occasion, she required hospital admission and packed red blood cell transfusion due to symptomatic anemia.

**Introduction**

Physicians and patients share concerns about bleeding complications associated with anticoagulants; overall, direct oral anticoagulant (DOAC)-treated patients have a lower rate of life-threatening bleeding when compared with low-molecular-weight heparin (LMWH)/vitamin K antagonist (VKA)-treated patients.\(^1\) Despite this, there is an increasing focus on the role that DOACs may play in
causing abnormal uterine bleeding (aub), including hmb.2,3 since hmb is not usually life-threatening, is chronic in nature, and is not usually a separate pre-specified endpoint in clinical trials of anticoagulant therapy, it is underrecognized by physicians. there are limited data on hmb in anticoagulated women and, to our knowledge, no published or proposed practice guidelines for the management of anticoagulant-associated hmb.4 this is despite the major impact hmb has on quality of life, especially in women who require long-term anticoagulation. hmb is likely to be associated with both a need for direct treatment of its consequences and compromise of anticoagulant compliance, paradoxically increasing the risk of recurrent thromboembolism.5

**definition and brief discussion of etiology of hmb**

A normal menstrual cycle is defined in terms of frequency of 24 to 38 days (the regularity of which can vary between ± 2 to 20 days) with a duration of flow between 4.5 to 8 days and a volume of monthly blood loss between 5 to 80 ml per cycle.6 the term “menorrhagia” has been discarded and replaced by “heavy menstrual bleeding” by the international federation of gynecology and obstetrics (figo) classification, due to a lack of both specificity and standardization.7 hmb is defined as menstrual blood loss of more than 80 ml per cycle or clinically excessive menstrual blood loss that interferes with physical, social, emotional and/or material quality of life of a woman.8,9 aub is a broader term that includes
abnormal bleeding during a menstrual cycle (menstrual bleeding) or abnormal bleeding outside of a regular menstrual cycle (intermenstrual bleeding).

The FIGO has classified the causes of AUB into 9 categories. Abnormalities of the uterus causing AUB include polyps, adenomyosis, leiomyoma, and malignancy or hyperplasia. Other causes include coagulopathy, ovulatory dysfunction, endometrial dysfunction, iatrogenic etiologies, and those not yet classified. Anticoagulant therapy-associated AUB falls into the non-structural, coagulopathy category, which also includes other hemostatic disorders, such as von Willebrand disease, platelet function disorders, coagulation factor deficiencies, or defects of fibrinogen.

**Does anticoagulant use cause heavy menstrual bleeding?**

**Vitamin K antagonists**

HMB (with varying definitions) has been reported with VKA use. In observational studies, the incidence of HMB has ranged from 22-65% in women treated with VKA. A retrospective study reported an increase in HMB from 44% to 71% of patients before and after VKA treatment. VKA significantly increased the duration of menstruation flooding, passage of clots, and intermenstrual bleeding.
Direct oral anticoagulants

Cohort studies report that the incidence of HMB in women treated with rivaroxaban ranges from 20 to 27%.\textsuperscript{15-17} Again, the definition used for HMB varies between studies. A post-hoc analysis of a cohort from the EINSTEIN DVT-PE study found that AUB occurred more frequently in the rivaroxaban group compared with the LMWH/VKA group (Hazard ratio [HR] 2.13, 95% CI 1.57-2.89).\textsuperscript{18} In non-hormonally-treated women, the incidence density of AUB was 30.7%/year in those receiving rivaroxaban compared with 13.4%/year in warfarin-treated women. Prospective data from the EINSTEIN CHOICE study demonstrated a decrease in menstrual flow length and intensity with 10 mg of rivaroxaban compared with 20 mg of rivaroxaban.\textsuperscript{19} An observational study reported a high incidence of mucosal bleeding, especially uterine/ovarian bleeding, in women with VTE who were treated with rivaroxaban.\textsuperscript{20}

