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ORIGINAL ARTICLE

Heavy menstrual bleeding in women on anticoagulant treatment for venous thromboembolism: Comparison of high- and low-dose rivaroxaban with aspirin

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Abstract

Background: Rivaroxaban may induce heavy menstrual bleeding. It is unknown if this effect is dose related or if rivaroxaban is associated with more menstrual bleeding than aspirin.

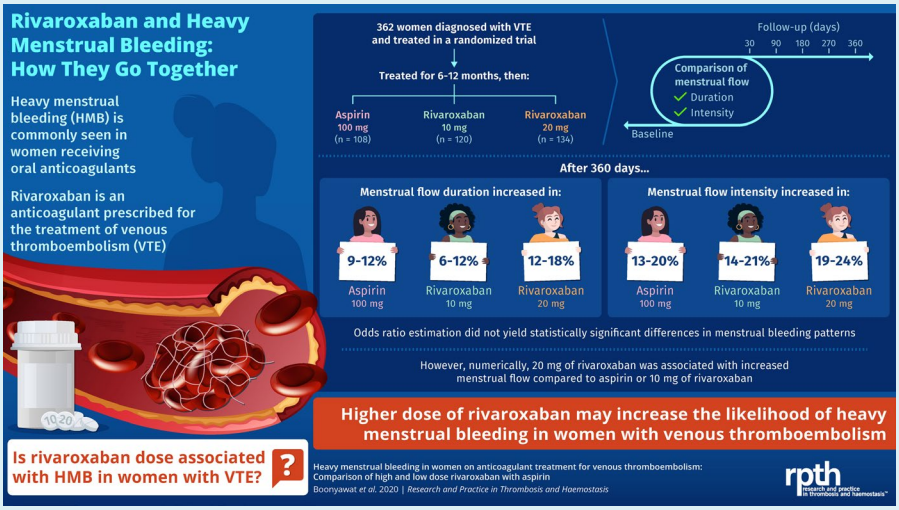
Objectives: To demonstrate and compare menstrual patterns and actions taken among women receiving aspirin and two doses of rivaroxaban.

Methods: The EINSTEIN-CHOICE trial compared once-daily rivaroxaban 20 mg, rivaroxaban 10 mg, and aspirin 100 mg for extended treatment of venous thromboembolism in patients who had completed 6 to 12 months of anticoagulant therapy. In 362 women with menstrual cycles, menstrual flow duration and intensity assessed at days 30, 90, 180, and 360 were compared with those before starting anticoagulant therapy.

Results: Menstrual flow duration increased in 12%-18% of the 134 women given 20-mg rivaroxaban, in 6% to 12% of 120 women given 10-mg rivaroxaban, and in 9% to 12% of 108 women given aspirin. Corresponding increases in flow intensity were 19% to 24%, 14% to 21%, and 13% to 20%. The odds ratios (ORs) for increased

menstrual flow duration were 1.36 (95% confidence interval [CI], 0.62-2.96) for rivaroxaban 20 mg versus aspirin, 0.77 (95% CI, 0.33-1.81) for rivaroxaban 10 mg versus aspirin, and 0.57 (95% CI, 0.26-1.25) for rivaroxaban 10 mg versus 20 mg. The ORs for increased menstrual flow intensity were 1.41 (95% CI, 0.67-2.99), 1.07 (95% CI, 0.49-2.34), and 0.76 (95% CI, 0.37- 1.57), respectively.

Conclusions: There were no statistically significant differences in menstrual hemorrhage patterns between women treated with 10 or 20 mg of rivaroxaban and aspirin. Compared with 10-mg rivaroxaban or aspirin, 20-mg rivaroxaban showed numerically more often increased menstrual flow duration and intensity.



KEYWORDS
anticoagulants, aspirin, heavy menstrual bleeding, rivaroxaban, venous thromboembolism

Essentials

- It is unknown if rivaroxaban associated heavy menstrual bleeding (HMB) is dose related.
- Menstrual bleeding patterns and actions taken were collected in this substudy of the EINSTEIN CHOICE trial.
- Rivaroxaban 20 mg may increase menstrual bleeding compared with the lower dose or aspirin.
- Rivaroxaban 10 mg is reasonable for the extended treatment in women who are experiencing HMB.

