Incidence and impact on quality of life of heavy menstrual bleeding in women on oral anticoagulant therapy at an academic hospital in Johannesburg, South Africa - A prospective cohort study

Naseerah Hassan, MBChB

450148

A research proposal submitted to the Faculty of Health Sciences,

University of the Witwatersrand,

in partial fulfilment of the requirements for the degree of Masters of Medicine.

Declaration

I, Naseerah Hassan, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Molecular Medicine and Haematology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

10th day of February 2025 in Johannesburg, South Africa

Abstract

Heavy menstrual bleeding affects up to two thirds of women on oral anticoagulation. The rates of heavy menstrual bleeding, its impact on quality of life and associated risk factors in women attending anticoagulation clinics in South Africa are largely unknown. A prospective cohort study was performed over an eight-month period in 30 women on Warfarin and 27 on Rivaroxaban for a median [interquartile range] duration of 15.5 [78.0] months attending the Anticoagulation Clinic at Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa. Heavy menstrual bleeding was assessed over one menstrual cycle using the validated pictorial blood loss assessment charts (PBAC) and the menstrual bleeding questionnaire (MBQ).

In this population of predominantly African ethnicity, with a median [interquartile range] age of 39 [8] years, 39 (68.4%) women experienced heavy menstrual bleeding, defined as a PBAC score of >100. Median cycle length on anticoagulation and MBQ scores were significantly higher among women with a PBAC score of >100 ($p>0.05$). Univariate analysis identified Rivaroxaban as a risk factor for heavy menstrual bleeding (OR 5.03, 95% CI 1.40-18.12). Heavy menstrual bleeding required treatment in 29 (74.4%) women which included management of iron deficiency, anti-fibrinolytics, modification of anticoagulation and hormonal contraception. Heavy menstrual bleeding was associated with a considerable negative impact on quality of life. This was most significant for women on Rivaroxaban as compared to Warfarin. It is essential to monitor and appropriately treat heavy menstrual bleeding in at risk women on anticoagulant treatment.

Acknowledgements

I wish to thank my supervisors for their tremendous patience and support with this project:

Prof Elise Schapkaitz,
Dr Haroun Rhemtula
and Dr Nolukholo Ncete

I would also like to thank the following staff at the Anticoagulation clinic for their assistance.
Sister Johanna Sithole
and Sister Morongwa Masebe

Finally, I would like to thank the patients for their participation, co-operation and willingness.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Nomenclature

CMJAH	**Charlotte Maxeke Academic Johannesburg Hospital**
CI	**Confidence interval**
DOAC	**Direct oral anticoagulant**
FIGO	**International Federation of Gynaecology and Obstetrics**
HIV	**Human Immunodeficiency Virus**
HMB	**Heavy menstrual bleeding**
IQR	**Interquartile range**
INR	**International Normalised Ratio**
MBQ	**Menstrual bleeding questionnaire**
PBAC	**Pictorial Blood Loss Assessment Chart**
SD	**Standard deviation**
SF-36	**Short Form 36 Health Survey Questionnaire**
VTE	**Venous thromboembolism**

1. BACKGROUND

1.1 Definition of heavy menstrual bleeding.

Heavy menstrual bleeding is a common complaint, affecting approximately 15-30% of women in the reproductive age group (1). Objectively, heavy menstrual bleeding is defined as the quantitative measurement of more than 80ml of blood loss per cycle. The International Federation of Gynaecology and Obstetrics (FIGO) defines heavy menstrual bleeding as an increase in frequency, irregularity, duration and volume of menstrual blood loss as well as intermenstrual bleeding (2). This is based on visualization of clots of more than one inch in diameter, a low ferritin of <20 ng/mL and/or the need to change sanitary pads at least every hour (3). In clinical practice, accurate quantification is difficult. More recently, a more practical definition has been suggested as heavy menstrual bleeding that affects a patient's physical, emotional and social quality of life (4).

1.2 Heavy menstrual bleeding and anticoagulation.

Oral anticoagulant treatment for the management and prevention of venous and arterial thrombo-embolism is associated with an increased risk of bleeding, including heavy menstrual bleeding (5). In women receiving long-term anticoagulation, heavy menstrual bleeding can have a considerable impact on quality of life (6). Heavy menstrual bleeding has been reported to affect up to two thirds of women on anticoagulation (7). In a retrospective study conducted in 104 women in Belgium, 70.2% of anticoagulated women reported heavy menstrual bleeding (8). According to a recently conducted study in the United Kingdom, anticoagulated women reported a significantly increased median duration of menstrual bleeding from five to six days ($p<0.05$). This was associated with a negative impact on quality of life, including avoiding social activities, bleeding that soaked outer clothing and unpredictable cycles, as compared to

the control group of women (9). Local data, however, from women on anticoagulation is limited (10).

Oral anticoagulants include vitamin K antagonists and more recently direct oral anticoagulants (DOAC). Direct oral anticoagulants namely, factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and the thrombin inhibitor dabigatran offer many advantages over vitamin K antagonists (11). In addition to improved pharmacodynamic and pharmacokinetic properties, the risk of intracranial bleeding is reduced, as compared to vitamin K antagonists (12). Randomized controlled studies have shown an equivalent or reduced incidence of major bleeding and clinically relevant non-major bleeding in DOAC treated patients as compared to patients treated with vitamin K antagonists (13,14). To date, however, few studies have assessed heavy menstrual bleeding specifically as an outcome of anticoagulant use.

Following the wide-spread use of the DOACs, case series and small cohort studies emerged reporting increased rates of heavy menstrual bleeding compared with vitamin K antagonists (8,9,11). In particular, an increased risk of heavy menstrual bleeding has been described in the subgroup of women treated with factor Xa inhibitors as compared to women treated with vitamin K antagonists (9,15). Subsequently, research has been performed to determine the risks associated with different classes of factor Xa inhibitors. An increase in heavy menstrual bleeding in women on rivaroxaban, as compared to warfarin has been described (16). This finding was confirmed in post hoc analyses of the EINSTEIN trial which reported increased rates of heavy menstrual bleeding for rivaroxaban (hazard ratio, 2.1; 95% confidence interval [CI], 1.6-2.9) as compared to vitamin K antagonists (17). Edoxaban also demonstrated a higher risk of heavy menstrual bleeding as compared to warfarin (hazard ratio, 1.9; 95% CI, 1.1-2.5)

(18). In the AMPLIFY trial, the rate of heavy menstrual bleeding did not differ between apixaban and vitamin K antagonists (5). Further it appears that dabigatran is associated with a lower risk of heavy menstrual bleeding as compared to vitamin K antagonists (17). An American study, RAMBLE (NCT02829957) is currently investigating the rates of heavy menstrual bleeding between rivaroxaban and apixaban to determine whether there is indeed a class effect.

1.3 Tools used to assess heavy menstrual bleeding.

A bleeding, menstrual, gynaecological and obstetric history is required prior to starting anticoagulation as these factors may be independent risks for heavy menstrual bleeding (7). Specifically, pathologies in the FIGO acronym PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy, Coagulopathy, Ovulatory Disorders, Endometrial Disorders, Iatrogenic Causes, and Not Classified) should be excluded(19). Prior to the introduction and validation of menstrual bleeding assessment tools, the HAS- BLED score was used as a general assessment of bleeding (20). Menstrual bleeding assessment tools of blood loss quantitation and its effect on quality of life include the alkaline-haematin methods, pictorial blood loss assessment charts (PBAC) and the menstrual bleeding questionnaire (MBQ) (21). The gold standard, alkaline-haematin method which involves the extraction of haemoglobin from used sanitary products for the quantitative assessment of menstrual bleeding, is an impractical and expensive method. The PBAC is an alternative semi-quantitative method which is widely used in clinical studies. It is a simple visual score which measures the degree of blood loss from multiple types of sanitary products (22). The PBAC has been associated with a sensitivity of 58–99% and a specificity 75–89% for scores above 100 for heavy menstrual bleeding (21). According to this visual score, a PBAC score of 100 equates to 80ml of menstrual blood loss.

Since its introduction in 1990 by Higham et al. the PBAC has been validated with newer sanitary products (22 and 23). Lastly, the MBQ was developed and validated for measuring quality of life in women of reproductive age in different ethnic groups (24). The MBQ consists of 20 questions related to menstrual bleeding quantity, regularity and associated pain, as well as the impact of symptoms on mental health, specifically social embarrassment (24). The MBQ is more specific to the effects on quality of life caused by heavy menstrual bleeding as compared to the SF-36, which is a general patient-reported survey of physical and mental health functioning (24).

1.4 Management of heavy menstrual bleeding and iron-deficiency

Heavy menstrual bleeding is under reported by women attending anticoagulation clinics (12). Women are often unaware of the extent of menstrual blood loss and often seek medical care only when their quality of life is affected or as a result of iron deficiency anaemia (7). According to a Spanish study, patients' primary concerns were the effects on functional, professional, social and family responsibilities (25). Iron deficiency anaemia is an important complication of heavy menstrual bleeding which can lead to reduced cognitive ability, physical strength and immunity (15). In particular, iron deficiency anaemia impairs attention, memory, and learning. The treatment of iron deficiency anaemia includes oral and intravenous forms with emergency cases requiring transfusions (25). Treatment of heavy menstrual bleeding results in an improvement of symptoms. Women who present with anticoagulant associated heavy menstrual bleeding require an individualised management approach in consultation with gynaecology. Treatment options include prescribing hormone contraception, antifibrinolytic agents, haematinics or uterine surgical interventions (26).

The most commonly used intervention is progesterone-based contraceptives which include oral and patch forms or levonorgestrel intrauterine systems (3). Levonorgestrel intrauterine systems are safe and effective and have been associated with blood loss reduction by 80%, improved compliance and low side effect profiles and as such are the preferred modality (27). They result in amenorrhea in 50% of women. The etonogestrel subdermal implant results in amenorrhea in approximately 20% of women and depot-medroxyprogesterone acetate results in amenorrhea in greater than 50% of women. Furthermore, the combined oral contraceptive is an alternative which has not been associated with a significantly increased risk of recurrent thrombosis in women on anticoagulation therapy. The EINSTEIN trials demonstrated no increased risk of VTE on hormonal therapy (adjusted hazards ratio, 0.56; 95% confidence interval [CI], 0.23-1.39). Moreover, the risk of venous thrombo-embolism (VTE) with oestrogen-containing and progestin-only therapies were similiar (17). In contrast, reducing the duration of anticoagulation or omitting doses has been associated with five-fold increased risk of recurrent thrombosis (28). Recent evidence, however, supports a dose reduction for rivaroxaban and apixaban. The results of the EINSTEIN-CHOICE sub-study, suggest that in women with heavy menstrual bleeding, the dose of rivaroxaban can be safely reduced to 10 mg daily after six completed months of treatment (29). With the availability of several anticoagulant agents, switching agents is another reliable option (7). The MEDEA trial is a Dutch multicentre, randomized trial in women with heavy menstrual bleeding on factor Xa inhibitor treatment. The study is currently randomising women to either switch to dabigatran, continue on the factor Xa inhibitor with the addition of an antifibrinolytic agent or to continue on the factor Xa inhibitor with no intervention (30). In particular, the anti-fibrinolytic agent tranexamic acid has been associated with a decrease in heavy menstrual bleeding by 26 to 54% (24).