A cohort study reported that HMB occurred in 9.3% of apixaban treated women.\textsuperscript{17} In a cohort from the AMPLIFY study, clinical-relevant non-major vaginal bleeding occurred in 28/1122 (2.5%) of apixaban-treated and in 24/1106 (2.1%) of warfarin-treated women (odds ratio [OR] 1.2, 95% CI 0.67-2.0). However, although the absolute number of vaginal bleeding events was comparable between apixaban and enoxaparin/warfarin recipients, the relative occurrence of vaginal bleeds among all clinically relevant non-major bleeds was
higher in apixaban-treated women (OR 3.4, 95% CI 1.8-6.7). \textsuperscript{21} In the Hokusai study, vaginal bleeding occurred in 158 (9\%) patients treated with edoxaban, as compared to 126 (7.1\%) patients treated with enoxaparin/warfarin. \textsuperscript{22} A post-hoc analysis of a cohort of 1,280 women from the pooled RE-COVER I, II and RE-MEDY trials reported a significantly lower rate of AUB in women treated with LMWH/dabigatran compared with those treated with LMWH/warfarin (5.9\% vs. 9.6\%, OR 0.59, 95\% CI 0.39-0.90). \textsuperscript{23}

While DOACs have not been compared directly in clinical trials, data derived from a German DOAC registry demonstrated that the frequency of vaginal bleeding (both cycle related and non-cycle related bleeding) was comparable for all factor Xa inhibitors (50/156 (32\%) with rivaroxaban, 5/18 (28\%) with apixaban and 1/4 (25\%) with edoxaban). \textsuperscript{24}

**Unfractionated Heparin/ Low-molecular-weight heparin**

In theory, unfractionated heparin (UFH)/LMWH should have a similar effect on menstrual bleeding as other anticoagulants. However, no study has reported or specifically investigated the effect of UFH/LMWH on menstrual bleeding. The effect of UFH/LMWH on bleeding will be difficult to evaluate since most UFH/LMWH is used for a short duration and/or at a prophylactic dose. In addition, many patients who receive extended therapeutic doses of UFH/LMWH (such as
those with cancer-associated thrombosis or who are pregnant), are not representative of women with regular menstruation.

In summary, HMB associated with anticoagulant use is common. Current evidence suggests the direct factor Xa inhibitors may be associated with a higher risk of this complication than warfarin therapy, while the risk may be lower with dabigatran. More data are needed to confirm this hypothesis.

How to assess heavy menstrual bleeding in clinical and research settings

In the clinical setting, women treated with oral anticoagulants usually do not spontaneously report their change in menstrual bleeding pattern since they initiated or modified their anticoagulant treatment. Hence, HMB is likely underrecognized by physicians. Discussing the potential effect of anticoagulant treatment on menstrual bleeding at the time of anticoagulant initiation will raise patient awareness of the potential for HMB.

Menstrual bleeding history in reproductive age women who are treated with anticoagulants should be specifically sought. A requirement of changing sanitary pad or tampon more often than hourly, clots at least 1 inch in diameter, or a low ferritin level are clinical predictors for HMB. An inherited bleeding disorder should be suspected when patients have long-standing HMB or HMB since their menarche. Suspicion of a bleeding disorder based on clinical or family history
should trigger further evaluations. Women who report increased bleeding should be assessed for its severity, consequences and the impact it has on their quality of life. A complete blood count, serum ferritin, INR in women receiving VKA, serum creatinine in those receiving DOACs, and pregnancy testing should be performed. Other concomitant drugs that could potentiate bleeding should be reviewed. Referral to a gynecologist should be considered to exclude other causes of AUB.