1 | INTRODUCTION

Heavy menstrual bleeding (HMB) has been defined as excessive menstrual blood loss that interferes with the woman's physical, emotional, social, and material quality of life, which can occur alone or in combination with other symptoms.[1] HMB is a common complaint in women receiving oral anticoagulants including vitamin K antagonists and direct oral factor Xa inhibitors[2,3], whereas no such signal was observed with dabigatran.[4] Rivaroxaban is associated with increased and/or prolonged menstrual bleeding in up to 30% of women receiving therapeutic doses (20 mg) for the treatment of venous thromboembolism.[5-7] Post hoc analysis of the pooled EINSTEIN-DVT and EINSTEIN-PE trials showed a higher rate of HMB in rivaroxaban-treated women compared with those treated with enoxaparin overlapped and followed by a vitamin K antagonist.[8] HMB leading to transfusion of red blood cells mainly occurred in women with anemia (hemoglobin < 12 g/L) or gynecological disorders, such as uterine fibroids and/or adenomyosis at randomization. Also, in these open-label studies, rivaroxaban-treated women more frequently needed a medical or surgical intervention to reduce abnormal uterine bleeding than those treated with a vitamin K antagonist.[9]

Although HMB associated with rivaroxaban is rarely life threatening, it may have a negative impact on the quality of life, especially in women requiring extended anticoagulant therapy. Temporary interruption of rivaroxaban during menses or use of reduced doses has been used to manage HMB.[5,6,10] However, both strategies may be associated with an increased risk of recurrent venous thromboembolism.

EINSTEIN-CHOICE compared once-daily rivaroxaban 20 mg, rivaroxaban 10 mg, or aspirin 100 mg for extended treatment in

patients who had completed 6 to 12 months of anticoagulation for their index event. Compared with aspirin, both doses of rivaroxaban reduced the risk of recurrence by about 70% without significantly increasing the risk of major bleeding.[11] As part of the study, we prospectively collected data on the duration and intensity of menstrual bleeding as well as the actions taken to manage it.

2 | METHODS

2.1 | Patients

For this substudy, we prospectively collected data on the duration and intensity of menstrual bleeding from women enrolled in the EINSTEIN-CHOICE trial who reported having menstrual cycles. In brief, EINSTEIN-CHOICE was a 3-arm, parallel-group, multicenter, double-blind, and double-dummy randomized trial. Patients were eligible for inclusion in the study if they were ≥18 years of age; had objectively confirmed, symptomatic proximal deep vein thrombosis or pulmonary embolism; had been treated for 6 to 12 months with an anticoagulant, either a vitamin K antagonist or direct oral anticoagulants such as dabigatran, rivaroxaban, apixaban, or edoxaban; and had not interrupted therapy for more than 7 days before randomization. Patients were ineligible if they had a contraindication to continued anticoagulant therapy or if they required extended therapy with anticoagulants at therapeutic doses or antiplatelet therapy. Additional ineligibility criteria included a calculated creatinine clearance of <30 mL/min or hepatic disease associated with a coagulopathy. Participants were randomly assigned to receive once-daily rivaroxaban 20 mg, rivaroxaban 10 mg, or aspirin 100 mg for up to 1 year. The protocol was approved by the institutional review board at each participating center, and signed informed consent was obtained from all the patients.

2.2 | Assessment of duration and intensity of menstrual bleeding

Standardized data entry forms were developed to document the duration and intensity of menstrual bleeding. During follow-up visits at days 30, 90, 180, 270, and 360, women who reported having

TABLE 1 Demographic and clinical characteristics at baseline

Characteristics	Rivaroxaban 20 mg n = 134	Rivaroxaban 10 mg n = 120	Aspirin 100 mg n = 108
Age, y, median (IQR)	38 (32-44)	38 (30-46)	39 (32-45)
Weight, n (%)			
≤70 kg	64 (47.8)	54 (45.0)	57 (52.8)
70 to ≤90 kg	36 (26.9)	32 (26.7)	26 (24.1)
>90 kg	34 (25.4)	34 (28.3)	25 (23.1)
Body mass index, n (%)			
<30 kg/m2	87 (64.9)	78 (65.0)	75 (69.4)
≥30 kg/m2	47 (35.1)	42 (35.0)	33 (30.6)
Creatinine clearance, n (%)			
<50 mL/min			
50 to <80 mL/min	11 (8.2)	7 (5.8)	5 (4.6)
≥80 mL/min	123 (91.8)	113 (94.2)	103 (95.4)
Prior anticoagulation, n (%)			
DOACs	53 (39.5)	51 (42.5)	52 (48.1)
Heparin/VKA	69 (50.7)	57 (47.5)	48 (44.4)
Combinations DOACs/heparin/VKA	12 (9.0)	12 (10.0)	8 (7.4)
Hemoglobin, g/dL, median (IQR)	13.3 (12.4-14.2)	13.1 (12.4-13.8)	13.3 (12.4-13.9)
Hemoglobin < 12 g/dL, n (%)	27 (20.1)	23 (19.2)	22 (20.4)
Iron supplementation, n (%)	7 (5.2)	12 (10.0)	5 (4.6)
NSAID use, n (%)	0	1 (8.3)	0
History of heavy menstrual bleeding, n (%)	2 (1.5)	3 (2.5)	0
Gynecological disorders, n (%)	3 (2.2)	5 (4.2)	7 (6.5)