2. STUDY AIM AND OBJECTIVES

Rationale

Bleeding is a common complication of oral anticoagulant therapy, however rates of heavy menstrual bleeding in users of the oral anticoagulant are largely unknown in South Africa.

Aim

The aim of this prospective cohort study is to determine the incidence rate of heavy menstrual bleeding, and its impact on quality of life in women prescribed oral anticoagulation (Warfarin and Rivaroxaban) at a single academic centre.

Objectives

1. To assess the incidence rate and symptoms of heavy menstrual bleeding in women of child bearing age prescribed oral anticoagulation using the validated PBAC and MBQ.

2. To identify risk factors for heavy menstrual bleeding in women on oral anticoagulation

3. To assess the impact of heavy menstrual bleeding on quality of life in women prescribed oral anticoagulation using the MBQ.

4. To identify iron deficiency anaemia as a complication of heavy menstrual bleeding in women prescribed oral anticoagulation.

3. METHODS

Research Design

A prospective cohort study.

Study Site

Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and National Health Laboratory Service, Anticoagulation Clinic Johannesburg, South Africa. The anticoagulation clinic currently has approximately 400 patients.

Study Population

This study included consecutive women, aged 18-45 years old, who were prescribed one of the following oral anticoagulants: Rivaroxaban 20 mg, Rivaroxaban 10 mg, Warfarin (international normalized ratio, INR 2-3) or Warfarin (INR 2.5-3.5). The following participants were excluded: pregnant women, postmenopausal women with premature ovarian failure, women with bleeding disorders, women with cervical or uterine preneoplastic lesions or active malignancy and women with creatinine clearance of <30 mL/min or liver disease.

Study period

The study was conducted over an 8-month period from 1 November 2023 to 30 June 2024.

Data collection

At enrolment, participants received a participant information sheet and the study was explained to them in their language of preference, with an interpreter (Appendix A). Written informed consent was obtained from all study participants, and the study protocol was approved by the

Institutional Review Board (M-230809). (Appendix B and F). A face-to-face interview was conducted and the following data was collected: demographic characteristics, indications for anticoagulation, current anticoagulant therapy, dose and duration, and concomitant medications (Appendix C). A history which included a gynaecological history to exclude women with features indicative of cervical preneoplastic lesions or active malignancy symptoms and signs of premature ovarian failure as well as a medical history to assess other major and minor events. Subsequently information around menstrual bleeding was collected, namely the type of sanitary products, the average length of the menstrual cycle prior to commencing anticoagulation and management of heavy menstrual bleeding, if present. The most recent supporting laboratory investigations for iron deficiency anaemia (full blood count and iron studies) performed as part of routine patient care and human immunodeficiency virus (HIV) was documented from record review.

Participants were asked to complete a MBQ using the MBQ tool developed and validated by Matteson for three consecutive menstrual cycles (Appendix D) (24). The MBQ consists of 20 questions regarding bleeding symptoms, menstrual pain, and quality of life. The responses were added to obtain a minimum score of 0 and a maximum score of 75. Participants were asked to self-complete a PBAC daily for one menstrual cycle during the study using the PBAC tool developed by Higham et al. and subsequently modified by Spence et al. (Appendix E) (23). Participants were required to record the number of sanitary products used daily and the degree to which these are soaked on a PBAC, which provides a visual reference. This was returned electronically or in person after one month. The total menstrual blood loss in ml will be estimated by dividing the total PBAC score by 1.25. The PBAC provides an objective assessment of menstrual blood loss, with a PBAC score >100 indicating heavy menstrual bleeding (Appendix E). Management of heavy menstrual bleeding diagnosed during the study was at the discretion of the treating health care provider and not part of study procedures. This

included treatment of the iron deficiency, relevant referral to a gynaecologist and necessary investigations as subsequent management of the bleeding which included oral or intrauterine devices, antifibrinolytics or surgical intervention to reduce the bleeding or further interventions at the discretion of the treating multidisciplinary-team.

4. DATA ANALYSIS

Sample size

Considering an estimated incidence of heavy menstrual bleeding of 65% in women on anticoagulation, a sample size 60 was calculated at a CI of 90% using Stata software (Texas, USA) (1 and 7). In order to identify significant predictors of heavy menstrual bleeding using multiple linear regression analysis, at least 15 per group were estimated per independent variable. A sample size was not calculated for subgroup analysis of Rivaroxaban versus Warfarin as the difference in heavy menstrual bleeding was too small (9).

Statistical methods

Data was analyzed using Statistica 13.2 software (California, USA). The incidence of heavy menstrual bleeding defined as a PBAC >80ml, was calculated with corresponding 95% CI. Normally distributed, continuous data is presented as mean ± SD and variables with non-Gaussian distribution as median [interquartile range (IQR)]. Comparisons for numerical measurements between women with and without heavy menstrual bleeding was performed using a parametric unpaired t-test or non-parametric Mann-Whitney test. Comparisons for categorical measurements was performed using chi-square test or Fisher's exact test when necessary. Univariate logistic regression analysis was conducted to identify risk factors for heavy menstrual bleeding with the correspondent unadjusted odds ratios (OR) and 95% CI. Significance level is set at <0.05.

5. RESULTS

5.1 Clinical and laboratory characteristics

During the study 65 women on anticoagulation were interviewed of whom 57 were eligible for inclusion (Fig 2.). The baseline demographics and clinical characteristics of the study participants are described in Table 1. The majority of the women (median [IQR] age of 39 [8] years) were of African ethnicity (n=52, 91.2%) in keeping with the demographics of the population served by CMJAH. Venous thromboembolism (n=31, 54.4%) was the most common indication for anticoagulation, followed by valvular heart disease (n=24, 42.1%). At enrolment, the median duration of anticoagulation was 15.5 [78.0] months. Fifteen (26.3%) women were living with HIV, consistent with the national rates of infection. No participants were receiving concomitant antiplatelet therapy. The mean ± SD haemoglobin was 11.1 ± 2.2 g/dL, which was below the normal reference range (Table 2).

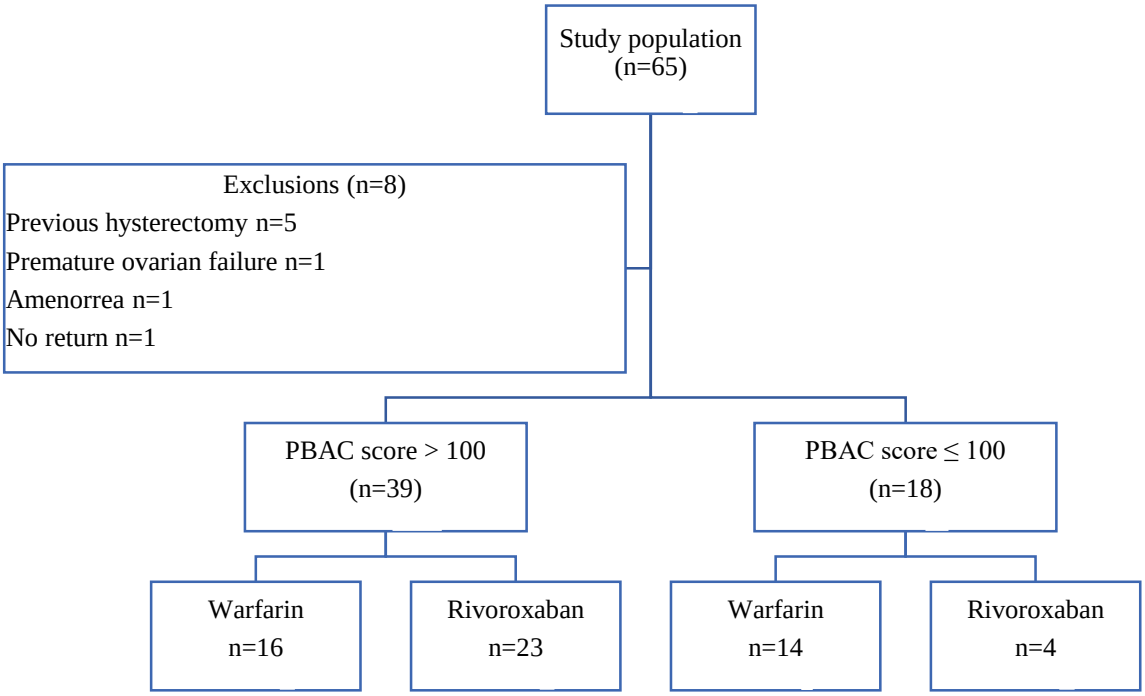


Figure 1. Flow diagram of study population

Table 1 Baseline characteristics of study population

Demographics	n=57
Age at study entry (years), median [IQR]	39.00 [8.00]
Ethnicity Black African (n,%) Non- African (n,%)	 52 (91.22%) 5 (8.77%)
Characteristics	
Anticoagulant Warfarin (n,%) Rivaroxaban (n,%)	 30 (52.63) 27 (47.37)
Indication for anticoagulation Venous thrombo-embolic disease (n,%) Valvular heart disease (n,%) Non- valvular heart disease (n,%)	 31 (54.39%) 24 (42.10%) 2 (3.51%)
Duration of anticoagulation (months), median [IQR]	15.50 [78.00]
Co-morbidities Cardiac conditions (n,%) Autoimmune conditions (n,%) Neurological conditions (n,%) HIV infected (n,%)	 6 (10.5%) 4 (7.02%) 2 (3.50%) 15 (26.32%)
Concomitant medications (n,%)	35 (61.40%)
Key: IQR, Inter- quartile range, HIV, Human Immunodeficiency virus Of the participants on warfarin, no participants were receiving CYP2C9 inhibitors. Of the participants on rivaroxaban, no participants were receiving CYP3A4 inducers.	

Table 2 Laboratory characteristics on anticoagulation

Laboratory characteristics	n=57
Haemoglobin (g/dL), mean ± SD (ref: 11.6-16.4)	11.12 ± 2.16
Mean cell volume (fL), mean ± SD (ref: 78.9 - 98.5)	85.91 ± 8.66
Mean corpuscular haemoglobin concentration (g/dL), median [IQR] (ref: 32.7 - 34.9)	31.60 [2.50]
Serum iron (µmol/L), mean ± SD (ref: 9-30.4)	8.67 ± 5.46
Transferrin (g/L), median [IQR] (ref: 2.5-3.8)	3.80 [8.10]
Transferrin % saturation, median [IQR] (ref: 15-50)	3.75 [9.10]
Ferritin (µg/l), median [IQR] (ref: 15-150)	34.50 [28.00]
Estimated glomerular filtration rate (mL/min), mean ± SD (ref: 71-121)	59.88 ± 0.71
International normalised ratio on warfarin, mean ± SD Range 2.0-3.0 Range 2.5-3.5	 2.51 ± 0.83 2.43 ± 0.78
Key: IQR, Inter- quartile range, SD, standard deviation	

5.2 Menstrual cycle characteristics and impact on quality of life

The median cycle length was 6 [4] days on anticoagulation as compared to 5 [2] days prior to commencing anticoagulation (p<0.001) (Fig 2.). The median cycle length was 5 [1] days on warfarin as compared to 9 [6] days on rivaroxaban (p<0.001) (Fig 4.)