In the research setting, the severity of menstrual bleeding can be assessed using quantitative or qualitative methods. The volume of menstrual blood loss can be measured by using the alkaline hematin method but its complexity has precluded widespread use. The pictorial blood assessment chart (PBAC) is a semi-objective measurement tool that has been validated in the diagnosis of HMB and in the assessment of response to HMB-related treatments. However, its sensitivity and specificity vary widely. For a qualitative assessment, several menstrual bleeding-specific questionnaires that incorporate quality of life assessment have been employed. However, a standardized and validated questionnaire is needed to attenuate variability in outcomes and to increase generalizability.

Management of anticoagulant-associated HMB

Outpatient management
As outlined in Figure 1, patients with iron depletion should receive iron therapy, along with specific HMB-related treatments. Although gynecologists usually initiate specific HMB-related treatments, hematologists are frequently asked to provide an opinion regarding thrombotic risk and anticoagulant management. Likewise, hematologists may be asked to advise on the management of iron deficiency anemia if that has occurred as a complication of the HMB. HMB-related therapies in anticoagulated patients include 1) hormonal therapy, 2) tranexamic acid, 3) anticoagulant management, and 4) surgical interventions.

1) **Hormonal therapy**

   **Combined hormonal contraceptives (CHCs)**

   Although not studied in anticoagulated women, the use of cyclical combined oral contraceptives (COCs) significantly decreases menstrual blood loss and increases hemoglobin levels in women with HMB.³²-³⁴ Combined contraceptive patches or vaginal rings have not been specifically studied in women with HMB.

   Major side effects of COCs include breakthrough bleeding, nausea, headache, and abdominal bloating. The most commonly reported side effect with extended or continuous COC is breakthrough vaginal bleeding.

   **Progestin-only contraceptives**
The progestin-only pill containing low-dose progestin is an effective contraceptive but has not been studied for the management of HMB. A meta-analysis concluded that the use of short-course cyclic high-dose progestin (Norethisterone or norethindrone 5 mg given 2-3 times/day for 7-11 days) for HMB treatment was less effective than tranexamic acid, danazol and the progesterone-releasing intrauterine system. An extended regimen of high-dose progestin (Norethisterone 5 mg given 3 times/day for 21 days) seems to be effective in reducing menstrual blood loss in women with AUB, though it has not been evaluated in anticoagulated women.

Depot medroxyprogesterone acetate (DMPA), an injectable progestin, provides effective contraception and has been used for the management of HMB. A study reported that amenorrhea occurred in 50% of normal menstruating women during the first year of administration. Short-term treatment with DMPA also reduces menstrual blood loss in perimenopausal women with HMB.

Major side effects of progestin-only contraceptives are irregular spotting and breakthrough bleeding. Other common side effects of DMPA are weight gain, greasy skin and hair, acne and abdominal bloating.

Levonorgestrel Intrauterine system (LNG-IUS)

The efficacy of LNG-IUS in reducing HMB has been evaluated in patients treated with VKA and in patients with bleeding disorders. Observational studies
have shown a reduction in the amount and duration of menstrual bleeding with LNG-IUS. To date, however, only one randomized trial has been published. That study enrolled 40 women with HMB receiving VKA after cardiac valve replacement. Patients were randomized to LNG-IUS or to a “no treatment” group. In the LNG-IUS group, there was a significant decrease in the PBAC bleeding score and the number of bleeding days per cycle at 3 and 6 months, compared with baseline pre-insertion, while no change was noted in the control group. The mean of hemoglobin and ferritin levels were significantly increased at 3 months but not at 6 months in those randomized to LNG-IUS.

LNG-IUS may increase pelvic pain and breast tenderness. Breakthrough bleeding often occurs in the first 3 to 6 months. Other serious but rare complications of LNG-IUS include pelvic infection, device expulsion, and uterine perforation.