Abbreviations: DOACs, direct oral anticoagulants; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; VKA, vitamin K antagonist.

TABLE 2 Menstrual flow duration patterns across treatment arms

Flow duration	Rivaroxaban 20 mg n = 134			Rivaroxaban 10 mg n = 120			Aspirin 100 mg n = 108		
Follow-up visit, n (%)	Shorter than usual	As usual	Longer than usual	Shorter than usual	As usual	Longer than usual	Shorter than usual	As usual	Longer than usual
Day 30	7 (5.6)	94 (75.8)	16 (12.9)	5 (4.6)	87 (80.6)	6 (5.6)	8 (8.2)	74 (76.3)	12 (12.4)
Day 90	4 (3.4)	93 (78.8)	14 (11.9)	4 (4.0)	78 (77.2)	12 (11.9)	12 (13.0)	67 (72.8)	11 (12.0)
Day 180	8 (7.1)	87 (77.0)	14 (12.4)	9 (9.3)	76 (78.4)	8 (8.2)	9 (10.6)	65 (76.5)	8 (9.4)
Day 270	6 (7.6)	56 (70.9)	14 (17.7)	4 (5.7)	58 (82.9)	6 (8.6)	8 (12.3)	50 (76.9)	6 (9.2)
Day 360	4 (5.0)	59 (73.8)	14 (17.5)	4 (5.9)	59 (86.8)	4 (5.9)	6 (9.2)	49 (75.4)	8 (12.3)

menstrual cycles at baseline were asked to compare menstrual flow duration and intensity of their last menstruation with their menstruation before the start of any anticoagulant therapy. Change in menstrual flow duration was reported as shorter than usual, as usual, or longer than usual, and change in menstrual intensity was reported as less than usual, as usual, or more than usual. Actions taken to manage menstrual bleeding were recorded, including interruption or stop of study medication, changes in contraceptive therapy, blood transfusion, use of prohemostatic or antifibrinolytic drugs, use of other concomitant medications, or referral to a gynecologist.

2.3 | Statistical analysis

Baseline characteristics and outcomes for each group were summarized using descriptive statistics. Data on menstrual flow duration and intensity were considered during the study treatment period, but only from the time of administration of the first dose of study medication to 48 hours after the administration of the last dose. Because the clinical question of interest is longer or more intense menstruation, general linear mixed modeling with binary distribution and logit link function was applied, calculating odds ratios (ORs) for longer or more intense versus other responses. Calculations were performed separately for duration and intensity of menstrual bleeding, allowing for within-subject correlation and missing data, by including random effect, and adjusted for the presence of a history of HMB; 95% confidence intervals (CIs) and *P* values were adjusted for multiple comparisons.

3 | RESULTS

From March 2014 to March 2016, 1500 women were enrolled in the EINSTEIN-CHOICE trial, of whom 377 (25.1%) reported having menstrual cycles. Data on menstrual flow duration and intensity were collected from 362 women (96.0%), of whom 134 (37.0%) received rivaroxaban 20 mg, 120 (33.1%) received rivaroxaban 10 mg, and 108 (29.8%) received aspirin. Iron supplementation at baseline was reported in 7 (5.2%), 12 (10.0%), and 5 (4.6%) women in the rivaroxaban 20 mg, rivaroxaban 10 mg, and aspirin groups, respectively, whereas a history of HMB was reported in 2 (1.5%), 3 (2.5%), and 0 women, respectively. Other baseline characteristics are presented in Table 1.