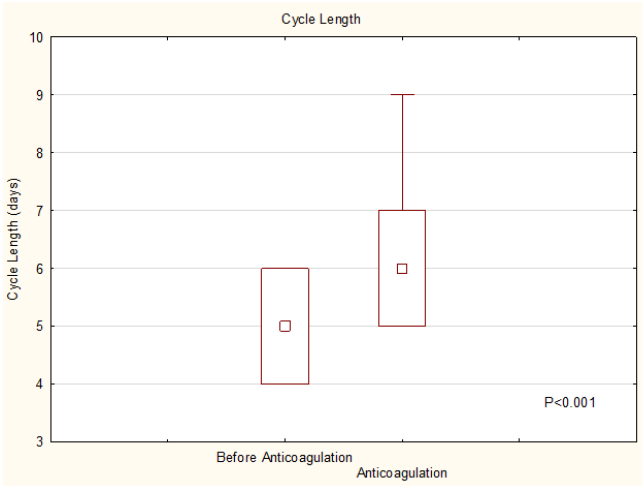


Figure 2. Box and whisker plot of median menstrual cycle length reported before anticoagulation and on anticoagulation

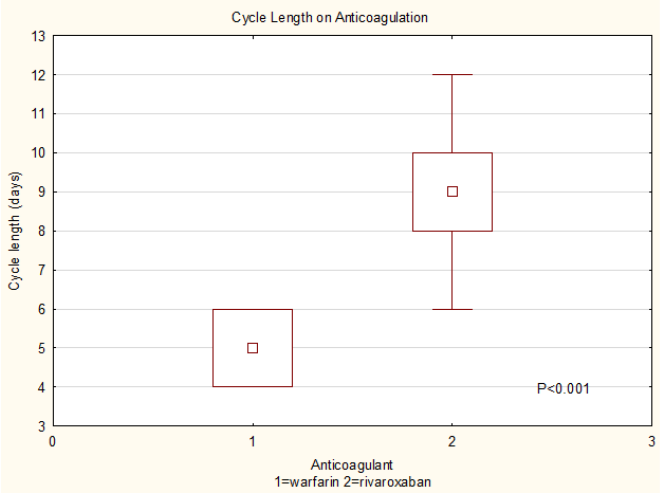


Figure 3. Box and whisker plot of median menstrual cycle length on Warfarin compared to Rivaroxaban

The median total estimated menstrual blood loss was 120.0 [160.0] ml and the median PBAC score was 155.0 [200.0] in the study population. Thirty-nine (68.4%, 95% CI 0.55-0.79) women experienced heavy menstrual bleeding, defined as a PBAC score of >100. Median cycle length on anticoagulation and the MBQ score were significantly higher among women with a PBAC score of >100 (Table 3.). The PBAC score correlated positively with the MBQ score ($r=0.547$, $p<0.001$). A non-significant decline in mean PBAC scores was observed with anticoagulation categorised according to duration ($p=0.514$) (Fig 5.)

Table 2 Characteristics of participants with PBAC scores > 100 and PBAC < 100

Variable	**PBAC > 100 n=39**	**PBAC ≤100 n=18**	**p value**
Age (years), median [IQR]	39.00 [7.00]	40.50 [10.00]	0.916
Menstrual cycle length before anticoagulation (days), median [IQR]	5.00 [3.00]	4.00 [1.00]	0.153
Menstrual cycle length on anticoagulation (days), median [IQR]	7.00 [5.00]	5.00 [2.00]	0.002
Duration on anticoagulation (months), median [IQR]	15.00 [70.00]	60.00 [126.00]	0.196
MBQ Score, median [IQR]	26.00 [22.00]	9.50 [13.00]	<0.001
Haemoglobin (g/dL), mean ± SD	11.12 ± 2.32	11.02 ± 1.82	0.874
% saturation, median [IQR]	3.75 [16.40]	3.72 [3.10]	0.895
Ferritin (µg/l), median [IQR]	34.00 [29.00]	40.00 [35.00]	0.333
Key: IQR, Inter- quartile range, SD, standard deviation, MBQ, menstrual bleeding questionnaire, PBAC, pictorial blood loss assessment chart.			

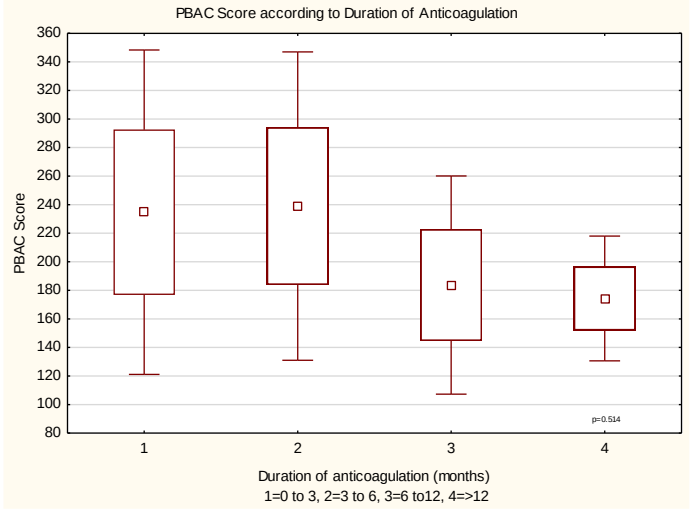


Figure 4. Box and whisker plot of median PBAC scores according to duration of anticoagulation.

Median total estimated menstrual blood loss, PBAC scores and MBQ scores were higher among participants on Rivaroxaban as compared to Warfarin ($p<0.001$) (Table 4, Fig 6-7). Median cycle length on Rivaroxaban was 9.00 [6.00] as compared to Warfarin 5.00 [1.00] ($p<0.001$). Twenty-three (85.2%) of the participants on Rivaroxaban and 16 (53.3%) of the participants on Warfarin had PBAC scores of >100 ($p<0.010$). There was no difference in haemoglobin levels and iron studies according to anticoagulant groups.

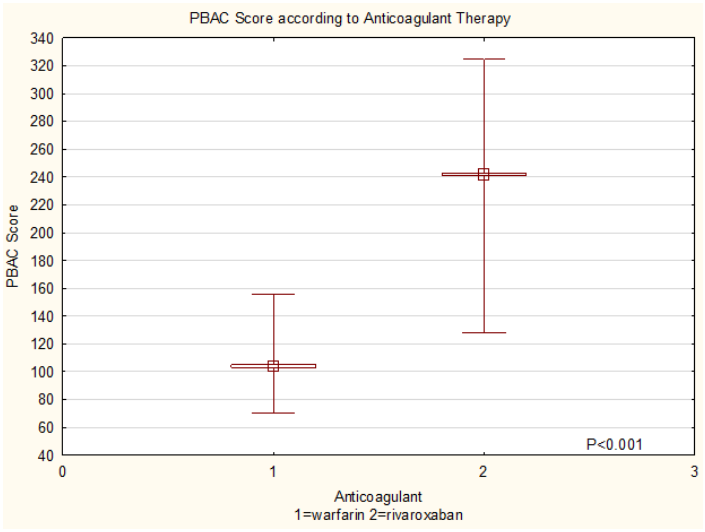


Figure 5. Box and whisker plot of median PBAC score on Warfarin compared to Rivaroxaban

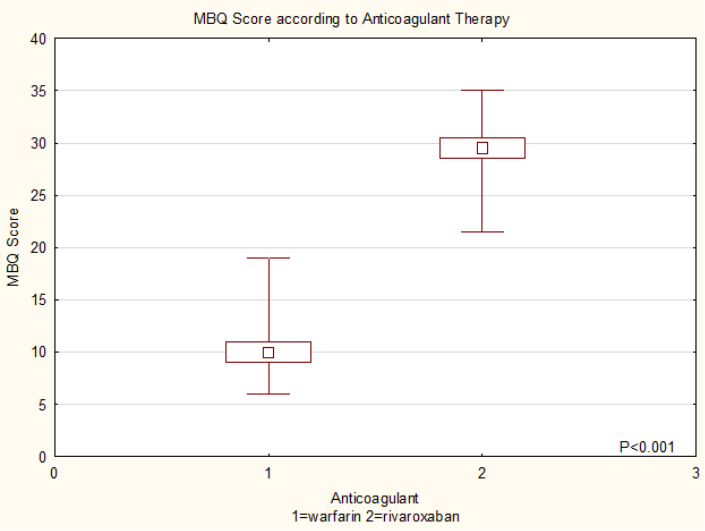


Figure 6. Box and whisker plot of median MBQ score on Warfarin compared to Rivaroxaban

Table 4 Characteristics of participants on Warfarin and Rivaroxaban

Variable	**Warfarin n=30**	**Rivaroxaban n=27**	**p value**
Age (years), median [IQR]	38.50 [10.00]	39.00 [7.00]	0.471
Menstrual cycle length before anticoagulation (days), median [IQR]	5.00 [1.00]	5.00 [2.50]	0.418
Menstrual cycle length on anticoagulation (days), median [IQR]	5.00 [1.00]	9.00 [6.00]	<0.001
Duration on anticoagulation (months), median [IQR]	80.00 [114.00]	8.00 [10.50]	<0.001
Haemoglobin (g/dL), mean ± SD	10.82 ± 1.86	11.40 ± 2.41	0.323
Serum iron (µmol/L), mean ± SD	8.77 ± 5.71	8.57 ± 5.41	0.922
% saturation (%), median [IQR]	4.00 [9.00]	3.43 [13.50]	0.868
Ferritin (µg/l), median [IQR]	30.00 [37.00]	39.00 [30.00]	0.934
Blood loss (ml), median [IQR]	83.20 [68.80]	193.60 [157.60]	<0.001
PBAC Score, median [IQR]	104.00 [86.00]	242.00 [197.00]	<0.001
MBQ score, median [IQR]	10.00 [13.00]	29.50 [13.50]	<0.001
Key: IQR, Inter- quartile range, SD, standard deviation, MBQ, menstrual bleeding questionnaire, PBAC, pictorial blood loss assessment chart			

Fig. 7 describes the PBAC and MBQ scores according to Warfarin INR range of 2-3 and 2.5-3.5 on and Rivaroxaban dose of 10mg and 20mg. Median cycle length on Warfarin INR 2-3 and 2.5-3.5 was 6.00 [3.00] and 5.00 [2.00] days respectively. Median cycle length on Rivaroxaban 10mg and 20mg was 9.00 [4.00] and 10.00 [10.00] days respectively.