Risk of VTE in users of hormonal therapy during anticoagulant treatment

Anticoagulants reduce the risk of recurrent thromboembolic events and recent evidence suggests that the effect of therapeutic dose anticoagulants is sufficient to overcome the incremental prothrombotic risk associated with hormonal contraceptives. In a post-hoc analysis of the EINSTEIN-DVT and PE study, women on hormonal therapy (CHCs and progestin-only contraceptives)
during the anticoagulant period had a comparable risk of recurrent VTE as women not using hormonal therapy (adjusted HR 0.56, 95% CI 0.23-1.39).\textsuperscript{18}

The results of this study have challenged the World Health Organization Guideline for CHCs that states that established VTE on anticoagulant therapy is a condition that represents an unacceptable health risk for CHCs when used for contraceptive purposes.\textsuperscript{45} The results do, however, support the guideline of the International Society on Thrombosis and Hemostasis that suggests that hormonal therapy can be continued in selected patients after initiation of anticoagulants.\textsuperscript{46}

Taken together, these observations suggest that informed patients may choose to continue CHCs or progestin-only therapy while receiving therapeutic dose anticoagulants or while in a process of transitioning to other hormonal therapies. This treatment will both provide effective contraception and will reduce the risk of new or recurrent HMB. In addition, by suppressing ovulation, CHCs, DMPA, and possibly progestin-only pills, can reduce the risk of ovarian hemorrhage.\textsuperscript{47} It is important to note that adequate anticoagulant therapy is required in order to safely use CHCs and progestin-only therapies associated with an increased risk of VTE. These agents should be discontinued before anticoagulants are stopped.

\textbf{Risk of VTE in users of hormonal therapy without anticoagulant treatment}
Since data in women treated with anticoagulants are limited, data from the non-anticoagulated general population can help inform management decisions by providing information on potential venous thromboembolic risks with hormonal therapy, as well as the safety of reduced intensity anticoagulation or withdrawal of anticoagulant therapy while continuing hormonal therapy in women with serious bleeding. When compared with a non-user group, patients receiving COCs in the general population have about a four-fold increase in their risk of VTE.48 The combined contraceptive patch and vaginal ring also increase the risk of VTE.49 Estrogen dose and subtype of progesterone play a major role in thrombotic risk with COCs.50,51 The use of low-dose progestin-only pills for contraceptive purposes is not associated with an increased risk of VTE.52 However, the risk of VTE is increased by about five-fold with progestin use for therapeutic indications 53,54, and by about two-fold with DMPA.52,55 LNG-IUS is effective for HMB treatment in anticoagulated women and does not appear to increase the risk of thrombosis when used in women without prior thrombosis.49,56

2) Tranexamic acid

Tranexamic acid, an antifibrinolytic agent, is effective in the treatment of HMB in non-anticoagulated women.57 However, a post-marketing report suggests that it increases the risk of thromboembolic events. The product monograph
indicates that tranexamic acid is contraindicated in patients with active VTE or with a history of VTE.

Despite a label warning by the FDA, the association of tranexamic acid and thrombotic risk in patients with VTE has not been definitively confirmed. The use of tranexamic acid was not associated with an increased risk for VTE in one case-control study (OR 0.55, 95% CI 0.31-0.97). A nested case-control study in women with HMB did not demonstrate a statistically significant association between tranexamic acid use and the risk of VTE (adjusted OR 3.2, 95% CI 0.65-15.78). It is worth noting that tranexamic acid use for bleeding associated with severe trauma and general or obstetrical surgery does not appear to significantly increase the risk of thrombosis.

Therefore, current evidence does not support the hypothesis that tranexamic acid is associated with an unacceptable risk of thrombosis in anticoagulated women. How tranexamic acid interacts with hormonal therapies used to treat HMB is unknown.