3.1 | Duration and intensity of menstrual bleeding

The observed frequencies of shorter/less than usual, as usual, and longer/more than usual duration/intensity of menstruation are provided in Tables 2 and 3. Over the 5 follow-up visits, in women randomly assigned to rivaroxaban 20 mg, rivaroxaban 10 mg, or aspirin, the frequency of a menstrual flow duration of longer than usual ranged from 12% to 18%, 6% to 12%, and 9% to 12%, respectively, whereas the frequency of a menstrual flow intensity of more than usual ranged from 19% to 24%, 14% to 21%, and 13% to 20%, respectively.

3.2 | Comparisons among treatment groups

Rivaroxaban 20 mg versus aspirin. The frequency of increased menstrual flow duration and intensity was numerically (but not statistically significantly) higher in the rivaroxaban 20-mg group compared with the aspirin group (OR, 1.36; 95% CI, 0.62-2.96; *P* = .63; and OR, 1.41; 95% CI, 0.67-2.99; *P* = .52, respectively).

Rivaroxaban 10 mg versus aspirin. The frequency of increased menstrual flow duration (OR, 0.77; 95% CI, 0.33-1.81; *P* = .76) and intensity (OR, 1.07; 95% CI, 0.49-2.34; *P* = .98) were numerically (but not statistically significantly) lower in the rivaroxaban 10-mg group compared with the aspirin group.

Rivaroxaban 10 mg versus rivaroxaban 20 mg. The frequency of increased menstrual flow duration and intensity was numerically (but not statistically significantly) lower (OR, 0.57; 95% CI, 0.26-1.25; *P* = .21; and OR, 0.76; 95% CI, 0.37-1.57; *P* = .64, respectively) in the rivaroxaban 10-mg group compared with the rivaroxaban 20-mg group.

3.3 | Actions taken to manage HMB

The types of actions taken for the management of HMB are presented in Table 4. Overall, 21 (15.7%), 15 (12.5%), and 15 (13.9%) women in the rivaroxaban 20-mg, rivaroxaban 10-mg, and aspirin

TABLE 3 Patterns of menstrual flow intensity across treatment arms

Flow intensity	Rivaroxaban 20 mg n = 134			Rivaroxaban 10 mg n = 120			Aspirin 100 mg n = 108		
Follow-up, n (%)	Less than usual	As usual	More than usual	Less than usual	As usual	More than usual	Less than usual	As usual	More than usual
Day 30	9 (7.3)	78 (62.9)	30 (24.2)	5 (4.6)	77 (71.3)	18 (16.7)	14 (14.4)	61 (62.9)	19 (19.6)
Day 90	6 (5.1)	78 (66.1)	27 (22.9)	6 (5.9)	68 (67.3)	21 (20.8)	15 (16.3)	60 (65.2)	15 (16.3)
Day 180	10 (8.8)	75 (66.4)	24 (21.2)	7 (7.2)	69 (71.1)	18 (18.6)	10 (11.8)	61 (71.8)	11 (12.9)
Day 270	7 (8.9)	54 (68.4)	15 (19.0)	4 (5.7)	54 (77.1)	10 (14.3)	9 (13.8)	43 (66.2)	12 (18.5)
Day 360	4 (5.0)	55 (68.8)	18 (22.5)	6 (8.8)	49 (72.1)	12 (17.6)	5 (7.7)	45 (69.2)	13 (20.0)

TABLE 4 New action taken for management of heavy or prolonged menstrual bleeding during study treatment

Actions	Rivaroxaban 20 mg n = 134	Rivaroxaban 10 mg n = 120	Aspirin n = 108
Patients with any action, n (%)	21 (15.7)	15 (12.5)	15 (13.9)
Change in hormonal therapy	9 (6.7)	9 (7.5)	8 (7.4)
Stop or interruption of study medication	6 (4.5)	2 (1.7)	2 (1.9)
Referral to gynecologist	4 (3.0)	4 (3.3)	4 (3.7)
Blood transfusion	2 (1.5)	0	0
Prohemostatic/antifibrinolytic therapy	1 (0.7)[a]	0	0
Iron supplementation	0	1 (0.8)	1 (0.9)

[a]Tranexamic acid.

groups, respectively, had an action taken. Stopping or interruption of study medication, use of blood transfusion, and use of prohemostatic/antifibrinolytic therapy were reported 9 times in the rivaroxaban 20-mg group compared with 2 times in the other two treatment groups. However, there were no statistical differences between groups.