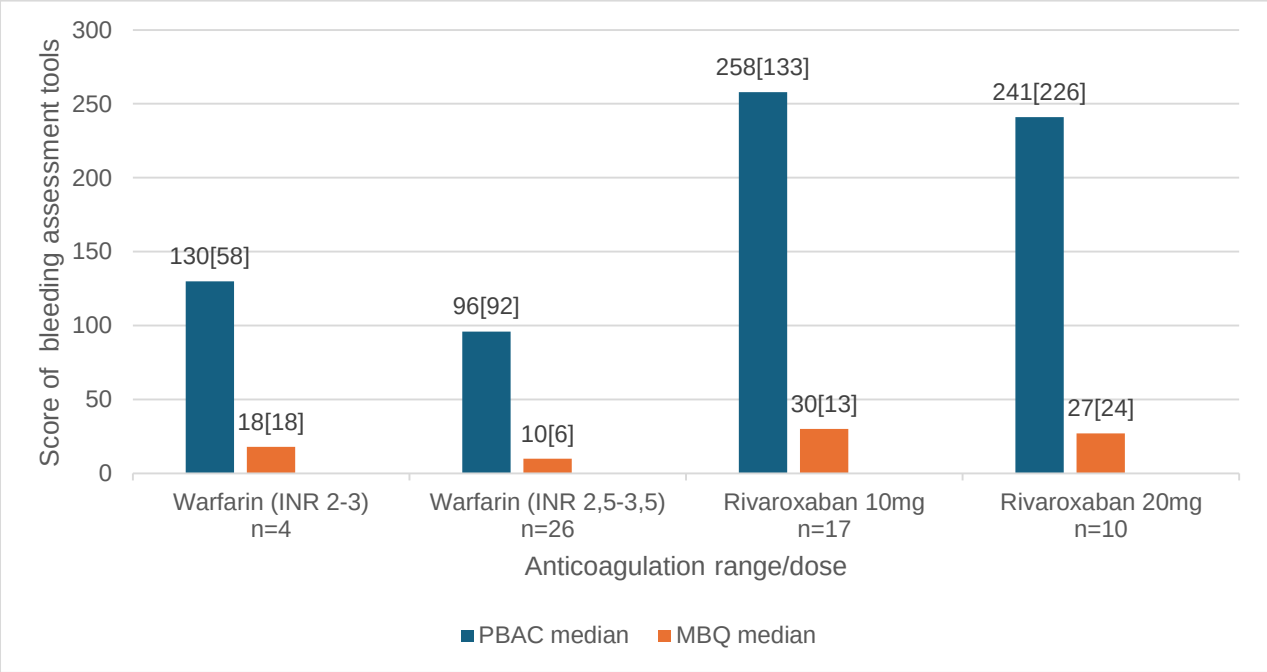


Figure 7. Median PBAC and MBQ scores according to anticoagulant range/dose

Median MBQ scores of impact on quality of life were significantly higher among participants on Rivaroxaban as compared to Warfarin for all 20 questions except question 19 on predictability of menstrual period start date (Supplementary Table 1). The key factors impacting on quality of life are described in Table 5. 44.0% (12) of women on Rivaroxaban were employed, women on Rivaroxaban were more likely to miss days of work because of menstrual bleeding as compared to Warfarin (0, 0.0%) ($p<0.001$). There were 2 (7.4%) women on Rivaroxaban who reported missing >13 days of work.

Table 5 MBQ factors impacting on women's quality of life, according to Warfarin and Rivaroxaban

Factor	**Total n=57**	**Warfarin n=30**	**Rivaroxaban n=27**	**p value**
Changing sanitary products at night, during sleep (MBQ Q5 score ≥1) (n, %)	23 (40.35%)	7 (23.33%)	16 (59.26%)	0.006
Passing of blood clots staining clothing (MBQ Q7 score ≥1) (n, %)	37 (64.91%)	13 (43.33%)	24 (88.89%)	<0.001
Pain related to menstrual period (MBQ Q8 score ≥1) (n, %)	27 (47.37%)	8 (26.67%)	19 (70.37%)	0.001
Difficulty with work because of menstrual bleeding (MBQ Q10 score ≥1) (n, %)	21 (36.84%)	5 (16.67%)	16 (59.26%)	0.002
No. of days avoiding family activities (MBQ Q12 score ≥1) (n, %)	22 (38.60%)	5 (16.67%)	17 (62.96%)	0.003
No. of days avoiding social activities (MBQ Q14 score ≥1) (n, %)	16 (28.07%)	5 (16.67%)	11 (40.74%)	0.141
Extreme concern about blood staining clothes (MBQ Q18, scale 0-10), median [IQR]	2.00 [6.80]	2.00 [2.00]	7.00 [7.00]	<0.001
Not being able to predict at all when period will end (MBQ Q20 score >1)	21 (36.84%)	5 (16.67%)	16 (59.26%)	0.001
Key: IQR, Inter- quartile range, MBQ, menstrual bleeding questionnaire				

Table 6 Characteristics of participants with and without iron deficiency

Variable	**Participants with iron deficiency n=27**	**Participants without iron deficiency n=3**
Duration on anticoagulation (months), median [IQR]	36.00 [9.00]	15.00 [96.00]
Menstrual cycle length on anticoagulation (days), median [IQR]	6.00[5.00]	9.00 [9.00]
PBAC Score, median [IQR]	171.00[221.00]	531.00 [471.00]
MBQ Score, median [IQR]	23.00 [20.00]	30.00 [9.00]
Haemoglobin (g/dL), mean ± SD	11.00 ± 2.69	12.27 ± 1.27
MCV, mean ± SD	83.83 ± 9.44	81.07 ± 9.06
Key: IQR, Inter- quartile range, SD, standard deviation, MBQ, menstrual bleeding questionnaire, PBAC, pictorial blood loss assessment chart , MCV, mean cell volume Diagnostic criteria for iron deficiency: ferritin of <30 µg/L or ferritin of 30-100 µg/L and transferrin saturation of <20%		

Iron studies were available in 30 participants of which 27 (90.0%) were classified as iron deficiency (Table 6.). Of the participants with iron deficiency, 12 (40.0%) were on Rivaroxaban and 15 (50.0%) on Warfarin.

Table 7 Univariate logistic regression analysis of heavy menstrual bleeding

Variable	**OR**	**95% CI**	**p value**
Duration on anticoagulation	0.73	0.20 -2.70	0.634
Previous history of bleeding	2.80	0.69-11.37	0.150
Contraception use	1.00	0.30-3.32	1.000
Co-morbidities	1.04	0.34-3.19	0.060
Rivaroxaban anticoagulation	5.03	1.40-18.12	0.014
Warfarin range (2.5-3.5)	0.33	0.03-3.37	0.368
Rivaroxaban dose (20mg)	0.15	0.01-1.66	0.121
Key: CI, confidence interval, OR, odds ratio			

On univariate analysis, the odds of heavy menstrual bleeding increased approximately 5-fold (OR 5.03, 95% CI 1.40-18.12, p<0.014) with Rivaroxaban (Table 7.).

5.2 Management

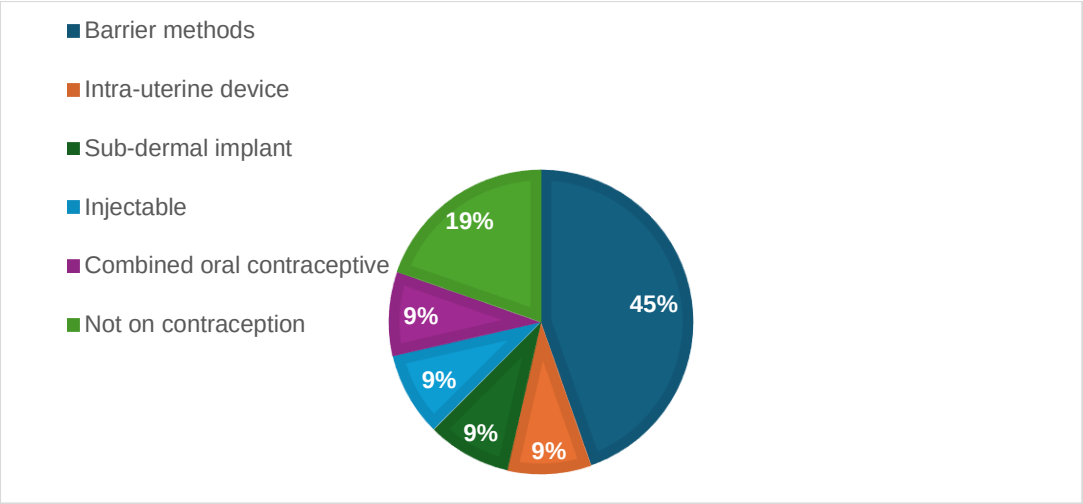


Figure 8. The use of contraception at baseline

On record review, contraception included barrier methods (n=26, 45.6%), intra-uterine contraceptives, (n=5, 8.8%), subdermal implants (n=5, 8.8%), contraceptive injection, (n=5, 8.8%), and combined oral contraceptive (n=5, 8.8%). (Fig 9.)

Twenty-nine (74.4%) participants on long term anticoagulation received management for heavy menstrual bleeding including its complication of iron deficiency (Table 8). The majority of participants with heavy menstrual bleeding were managed as out-patients and 3 (10.3%) required hospitalisation for red cell transfusions and/or tranexamic acid. In 8 (27.6%) women the anticoagulant was changed from Rivaroxaban to Warfarin (n=5) or Apixaban (n=3); following which 6 (75.0%) reported an improvement of symptoms. In a further 4 (13.8%) the dose of Rivaroxaban was reduced and anti-Xa levels monitored. This resulted in an improvement of symptoms in half. In 4 (13.8%) women referred to gynaecology for the management of heavy menstrual bleeding, symptoms were controlled with hormonal contraception alone.

Table 8 Management of heavy menstrual bleeding of study population

Treatment of HMB	**Number (n=29)**
Oral iron supplements (n, %)	23 (79.31%)
Intravenous iron infusion (n, %)	3 (10.34%)
Red cell transfusion (n, %)	3 (10.34%)
Tranexamic acid (n,%)	2 (6.90%)
Change of anticoagulant (n, %)	8 (27.58%)
Dose reduction of anticoagulation (n, %)	4 (13.79%)
Referral to gynaecology (n, %)	4 (13.79%)
Hospital admission (n, %)	3 (10.34%)
Key: HMB, heavy menstrual bleeding	

6. DISCUSSION

6.1 Incidence Rate of Heavy Menstrual Bleeding

This study, in a predominantly African ethnic population, found an incidence of heavy menstrual bleeding in women of child bearing age of 68.4% (95% CI 0.55-0.79). This finding is consistent with the incidence rates of 66-70% reported in European study populations (7, 8, 9). Cycle length increased significantly in participants after commencing anticoagulation, 6 [4] days as compared to 5 [2] days which is compatible with findings in the period study (9). Similar findings were noted in a study in 2015 which revealed an increase in menstruation from 6 (4.1-8.9) days vs. 5 (3.5-6.0) days previously, median (range), $p < 0.001$) as well as a study done in 2007 in where the mean duration of menstruation increased from 5.6 to 6.1 days ($p < 0.01$) (8,31).

In the current study, the median PBAC score was 155.0 [200.0] in women on anticoagulation for a median duration of 15.5 [78.0] months. This finding is comparable with an earlier study of women on long-term warfarin which reported a median PBAC score of 210 (range 14–1010) (26). In contrast, the more recent, TEAM-VTE study reported a lower median PBAC score following initiation of anticoagulation of 95.0 [221.0] for the first cycle (15). Moreover, the authors observed a non-significant decline in the rates of heavy menstrual bleeding over the follow-up six-month period. Future studies are indicated over consecutive menstrual cycles to assess the impact of anticoagulation beyond six-months on heavy menstrual bleeding and its impact on quality of life.