3) Anticoagulant management

Modification of anticoagulant treatment in the setting of HMB has become more common with the widespread use of DOACs. With warfarin, dose reduction or temporary interruption is not practical. However, DOACs can be transiently
withheld due to their short half-life and rapid return to therapeutic levels once resumed. Dose reduction and temporary interruption of rivaroxaban have been reported in observational studies. As noted above, recent evidence suggests that a 10 mg dose of rivaroxaban decreased menstrual bleeding without an increased risk of thrombosis when compared with a 20 mg rivaroxaban dose. The effectiveness of a lower-dose DOAC for prevention of recurrent thrombosis in patients who have received at least six months of therapy has been demonstrated with apixaban and rivaroxaban. One observational study reported successful HMB management by switching from rivaroxaban to apixaban in 5 of 7 (70%) women. In our practice, we do not temporarily discontinue or reduce the dose of rivaroxaban during the active treatment period (usually within three months of acute VTE). In women with HMB who are beyond three months from their acute VTE, we advise some patients taking rivaroxaban to reduce their dose to 10 mg during their menstrual period. Use of dabigatran for long term secondary prevention of VTE is also reasonable. Use of “usual doses” of apixaban might be an alternative option based on limited evidence. Low dose apixaban (2.5 mg given twice daily) probably attenuates HMB similarly with low dose rivaroxaban but evidence supporting this recommendation is lacking. However, it is important to note that in patients who require extended anticoagulant treatment, there is no evidence to support the use of low-dose rivaroxaban (10 mg orally daily) or low dose apixaban (2.5 mg orally bid) in combination with estrogen-containing...
hormonal therapy, DMPA or tranexamic acid for the treatment of HMB. Whether the reduced dose DOACs provide sufficient anticoagulant effect to overcome the prothrombotic risk of these therapies remains unknown. At this time, avoiding this combination of treatments seems reasonable.

4) Surgical treatment

Endometrial ablation has been widely used in healthy women with HMB who are refractory to hormonal therapy and do not wish to preserve their fertility. Small studies have demonstrated that hysteroscopic endometrial ablation to avoid hysterectomy in anticoagulated women resulted in a reduction in menstrual bleeding (or amenorrhea) in 80% of the women.66,67

Uterine artery embolization is another option for HMB associated with a fibroid or myoma. Though fertility may be preserved, amenorrhea has been reported in 1-7% following this intervention.68

Emergent management
In acute bleeding settings, should a patient discontinue anticoagulant therapy or should a reversal agent be used? Would a reversal agent increase the thrombotic risk? The answers to those questions are based on an individual patient’s risk profile. In patients with hemodynamic instability from bleeding, the anticoagulant should be withheld and a reversal agent considered. Other surgical interventions that might be considered in consultation with a gynecologist include intrauterine balloon tamponade, endometrial ablation, uterine artery embolization, and hysterectomy.\textsuperscript{69-71} Patients with a recent history of thrombosis (< 1 month) may be at a higher risk of recurrent thrombosis and, thus, attempts should be made to maintain some form of anticoagulation. In the latter situation, LMWH at intermediate or prophylactic doses might be considered, although this strategy has not been shown to be safe or effective in this situation. In patients judged to be at moderate to high long-term risk of recurrent thrombosis, reinstitution of anticoagulant therapy should be strongly considered as soon as bleeding is controlled.

Another common question from gynecologists is “Can a specific-HMB-related hormonal therapy be used to control the bleeding, and if so, what kinds of HMB-related hormonal therapy can be used with minimal impact on the risk of thrombosis?” In most patients with acute HMB, specific hormonal therapy including high dose intravenous or oral estrogen, high dose progestin or combined
oral contraceptives, is usually needed along with anticoagulant management in order to control bleeding. To our knowledge, no study has reported the risk of thrombosis with HMB-related hormonal therapy used to suppress menstrual bleeding in the acute setting. However, high dose estrogen therapy is likely to be associated with an increased risk of thrombosis.

Although it has not been specifically studied in acute HMB setting, we would consider tranexamic acid in patients with remote VTE event (>3 months) because their risk of recurrence is lower than those with recent history of VTE. Tranexamic acid is given in a single dose and bleeding is reassessed. With persistent bleeding, it can be repeated as required at 6 to 8 hour intervals. The recommended intravenous dose is 10 mg/kg/dose. The dosage should be adjusted according to the patient’s creatinine clearance.