4 | DISCUSSION

The results of this substudy of the EINSTEIN-CHOICE trial found that flow duration and intensity of menstrual bleeding, as well as actions taken to manage HMB, increased nonsignificantly in women treated with rivaroxaban 20 mg compared with either rivaroxaban 10 mg or aspirin. The comparison of rivaroxaban 10 mg with aspirin showed a small decrease in flow duration but an equally small increase in flow intensity with rivaroxaban, while the number of actions taken to manage HMB was comparable and approximates 15%. The EINSTEIN-CHOICE trial demonstrated that rivaroxaban 10 mg once daily had comparable efficacy in the prevention of recurrent venous thromboembolism compared with rivaroxaban 20 mg once daily and that the 10-mg dose appeared to be safer with regard to increased menstrual bleeding.[11] Hence, our findings suggest that in treating women with HMB, reducing the dose of rivaroxaban to 10 mg daily after 6 months of treatment is reasonable.[10]

Our study has several strengths. The current analysis was prospectively planned as a substudy of the double-blind EINSTEIN-CHOICE trial and included >100 women per treatment arm. Follow-up data were missing in only 15 (4.0%) of the 377 women who reported menstrual cycles at baseline. The proportions of missing data were relatively small and comparable for the three study arms (Table 2 and 3). Furthermore, missing data were taken into account in our statistical strategies. The strength of our conclusions is increased by the double-blind, randomized study design that minimizes the risk of confounding by indication.

For the limitations, since all women had been treated before the start of the study with therapeutic doses of anticoagulants for 6 to 12 months, the comparison of menstrual cycles during the study with cycles from before the start of any anticoagulation might not be fully accurate, but this imprecise recall applies equally to all patients in the three treatment groups. Women who had (severe) HMB in the months after the start of their initial anticoagulation might have had already actions taken before

enrollment in this study or may have declined extended anticoagulation and thus could not participate.[12] Though we have baseline hemoglobin levels, we did not have hemoglobin values during or at the end of the study. Finally, we defined actions taken to control HMB on the forehand; one might argue that stopping or interrupting the study medication and blood transfusion are clinically more important actions. Therefore, the inclusion of "change of hormonal therapy" and "referral to a gynecologist" might have reduced the difference between groups. Based on the frequency of stopping or interruption of therapy and blood transfusion (6% vs 2%), approximately 700 patients would be required for the comparison of rivaroxaban 20 mg versus 10 mg in a two-arm study.

In conclusion, there were no statistically significant differences in menstrual bleeding patterns between 10 or 20 mg of rivaroxaban and aspirin. Compared with 10-mg rivaroxaban or aspirin, 20-mg rivaroxaban showed numerically more often increased menstrual flow duration and intensity, whereas, compared with aspirin, there was less often increased flow duration, but more often increased flow intensity with 10-mg rivaroxaban. Our findings support the use of a 10-mg once-daily dose of rivaroxaban for the secondary prevention of venous thrombosis in appropriate women who are experiencing menses.

AUTHOR CONTRIBUTIONS

KB, AWAL, JB-W, MHP, and MC designed the study, led the study, analyzed the data, and wrote the manuscript; MHP and AFP performed the statistical analyses. PP, IM, SM, and JIW were study principal investigators, analyzed data, and edited the manuscript; MHP was a member of the adjudication committee. All authors reviewed the final manuscript and agreed to its submission in its current form.

RELATIONSHIP DISCLOSURE

KB declares no conflict of interest. AWAL and AFP are employees of Bayer AG; MHP reports receiving personal fees from Bayer AG; JB-W received personal fees and fees paid to his institution from Bayer, Daiichi Sankyo, DOASENSE, and Portola; and fees paid to his institution from Pfizer. IM received fees from Sanofi and Bayer. SM received grants and fees paid to her institution from GSK, BMS/Pfizer, Aspen, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Sanofi, and Portola. PP received personal fees from Bayer and Sanofi; JIW received, honoraria from Bayer AG, Pfizer, Bristol-Meyers Squibb, Daiichi Sankyo, Portola, Anthos, Ionis and Tetherex. MAC reports that in the past 24 months he has sat on a Data and Safety Monitoring Board for Bayer; has served on advisory boards for Servier Canada, Asahi Kasei, Precision Biologics, and Hemostasis Reference Laboratory; and has received personal fees from Pfizer, CSL Behring, and Diagnostica Stago.

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