Due to the lower risk profile and ease of use associated with DOACs, their use has become more common in our setting, especially for patients with VTE disease. A greater incidence of heavy menstrual bleeding was noted in the participants on Rivaroxaban (85.19%) compared to

those on Warfarin (53.33%) ($p<0.010$). The median menstrual cycle length on anticoagulation was significantly longer in the Rivaroxaban group (9 days) compared to the Warfarin group (5 days). Blood loss was significantly greater in participants on Rivaroxaban, 193.60 [157.60] ml compared to those on Warfarin 83.20 [68.80] ml. These findings are in keeping with those described in the EINSTEIN trial as well as smaller cohort studies (8, 9, 11, 17). A significant difference in the duration of treatment of participants on Warfarin 80.00 [114.00] compared to those on rivaroxaban 8.00 [10.50] was observed. This can be attributed to the recent introduction of DOACs in our clinical setting and as well as a large group of women with valvular heart disease who require lifelong treatment with Warfarin. The increasing use of DOACs in our setting requires careful consideration in women in the reproductive age group. Moreover, owing to the reduced monitoring requirements of Rivaroxaban, symptoms and complications of heavy menstrual bleeding may be identified later as compared to Warfarin.

6.2 Risk Factors for heavy menstrual bleeding

The study identified Rivaroxaban anticoagulation as a significant risk factor for heavy menstrual bleeding (OR 5.03, 95% CI 1.40-18.12, $p=0.014$). Duration on anticoagulation was not a significant predictor for heavy menstrual bleeding. However, a non-significant decrease in heavy menstrual bleeding was noted with a treatment of >6 months, similar to the TEAM-VTE study which observed a non-significant decline in the rates of heavy menstrual bleeding over the follow-up six-month period (15). Previous bleeding history (and co-morbidities, including HIV were not associated with a significant risk for heavy menstrual bleeding on anticoagulation.

6.3 Impact of heavy menstrual bleeding on Quality of Life

Importantly, heavy menstrual bleeding was associated with a considerable negative impact on quality of life. The impact on a woman's quality of life is greatly under-estimated, even by the woman herself. In a setting where women headed house-holds or single income house-holds are common, the physical, social and psychological demands are notably increased. Mental health-care, energy levels and sense of well-being were often not viewed by the women as part of total health care. This study found that heavy menstrual bleeding had a significant impact on activities of daily living with participants experiencing difficulty with work, social activities, and family activities due to menstrual bleeding. These findings are consistent with those reported in the period study and TEAM VTE study (9). The MBQ score was significantly higher in the Rivaroxaban group (29.50) compared to the Warfarin group (10.00). Participants on Rivaroxaban were more likely to miss work as a result of heavy menstrual bleeding with reports of up to 13 days of work being missed. In a resource strained economy, this adds financial stresses which compounds the negative effect on quality of life.

Under -reporting of heavy menstrual bleeding is an important consideration. On participant interview, it was noted that women are not forthcoming about their symptoms, as it is assumed 'normal' unless specifically asked, especially regarding the passing of blood clots and many aspects of quality of life. Social stigma also discourages woman from discussing their bleeding tendencies. The most commonly reported symptoms of heavy menstrual bleeding, using the PBAC and MBQ were passing of blood clots (64.9%), pain related to menstrual period (47.4%), and difficulty with work due to menstrual bleeding (36.8%). The PBAC and MBQ represent useful tools for daily practice. These tools were easy to explain (with the use of translators where required) and had a high completion rate, however, the difficulty of administration without a translator or in a rural clinical setting must be considered.

The presentation of participants was extremely variable, ranging from asymptomatic to unable to fulfil activities of daily living with ease and severe iron deficiency anaemia requiring

hospitalisation. An important consideration is adherence to anticoagulation considering the negative impact of heavy menstrual bleeding on quality of life. 35% of women were receiving hormonal contraception prior to the study. As such the reported rates of heavy menstrual bleeding in this population may be higher.

6.4 Management of heavy menstrual bleeding and iron deficiency

Iron deficiency was an important complication of anticoagulant treatment. We however, did not observe a significant difference in rates of iron deficiency between women with and without heavy menstrual bleeding and Rivaroxaban and Warfarin. As woman on Rivaroxaban in this study were on anticoagulation for a significantly shorter duration as compared to Warfarin, laboratory parameters may under estimate the clinical presentation and experience of the woman with heavy menstrual bleeding.

In the study population iron deficiency was managed with oral iron supplements in the majority. Intravenous iron infusion and red cell transfusions were received in a small proportion of participants. In approximately a third of the participants, modifications in the anticoagulant were required in by switching to Warfarin or Apixaban, and/or by reducing the dose. The EINSTEIN-CHOICE study confirmed that reducing the dosage of anti-coagulation resulted in decreased heavy menstrual bleeding for extended treatment of VTE after completion of 6 to 12 months of anticoagulation (29). In the current study, anti Xa levels were monitored to confirm therapeutic treatment in woman who had a dose reduction from 20mg of Rivaroxaban to 10mg of Rivaroxaban. Additionally, the ongoing MEDEA trial is investigating switching to an alternative agent such as Dabigatran and Tranexamic acid in patients with significant heavy menstrual bleeding (30). 13.8% were referred to gynaecology for hormonal contraception. Contraception included combined oral contraception, injectable hormonal

contraception as well as hormonal intra-uterine devices. Treatment options are often at the discretion of the treating clinician, owing to the lack of data comparing treatment options, to guide management decisions in clinical practice.

6.5 Strengths and weaknesses

The main strength of this study is its prospective study design with a PBAC and MBQ survey completion rate of 98.3%. Moreover, this study was performed in a well-defined geographic population of predominantly African ethnicity. Women with bleeding disorders, or gynaecological lesions were excluded from the study. This study evaluated women on anticoagulation for a median of 15.5 [78.0] months and thus could assess for complications of heavy menstrual bleeding including iron deficiency and/or anaemia. Furthermore, this study consisted of a large subgroup of women on Warfarin (52.6%) in contrast to studies from high income countries where DOACs are the predominant anticoagulant. This study describes the heavy menstrual bleeding characteristics of 24 (42.1%) women with valvular heart disease who required an INR of 2.5-3.5. Previous studies have evaluated predominantly VTE, requiring an INR of 2.0-3.0 (8,26).

Our results must however be interpreted in light of certain limitations. First, the PBAC and MBQ were assessed over one menstrual cycle. Nonetheless, the PERIOD study which assessed PBAC and MBQ scores over two cycles did not show a significant difference between cycles one and two (9). Second, subgroup analysis according to the range of INR and dose of Rivaroxaban could not be assessed owing to the small number of participants in particular with an INR range of 2.0-3.0. Third, iron studies were not available at baseline. Moreover, iron

studies on anticoagulation were available in only half of the study participants which can be attributed to the underreporting of symptoms of heavy menstrual bleeding. Fourth, cycle length prior to starting anticoagulation was determined retrospectively. Recall bias, in particular for patients on treatment >6 months (n=42, 73.7%), could have resulted in an inaccurate assessment of prior cycle length. Nonetheless previous studies performed at initiation of anticoagulation, showed similar median cycle lengths (8,9,31). Finally, the study employed the semi-quantitative PBAC assessment to quantify menstrual blood loss. The PBAC, however, is widely used in clinical studies and has been associated with a sensitivity of 58–99% and a specificity 75–89% for scores above 100 for heavy menstrual bleeding (21). Lastly, the PBAC has been validated in several populations, including Hong Kong, United Kingdom, the United States, and Australia, with generally consistent results. However, further validation in African populations is still needed to confirm its applicability.

7. CONCLUSION

In conclusion, this study adds to the evidence that heavy menstrual bleeding is a frequent complication during anticoagulation therapy, which was associated with a considerable negative impact on quality of life. This was most significant for women on Rivaroxaban as compared to Warfarin. It is thus important for anticoagulation clinics to incorporate into daily practice counselling about the possible changes in the menstrual cycle length and bleeding, monitoring and appropriate treatment for heavy menstrual bleeding and its associated complications such as iron deficiency. Owing to the observational study design and small number of participants on subgroup analysis according to anticoagulant ranges/doses, the results of ongoing randomized trials are awaited to assessing the optimal interventions for heavy menstrual bleeding in this group of patients.

8. REFERENCES

1. James AH. Heavy menstrual bleeding: work-up and management. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):236-242.

2. Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding innongravid women of reproductive age. Int J Gynaecol Obstet. 2011;113(1):3–13.

3. DeLoughery E, Bannow BS. Anticoagulant therapy for women: implications for menstruation, pregnancy, and lactation. Hematology. 2022 Dec 9;2022(1):467–73.

4. National Guideline A. National Institute for Health and Care Excellence: Clinical Guidelines. In Heavy Menstrual Bleeding (update) National Institute for Health and Care Excellence (UK). Copyright (c) NICE 2018, 2018.

5. Brekelmans MP, Scheres LJ, Bleker SM, Hutten BA, Timmermans A, Buller HR, et al. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. Thromb Haemost. 2017;117:809–15.

6. Karlsson TS, Marions LB, Edlund MG. Heavy menstrual bleeding significantly affects quality of life. Acta Obstet Gynecol Scand. 2014;93:52-57.

7. Micaily I, Samuelson Bannow BT. VTE and anticoagulation in menstruating women. Thromb Update. 2021 Dec 1;5. 100088

8. De Crem N, Peerlinck K, Vanassche T, Debaveye B, Middeldorp S , Verhame P et al. Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. Thromb Res. 2015;136(4):749-753.

9. Patel JP, Nzelu O, Roberts LN, Johns J, Ross J, Arya R. How do anticoagulants impact menstrual bleeding and quality of life? - The PERIOD study. Res Pract Thromb Haemost 2023 Feb 7 2:100072

10. Deiker M, BAloyi SM, Coetzee, Haupt L. The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa. University of Free State- DSpace http://hdl.handle.net/11660/11504

11. Myers B, Webster A. Heavy menstrual bleeding on Rivaroxaban - Comparison with Apixaban. Br J Haematol. 2017 Mar 1;176(5):833–5.

12. Speed V, Patel JP, Arya R. Bleeding issues in women prescribed anticoagulation. Thromb Update. 2021 Dec 1;5:100068.

13. van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood. 2014;124(12):1968–1975.

14. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320–328.

15. de Jong CMM, Blondon M, Ay C, Buchmuller A, Beyer-Westendorf J, Biechele J, et al. Incidence and impact of anticoagulation-associated abnormal menstrual bleeding in women after venous thromboembolism. Blood. 2022 Oct 20;140(16):1764–73.

16. Ferreira M, Barsam S, Patel JP, Roberts N, Patel K, Arya R et al. Heavy menstrual bleeding on rivaroxaban. Br J Haematol. 2016;173(2):314–315.

17. Martinelli I, Lensing AW, Middeldorp S, Levi M, Westendorp J, van Bellen B, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood. 2016;127(11):1417–1425.

18. Scheres L, Brekelmans M, Ageno W, Ay C, Buller R, Eischenger S, 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(12):1581-1589.

19. Sriprasert I, Pakrashi T, Kimble T, Archer DF. Heavy menstrual bleeding diagnosis and medical management. Contracept Reprod Med. 2017 Jul 24;2:20. 47-4

20. Roy-O'Reilly M, McCullough LD. Sex differences in stroke: the contribution of coagulation. Exp Neurol. 2014 Sep;259:16-27.

21. Magnay JL, O'Brien S, Gerlinger C, Seitz C. A systematic review of methods to measure menstrual blood loss. BMC Womens Health. 2018 Aug 22;18(1):142.

22. Higham JM, O'brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97(8):734-739.

23. Spence, M., de Repentigny, K., Bowman, M., Hopman, W., Thibeault, L. and James, P. (2021), Validation of the pictorial blood loss assessment chart using modern sanitary products. Haemophilia, 27: 632-635.