Other medical therapies that might be considered in the acute setting include epsilon aminocaproic acid, and the selective progesterone receptor modulator, ulipristal acetate. The latter has been shown effective in reducing HMB associated with uterine fibroids. Trials investigating the use of this drug in women with HMB without uterine fibroids are ongoing. How this drug changes the risk of VTE as compared to other hormonal contraceptive pills is unknown.

Back to case vignette 1
At the emergency department, the patient’s blood pressure was 108/73 mmHg, and heart rate was 134 bpm. Her hemoglobin level dropped to 4.5 g/dL. Since her last thrombotic episode had occurred more than 3 months prior, the potential morbidity from bleeding was felt to outweigh thrombotic risk. Therefore, rivaroxaban was held. A single dose of tranexamic acid was given. During admission, the patient was transfused with 4 units of red blood cells and a selective progesterone antagonist receptor was initiated. Endometrial ablation and hysterectomy were discussed should HMB recur. The patient was switched from rivaroxaban to warfarin. Subsequent visits revealed no further HMB. At present the patient does not require further HMB-related treatment or surgery she remains on warfarin at follow-up several years after her bleeding event.

**Back to case vignette 2**

The patient developed HMB following rivaroxaban treatment. We discussed switching to warfarin or an alternate DOAC, but she preferred once daily therapy and did not wish to undergo INR monitoring. Since her second VTE event was more than 6 months prior we advised the patient to decrease the dose of rivaroxaban to 10 mg once daily after informing her that this was an “off label” dose. We also referred her to a gynecologist for further investigation. With reduced dose of rivaroxaban, her HMB has resolved.
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Authorship

Contribution: K.B, S.H.O. and S.M.B. conceived this article; K.B. performed the literature review and wrote the first draft; S.H.O. and S.M.B reviewed and edited the final paper.

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Figure 1: Suggested strategies for outpatient management of HMB associated with anticoagulants

HMB on therapeutic doses of anticoagulant therapy

Clinical assessment
- Intensity of anticoagulant therapy
- Assess for iron depletion
- Review need for ongoing anticoagulation

Therapeutic-dose anticoagulation is needed

Receiving hormonal therapy
- CHCs
- POP
- DMPA
- LNG-IUS

Not receiving hormonal therapy

Referral to a gynecologist
- Consider alternative causes of HMB
- Initiate or adjust hormonal therapy

Continue therapeutic dose anticoagulation - consider switching to alternative anticoagulant*:
- Apixaban 5 mg orally bid
- Dabigatran 150 mg orally bid
- Warfarin
- Tranexamic acid

Continue usual therapeutic dose anticoagulation and use tranexamic acid 1.3 g orally 3 times a day for 5 days **start on the first day of menstruation***

or

Reduced dose DOAC therapy
- Rivaroxaban 10 mg orally OD during menses (duration of anticoagulant treatment >3 months)
- Apixaban 2.5 mg orally bid during menses (duration of anticoagulant treatment >3 months)
- Rivaroxaban 10 mg orally OD (completed anticoagulant treatment >6 months)
- Apixaban 2.5 mg orally bid (completed anticoagulant treatment >6 months)

Consider switching to an alternative anticoagulant
- Apixaban 5 mg orally bid
- Dabigatran 150 mg orally bid
- Warfarin

If menstrual bleeding does not improve considered gynecologist referral for surgical management

* Ensure good anticoagulant control if on warfarin therapy and compliance if receiving DOAC therapy. If started on CHC, high-dose oral progestagen or DMPA, hormonal therapy must be discontinued before cessation of anticoagulants.

** The recommended dose in the US, in Europe, the recommended dose is 1 g orally tid for up to 4 days (dose may be increased to maximum of 4 g /day).

*** Thrombotic risk unknown when combined with reduced dose DOACs.
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