24. Matteson, K. A., Scott, D. M., Raker, C. A., & Clark, M. A. (2015). The menstrual bleeding questionnaire: development and validation of a comprehensive patient-reported outcome instrument for heavy menstrual bleeding. BJOG : an international journal of obstetrics and gynaecology, 122(5), 681–689.

25. Fernandez-Jimenez MC, Moreno G, Wright I, Shih PC, Vaquero MP, Remacha AF. Iron Deficiency in Menstruating Adult Women: Much More than Anemia. Womens Health Rep. 2020 Dec 1;1(1):26–35.

26. Huq FY, Tvarkova K, Arafa A, Kadir RA. Menstrual problems and contraception in women of reproductive age receiving oral anticoagulation. Contraception. 2011;84(2):128–132.

27. Chen S, Liu J, Peng S, Zheng Y. LNG-IUS vs. medical treatments for women with heavy menstrual bleeding: A systematic review and meta-analysis. Front Med . 2022;9.

28. Beyer-Westendorf J, Michalski F, Tittl L, Hauswald-Dorschel S, Marten S. Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral anti-factor Xa inhibitor therapy: a case series. Lancet Haematol. 2016;3:480–488.

29. Boonyawat K, Lensing AWA, Prins MH, Beyer-Westendorf J, Prandoni P, Martinelli I, et al. Heavy menstrual bleeding in women on anticoagulant treatment for venous thromboembolism: Comparison of high- and low-dose rivaroxaban with aspirin. Res Pract Thromb Haemost. 2021 Feb 1;5(2):308–13.

30. Hamulyák EN, Wiegers HMG, Scheres LJJ, Hattin B, de Lange M, Timmermans A, et al. Heavy menstrual bleeding on direct factor Xa inhibitors: Rationale and design of the MEDEA study. Res Pract Thromb Haemost. 2021;5:223–230.

31. Själander A, Friberg B, Svensson P, Stigendal L, Lethagen S. Menorrhagia and minor bleeding symptoms in women on oral anticoagulation. J Thromb Thrombolysis. 2007;24(1):39-41.

APPENDICES

Appendix A: Patient information sheet

Appendix B: Consent form

Appendix C: Data collection sheet

Appendix D: Menstrual Bleeding Questionnaire (MBQ)

Appendix E: Pictorial Blood Loss Assessment Chart (PBAC)

Appendix F: HREC approval letter

Appendix G: Table 1S Median MBQ scores according to Warfarin and Rivaroxaban

Appendix H: Publication

Appendix A: Participant information sheet

INFORMATION DOCUMENT
Title of Study: Incidence and impact on quality of life of heavy menstrual bleeding in women on oral anticoagulant therapy at an academic hospital in Johannesburg, South Africa - A prospective cohort study

Good day.
My name is Naseerah Hassan and you are invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?
We have approached you because you are taking anticoagulation as part of your management. We would like to compare the heavy menstrual bleeding, and its impact on quality of life in women in women taking Rivaroxaban and Warfarin.

What will happen to me if I take part in this study and what do I have to do?
You will sit with the primary investigator and she will ask you a series of questions regarding your diagnosis, treatment, and assist you to fill in a bleeding assessment form and a questionnaire on how your menstrual bleeding affects your quality of life. It will take ~1 hour and will be done on the day you visit the clinic for your follow up appointment.

What are the side effects or risks of taking part?
There are no risks when participating in this study.

What are the Benefits for participating in the study?
This information will help us to know if women bleed more on certain types of anticoagulation and if it affects their quality of life. We can subsequently treat this and attempt to improve their quality of life and symptoms due to bleeding. There will be no direct benefits to the participants.

Is there reimbursement for study participation?
There will be no reimbursements and there will be no costs to you for any of the tests in the study.

Do I have to take part?
Your participation in this study is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this Information Sheet to keep and will be asked to sign an informed consent form. Should you wish to discontinue participation, you may do so freely at any time and without giving a reason. If you choose not to participate or to withdraw from the study this will not affect the care and treatment that you receive from the anticoagulation clinic in any way.

Will my taking part in this study be kept confidential?
All information obtained during this study will be kept confidential. All your medical information will remain filed at the clinic and only authorized study investigators will have access to this information.

Data may be reported in scientific journals and will not include any information that identifies you as a participant in this study.

Who is organizing and funding the research?
This study is being conducted by the University of Witwatersrand, Department of Haematology.

Whom do I call if I have questions or problems?
Principal Investigator:
Dr Naseerah Hassan
Telephone no. 011 489 8568
e-mail drnsrhassan@gmail.com

Supervisor:
Prof Elise Schapkaitz
Telephone no. 011 489 8568
e-mail elise.schapkaitz@nhls.ac.za

Appendix B: Consent form

PARTICIPANT CONSENT SHEET

Project Title : **Incidence and impact on quality of life of heavy menstrual bleeding in women on oral anticoagulant therapy at an academic hospital in Johannesburg, South Africa - A prospective cohort study**

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Principal Investigator:
Dr Naseerah Hassan
Telephone no. 011 489 8568
e-mail drnsrhassan@gmail.com

Supervisor:
Prof Elise Schapkaitz
Telephone no. 011 489 8568
e-mail elise.schapkaitz@nhls.ac.za

Ethics chairperson: Professor Paul Ruff
Ethics secretary:
Mapula Ramaila
011 717 2656/2700/1234 or by
email Mapula.Ramaila@wits.ac.za or HREC-Medical.ResearchOffice@wits.ac.za

Name of Participant: _____
Date: _____
Place: _____
Signature or mark _____

Witnessed by:

Name of Witness: _____
Signature: _____
Date: _____

Appendix C: Data collection sheet

Data Collection Sheet

Time interval:

Study number:

Characteristics:

Age (years):

Exclsuion criteria:"

□ Pregnancy □ Premature ovarian failure □ cervical/uterine pathology □pre-neoplastic lesions or active malignancy □creatinine clearance <30ml/min

Ethnicity : (self report) : □ Black □ Coloured □ Indian □ White

Indications for Anticoagulation:

□ non-valvular □ valvular heart disease □VTE □Arterial disease

Current anticoagulation :

□ Warfarin (INR 2-3) □ Warfarin (INR 2.5-3.5) □Rivaroxaban 10mg □ Rivaroxaban 20mg

Duration of anticoagulation (months):

Other medication :

□ Anti-platelet agents □Non-steroidal anti-inflammatories □Anti-metabolites □Other

Menstrual history:

Type of sanitary wear :

Sanitary pads	Tampons

Duration of menstruation prior to anticoagulation (days):

Current duration of menstruation(days):

Contraception use: □ Yes □ No

□ intrauterine device-IUS □ Subdermal implant □ Progestin-only pill

□ Combined oral contraceptive □ contraceptive injection DMPA/Noristerat

□ Tranaxemic acid □ Surgery

Management of HMB on anticoagulation: Any changes noted in menstruation after starting anticoagulation:

□ Levonorgestrel intrauterine device □ Subdermal implant □ DMPA □ Progestin-only pill

□ Combined oral contraceptive □ Tranexamic acid/antifibrinolytics □ Surgery

Lab investigations :

Laboratory No	Date	FBC	Iron Studies	HIV

Appendix D: Menstrual Bleeding Questionnaire (MBQ) (6)

Appendix S1: The Menstrual Bleeding Questionnaire

These questions ask for details about your period. Periods can be different from month to month. Please make sure you read all of the options. For this questionnaire, period refers to any bleeding that you have from your vagina, even if it is irregular.

Some of the questions may sound similar. Just read through each question carefully and give your best answer.

You may have other medical problems that could affect your answers. Please try to focus on questions and answers **ONLY** as they relate to your period.

During the past month, did you have ANY bleeding?

Yes..... [ ]

No..... [ ]

If you answered "YES" continue to question 1.
If you answered "NO" skip to question 10.

1. During the past month, how would you describe your periods?

Very Light.....	[ ]0
Light.....	[ ]1
Moderate.....	[ ]2
Heavy.....	[ ]3
Very Heavy.....	[ ]4

1. During the past month, how would you describe your periods?

Very Light.....	[ ]0
Light.....	[ ]1
Moderate.....	[ ]2
Heavy.....	[ ]3
Very Heavy.....	[ ]4

Instructions for questions 2, 3, and 4
"High absorbency" sanitary productes means any type of tampon or pad that is NOT a thin pantiliner.

"Soaked" means completely or almost completely stained and filled with blood.

2. On your heaviest day of bleeding during the past month, how many high absorbency sanitary products did you soak (either completely or almost completely)?

0.....	[ ]0
1-4.....	[ ]1
5-8.....	[ ]2
9-12.....	[ ]3
13-16.....	[ ]4
More than 16.....	[ ]5

3. During the past month, how often did you need to wear either an incontinence brief or more than one high absorbency sanitary product (either more than one pad, a pad and a tampon, more than one tampon) at a time to contain your bleeding?

Never.....	[ ]0
1-3 times.....	[ ]1
4-6 times.....	[ ]2
7-10 times.....	[ ]3
11 times or greater.....	[ ]4

4. During the past month, how many times have you had an episode of bleeding that soaked through your "outer" clothes (pants, skirt, dress)?

Never	[ ]0
1-3 times	[ ]1
4-6 times	[ ]2
Greater than 6 times	[ ]3

5. During the past month, how many times did you need to get out of bed in the middle of night (or during sleep hours) to change your sanitary products?

Never	[ ]0
1-3 times	[ ]1
4-6 times	[ ]2
7-10 times	[ ]3
11 times or greater	[ ]4

6. During the past month, how many times did you pass blood clots (clumps of blood)?

Never	[ ]0
1-3 times	[ ]1
4-6 times	[ ]2
Greater than 6 times	[ ]3

7. During the past month, how often did passing blood clots (clumps of blood) stain your clothing?

Never	[ ]0
1-3 times	[ ]1
4-6 times	[ ]2
Greater than 6 times	[ ]3

8. Please fill in the following statement about pain related to your period. During the past month, my period was associated with…

No pain	[ ]0
Slight pain	[ ]1
Moderate pain	[ ]2
Severe pain	[ ]3

9. During the past month, how many weeks did your periods last?

1 week or less out of 4 weeks	[ ]0
More than 1 week, less than 2 weeks out of 4 weeks	[ ]1
More than 2 weeks, less than 3 weeks out of 4 weeks	[ ]2
More than 3 weeks out of 4 weeks	[ ]3

10. During the past month, on how many days do think your work at your job suffered because you were bleeding?

I am currently not working outside of the home	[ ]**
Never, my bleeding does not affect my work	[ ]0
1-3 days	[ ]1
4-8 days	[ ]2
9-12 days	[ ]3
13 days or more	[ ]4

11. During the past month, on how many days did you miss work because you were bleeding?

I am currently not working outside of the home	[ ]**
Never, my bleeding does not affect my work schedule	[ ]0
1-3 days	[ ]1
4-8 days	[ ]2
9-12 days	[ ]3
13 days or more	[ ]4

12. During the past month, on how many days did you avoid family activities (grocery shopping, household chores) when you thought you would be bleeding?

Never	[ ]0
1-3 days	[ ]1
4-8 days	[ ]2
9-12 days	[ ]3
13 days or more	[ ]4

13. During the past month, when would you carry sanitary products (pads, tampons) with you (in your pocket, in your bag)?

Every day, in case I had any bleeding	[ ]2
On the days when I had bleeding and on days when I guessed that I might have bleeding	[ ]1
Only on the days that I had bleeding	[ ]0

14. During the past month, on how many days did you avoid social activities (such as getting together with friends, going shopping for fun, going sight-seeing) when you thought you would be bleeding?

Never	[ ]0
1-3 days	[ ]1
4-8 days	[ ]2
9-12 days	[ ]3
13 days or more	[ ]4

15. During the past month, on how many days did you plan <u>your</u> activities (work, social, or family) based on whether or not there was a bathroom nearby?

Never	[ ]0
1-3 days	[ ]1
4-8 days	[ ]2
9-12 days	[ ]3
13 days or more	[ ]4

16. During the past month, on how many days did you bring extra clothes with you (to work, out shopping) in case you had staining from your period?

Never	[ ]0
1-3 days	[ ]1
4-6 days	[ ]2
Greater than 6 days	[ ]3

17. During the past month, on how many days did you choose what to wear based on whether or not you were bleeding?

Never	[ ]0
1-3 days	[ ]1
4-8 days	[ ]2
9-12 days	[ ]3
13 days or more	[ ]4

18. On a scale of 0-10, with 0 being no concern at all and 10 being extremely concerned, please rate your overall concern about bleeding staining your clothes.

_____

19. During the past month, would you say that your period start date was…

Completely predictable	[ ]0
Somewhat predictable	[ ]1
Not at all predictable	[ ]2

20. During the past month, would you say that your period end date was…

Completely predictable	[ ]0
Somewhat predictable	[ ]1
Not at all predictable	[ ]2

** for women who are not working outside of the home, impute the score given on question number 12

Total Menstrual Bleeding Questionnaire Score is obtained by summing the values obtained on questions 1-20.

Appendix E: Pictorial Blood Loss Assessment Chart (PBAC) (22 and 23)

Pictorial blood loss assessment chart (Pads)

Each row represents a day of the month

Count the number of sanitary pads you use each day (24 hour period) and indicate with a line.

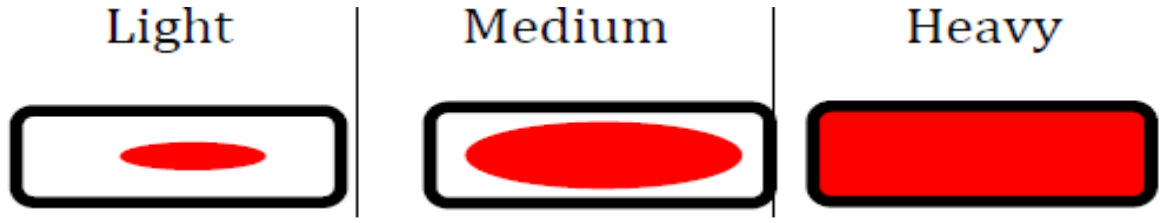
Bleeding between periods - If you also experienced bleeding between periods that required sanitary protection please record this on the relevant days.

Clots – if you pass clots, please indicate this on the relevant days and the approximate size.

Flooding – if you experience any episodes of 'flooding'/overflowing/staining of clothing/underwear please indicate the number of episodes on the relevant days.

Double protection – if you have used both a pad and tampon simultaneously and both sanitary items were stained with blood don't forget to include both sanitary items on the chart.

The score will be completed by the study investigator.



Day	Regular pad			Pad for heavy flow			Overnight pad			Clots		Flooding	Score
	Light Flow	Med Flow	Heavy Flow	Light Flow	Med Flow	Heavy Flow	Light Flow	Med Flow	Heavy Flow	21mm	27mm		
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
12													
13													
14													
15													
16													
17													
18													
19													
20													
21													
22													

23													
24													
25													
26													
27													
28													
29													
30													
31													

TABLE 1 Validated pictorial blood loss assessment chart (PBAC) pad scoring guide

Pad	Type	Mean blood absorption (mL)	New PBAC score
	Regular	3.12 mL (± 1.53 SD)	2
	Heavy	4.45 mL (± 2.31 SD)	3
	Night	7.73 mL (± 4.57 SD)	4
	Regular	10.43 mL (± 2.98 SD)	9
	Heavy	12.75 mL (± 2.63 SD)	13
	Night	21.49 mL (± 6.39 SD)	20
	Regular	18.09 mL (± 3.51 SD	18
	Heavy	23.99 mL (± 5.83 SD)	24
	Night	38.05 mL (± 5.90 SD)	40
Flooding	Regular	22.38 mL (± 2.16 SD)	25
	Heavy	31.89 mL (± 4.56 SD)	34
	Night	47.00 mL (± 3.25 SD)	55

The original scoring system from Higham et al[4] was adjusted for use of the AllNighter® Extra Heavy CleanWear® Ultra Thin Heavy Flow and CleanWear® Ultra Thin Regular Flow (U by Kotex®; Kimberly-Clark; Mississauga; Ontario) products. Mean blood absorption is the mean amount of blood (mL) required to achieve the level of saturation indicated by the corresponding pictogram (± standard deviation, SD). The new validated PBAC Scores for each pad were adjusted so that 80 mL of blood loss corresponded with a PBAC score of 100.

Pictorial blood loss assessment chart (Tampons)

Each row represents a day of the month

Count the number of tampons you use each day (24 hour period) and indicate with a line.

Bleeding between periods - If you also experienced bleeding between periods that required sanitary protection please record this on the relevant days.

Clots – if you pass clots, please indicate this on the relevant days and the approximate size.

Flooding – if you experience any episodes of 'flooding'/overflowing/staining of clothing/underwear please indicate the number of episodes on the relevant days.

Double protection – if you have used both a pad and tampon simultaneously and both sanitary items were stained with blood don't forget to include both sanitary items on the chart.

The score will be completed by the study investigator.

Day	Regular tampons			Super/super plus tampons			Clots		Flooding	Score
	Light flow	Med flow	Heavy flow	Light flow	Med flow	Heavy flow	21mm	27mm		
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										

25										
26										
27										
28										
29										
30										
31										

TABLE 2 Validated pictorial blood loss chart (PBAC) tampon scoring guide

Tampon	Type	Mean blood absorption (mL)	New PBAC score
	Regular	.77 mL (± .47 SD)	1
	Super	.80 mL (± .40 SD)	1
	Regular	2.17 mL (± .68 SD)	2
	Super	3.11 mL (± 1.48 SD)	3
	Regular	3.01 mL (± .67 SD)	3
	Super	4.91 mL (± 1.76 SD)	4
Flooding	Regular	3.54 mL (± .44 SD)	4
	Super	6.62 mL (± 1.50 SD)	7

The original scoring system from Higham et al[4] was adjusted for use of the Click® Tampons Regular and Super Compact (U by Kotex®; Kimberly-Clark; Mississauga; Ontario). The pictograms above do not look like tampons as the same pictograms were used for pads and tampons when participants scored. Mean blood absorption is the mean amount of blood (mL) required to achieve the level of saturation indicated by the corresponding pictogram (± standard deviation, SD). The new validated PBAC Scores for each tampon were adjusted so that 80 mL of blood loss corresponded with a PBAC score of 100.

Appendix F: HREC Approval letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Naseerah Hassan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M230809 MED23-07-085

NAME: (Principal Investigator)	Dr Naseerah Hassan
DEPARTMENT:	Molecular Medicine and Haematology
DEGREE:	Master of Medicine in Haematological Pathology
PROJECT TITLE:	*Incidence and impact on quality of life of heavy menstrual bleeding in women on oral anticoagulant therapy at an academic hospital in Johannesburg, South Africa - A prospective cohort study*
DATE CONSIDERED:	25/08/2023
DECISION:	Approved unconditionally
CONDITIONS:	This approval applies only to the study sites listed in Annex 1 attached. Further sites may be added on presentation of evidence of management approval to the HREC (Medical)
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - Nicoleen.Potgieter@wits.ac.za
SUPERVISOR:	Prof E. Schapkaitz and Dr N. Ncete
APPROVED BY:	Professor Paul Ruff, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/11/2023 **EXPIRY DATE:** 13/11/2028

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore be due in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

14/11/2023
Date

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Annex 1

Protocol No. M230809 MED23-07-085 **Dr Naseerah Hassan**

Study sites approved under this Clearance Certificate

Study sites	Date of HREC (Med) Approval
1. Charlotte Maxeke Johannesburg Academic Hospital	13/11/2023

Professor Paul Ruff
Chair: Human Research Ethics Committee (Medical)
University of the Witwatersrand, Johannesburg

Date: 13/11/2023

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix G: Median MBQ scores according to Warfarin and Rivaroxaban

Table 1S Median MBQ scores according to Warfarin and Rivaroxaban

Factor	Total n=57	Warfarin n=30	Rivaroxaban n=27	p value
Description of menstruation (light to heavy) (MBQ Q1, scores 0-4) median [IQR]	3.00 [2.00]	2.00 [2.00]	3.00 [1.50]	0.008
No. of sanitary products soaked (MBQ Q2, scores 0-5) median [IQR]	2.00 [1.00]	1.00 [2.00]	2.00 [1.00]	<0.001
Wearing an incontinence brief or more than one sanitary product at a time (MBQ Q3, scores 0-5) median [IQR]	1.00 [1.00]	0.00 [1.00]	1.00 [2.00]	0.008
Soaking through outer clothes (MBQ Q4, scores 0-3) median [IQR]	0.00 [1.00]	0.00 [0.00]	1.00 [1.00]	<0.001
Changing sanitary products at night, during sleep (MBQ Q5, scores 0-3) median [IQR]	0.00 [1.00]	0.00 [0.00]	1.00 [1.00]	0.006
Passing of blood clots (MBQ Q6, scores 0-3) median [IQR]	1.00 [2.00]	0.00 [1.00]	2.00 [1.00]	<0.001
Passing of blood clots staining clothing (MBQ Q7, scores 0-3) median [IQR]	1.00 [1.00]	0.00 [1.00]	1.00 [1.00]	<0.001
Pain related to menstrual period (MBQ Q8, scores 0-3) median [IQR]	0.00 [2.00]	0.00 [1.00]	1.00 [2.00]	0.006
Duration of period in weeks over last month (MBQ Q9, scores 0-3) median [IQR]	1.00 [1.00]	0.00 [1.00]	1.00 [1.50]	0.035
Difficulty with work because of bleeding (MBQ Q10, scores 0-4) median [IQR]	0.00 [1.00]	0.00 [0.00]	1.00 [2.00]	0.001
No. of work days missed due to bleeding (MBQ Q11, scores 0-4) median [IQR]	0.00 [0.00]	0.00 [0.00]	0.50 [1.00]	<0.001
No. of days avoiding family activities (MBQ Q12, scores 0-4) median [IQR]	0.00 [1.00]	0.00 [0.00]	1.00 [0.00]	0.001
Carrying extra sanitary products (MBQ Q13, scores 0-2) median [IQR]	0.00 [1.00]	0.00 [0.00]	2.00 [1.00]	<0.001
No. of days avoiding social activities (MBQ Q14, scores 0-4) median [IQR]	0.00 [1.00]	0.00 [0.00]	0.00 [1.00]	0.042
Planning activities around availability of a bathroom (MBQ Q15, scores 0-4) median [IQR]	0.00 [1.00]	0.00 [0.00]	1.00 [0.00]	0.001
Carrying extra clothes in case of staining (MBQ Q16, scores 0-3) median [IQR]	0.00 [1.00]	0.00 [0.00]	1.00 [2.00]	<0.001
Choice of clothing depending on bleeding (MBQ Q17, scores 0-4) median [IQR]	1.00 [1.00]	0.00 [1.00]	1.00 [2.00]	0.013
Extreme concern about blood staining clothes (MBQ Q18, scale 0-10), median [IQR]	2.00 [7.00]	2.00 [2.00]	7.00 [7.00]	<0.001
Not being able to predict when period will start (MBQ Q19, scores 0-2) median [IQR]	1.00 [1.00]	1.00 [0.00]	1.00 [1.00]	0.072
Not being able to predict at all when period will end (MBQ Q20, scores 0-2) median [IQR]	1.00 [1.00]	1.00 [0.00]	2.00 [1.00]	<0.001
Key: IQR, Inter- quartile range, MBQ, menstrual bleeding questionnaire				

Appendix H: Publication

Original Research Article

Clinical and Applied Thrombosis/Hemostasis
Volume 30: 1-8

DOI: 10.1177/10760296241281366
journals.sagepub.com/home/cat

Incidence and Impact on Quality of Life of Heavy Menstrual Bleeding in Women on Oral Anticoagulant Therapy

Naseerah Hassan, MD[1], Elise Schapkaitz, PhD[1], Haroun Rhemtula, MD, FCOG, MMED[2], and Nolukholo Ncete, MD, FCPATH, MMED[1]

Abstract

Introduction: Heavy menstrual bleeding affects up to two thirds of women on oral anticoagulation. The rates of heavy menstrual bleeding, its impact on quality of life and associated risk factors in women attending anticoagulation clinics in South Africa are largely unknown.

Materials and Methods: A prospective cohort study was performed over an eight-month period in women on Warfarin (n = 30) and Rivaroxaban (n = 27) for a median [interquartile range] duration of 15.5 [78.0] months attending an anticoagulation clinic in Johannesburg, South Africa. Heavy menstrual bleeding was assessed over one menstrual cycle using the validated pictorial blood loss assessment charts (PBAC) and the menstrual bleeding questionnaire (MBQ).

Results: In this population of predominantly African ethnicity, with a median age of 39 [8] years, 39 (68.4%) women experienced heavy menstrual bleeding, defined as a PBAC score of >100. Median cycle length on anticoagulation and MBQ scores were significantly higher among women with a PBAC score of >100 ($p > 0.05$). Univariate analysis identified Rivaroxaban as a risk factor for heavy menstrual bleeding (OR 5.03, 95% CI 1.40–18.12). Heavy menstrual bleeding required treatment in 29 (74.4%) women which included management of iron deficiency, anti-fibrinolytics, modification of anticoagulation and hormonal contraception.

Conclusion: Heavy menstrual bleeding was associated with a considerable negative impact on quality of life. This was most significant for women on Rivaroxaban as compared to Warfarin. It is essential to monitor and appropriately treat heavy menstrual bleeding in at risk women on anticoagulant treatment.

Keywords

heavy menstrual bleeding, warfarin, rivaroxaban, iron deficiency, pictorial blood loss assessment chart, menstrual bleeding questionnaire

Date received: 3 August 2024; revised: 19 August 2024; accepted: 21 August 2024.

Introduction

Heavy menstrual bleeding affects approximately 15–30% of women in the reproductive age group.[1] Objectively, heavy menstrual bleeding is defined as the quantitative measurement of more than 80 ml of blood loss per cycle. The International Federation of Gynaecology and Obstetrics (FIGO) defines heavy menstrual bleeding as an increase in frequency, irregularity, duration and volume of menstrual blood loss as well as intermenstrual bleeding.[2] This is based on visualization of clots of more than one inch in diameter, a low ferritin of <20 ng/mL and/or the need to change sanitary pads at least every hour.[3] In clinical practice, accurate quantification is difficult. A more

[1] Dept. of Molecular Medicine and Hematology, Charlotte Maxeke Johannesburg Academic Hospital, National Health Laboratory System Complex and University of the Witwatersrand, Johannesburg, South Africa
[2] Dept. of Obstetrics, Charlotte Maxeke Johannesburg Academic Hospital and University of the Witwatersrand, Johannesburg, South Africa

Corresponding Author:
Elise Schapkaitz, Dept. of Molecular Medicine and Hematology, Charlotte Maxeke Johannesburg Academic Hospital, National Health Laboratory System Complex and University of the Witwatersrand, South Africa.
Email: Elise.schapkaitz@wits.ac.za

practical definition which has been suggested is heavy menstrual bleeding that affects a woman's physical, emotional and social quality of life.[4]

Oral anticoagulant treatment for the management and prevention venous thrombo-embolism (VTE) is associated with an increased risk of bleeding, including heavy menstrual bleeding.[5] While, heavy menstrual bleeding has been reported to affect up to two thirds of women on anticoagulation, few studies, however, have assessed heavy menstrual bleeding specifically as an outcome of anticoagulant use.[6] A retrospective study conducted in 104 women in Belgium, reported heavy menstrual bleeding in 70.2% of anticoagulated women.[7] A recently conducted case-control study in the United Kingdom reported a significantly increased median duration of menstrual bleeding from five to six days in anticoagulated women ($p < 0.05$). This was associated with a negative impact on quality of life, including avoiding social activities, bleeding that soaked outer clothing and unpredictable cycles, as compared to the control group of women.[8]

Oral anticoagulants include vitamin K antagonists and direct oral anticoagulants (DOAC). DOAC have a lower risk of major bleeding, in particular intracranial haemorrhage, as compared to vitamin K antagonists. According to pooled safety data from phase 3 randomized trials in patients with VTE, DOAC were associated with a lower risk of major bleeding (odds ratio [OR] 0.6, 95% confidence interval [CI] 0.5-0.9), and a similar risk of gastrointestinal bleeding (OR 1.1, 95% CI 0.6-2.0) as compared to vitamin K antagonists. In patients with non-valvular atrial fibrillation the risk for gastrointestinal bleeding, however, was higher with DOAC.[9] Following the wide-spread use of the DOACs, case series and small cohort studies emerged also reporting increased rates of heavy menstrual bleeding compared with vitamin K antagonists.[7,8,10] In particular, an increased risk of heavy menstrual bleeding was described in the subgroup of women treated with factor Xa inhibitors as compared to women treated with vitamin K antagonists.[8,11] Subsequently, research has been performed to determine the risks associated with different classes of factor Xa inhibitors. An increase in heavy menstrual bleeding in women on Rivaroxaban, as compared to Warfarin has been described.[12] This finding was confirmed in post hoc analyses of the EINSTEIN trial which reported increased rates of heavy menstrual bleeding for Rivaroxaban (hazard ratio, 2.1; 95% CI, 1.6–2.9) as compared to vitamin K antagonists.[13] An American study, RAMBLE (NCT02829957) is currently investigating the rates of heavy menstrual bleeding between Rivaroxaban and Apixaban to determine whether there is indeed a class effect.

Heavy menstrual bleeding is underreported by women attending anticoagulation clinics.[14] Women are often unaware of the extent of menstrual blood loss and often seek medical care only when their quality of life is affected or as a result of iron deficiency anaemia.[15] According to a Spanish study, patients' primary concerns were the effects on functional, professional, social and family responsibilities.[16] Iron deficiency anaemia is an important complication of heavy menstrual bleeding which can lead to reduced cognitive ability, physical strength and immunity. In particular, iron deficiency anaemia impairs attention, memory, and learning. Treatment options including hormone contraception, anti-fibrinolytic agents, haematinics or uterine surgical interventions which can result in an improvement of symptoms.[17] However, data comparing treatment options, to guide management decisions in clinical practice, are lacking.

The rates of heavy menstrual bleeding, its impact on quality of life and associated risk factors in women attending anticoagulation clinics in South Africa are largely unknown.[18] A prospective cohort study was performed to assess the incidence and symptoms of heavy menstrual bleeding using the validated pictorial blood loss assessment charts (PBAC) and the menstrual bleeding questionnaire (MBQ). Moreover, this study aimed to identify risk factors for heavy menstrual bleeding on oral anticoagulation in order to improve the management of this subgroup.

Methods

Study Design and Population

A prospective study was performed over an eight-month period from 1 November 2023 to 30 June 2024 at the Anticoagulation Clinic at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and National Health Laboratory Service in Johannesburg, South Africa. Written informed consent was obtained from all study participants, and the study protocol was approved by the Institutional Review Board (M-230809).

The study included consecutive women, aged 18–45 years old, who were prescribed one of the following oral anticoagulants: Rivaroxaban 20 mg, Rivaroxaban 10 mg, Warfarin (international normalised ratio, INR 2–3) or Warfarin (INR 2.5–3.5). A bleeding, menstrual, gynaecological and obstetric history was obtained and the following were excluded: pregnant women, postmenopausal women with premature ovarian failure, women with laboratory confirmed bleeding disorders, women with cervical or uterine preneoplastic lesions or active malignancy and women with creatinine clearance of <30 mL/min or liver disease.

Data Collection

At enrolment the following data was collected on predesigned data collection sheets: demographic characteristics, indications for anticoagulation, current anticoagulant therapy, dose and duration, and concomitant medications. A medical history of minor, clinically relevant non major and major bleeding while on anticoagulation was collected. A menstrual history over one-cycle was collected, namely the type of sanitary products and the average length of the menstrual cycle prior to commencing anticoagulation.

Participants completed a MBQ using the MBQ tool developed and validated by Matteson for one menstrual cycles.[19] The MBQ consists of 20 questions regarding bleeding symptoms, menstrual pain, and quality of life. The responses were added to obtain a minimum score of 0 and a maximum score of 75. Participants self-completed a PBAC daily over one

menstrual cycle during the study using the PBAC tool developed by Higham et al and subsequently modified by Spence et al[20,21] Participants were required to record the number of sanitary products used daily and the degree to which these were soaked on a PBAC, which provided a visual reference. This was returned at completion. The total menstrual blood loss in millilitres was estimated by dividing the total PBAC score by 1.25. According to this visual score, a PBAC score of 100 equates to 80 ml of menstrual blood loss indicating heavy menstrual bleeding. Management of heavy menstrual bleeding as well as supporting laboratory investigations were documented from record review. Iron deficiency was defined according to diagnostic criteria: ferritin of <30 µg/L or transferrin saturation of <20%, and ferritin of 30–100 µg/L.[22]

Data Analysis

Considering an estimated incidence of heavy menstrual bleeding of 65% in women on anticoagulation, a sample size of 60 was calculated at a CI of 90% using Stata software (Texas, USA).[1,6] Data was analysed using Statistica 13.2 software (California, USA). Normally distributed, continuous data was presented as mean ± SD and variables with non-Gaussian distribution as median [interquartile range (IQR)]. Comparisons for numerical measurements between subgroups were performed using a parametric unpaired t-test or non-parametric Mann-Whitney test. Comparisons for categorical measurements were performed using chi-square test or Fisher's exact test when necessary. Univariate logistic regression analysis was conducted to identify risk factors for heavy menstrual bleeding with the correspondent unadjusted OR and 95% CI. Significance level was set at <0.05.

Results

Clinical and Laboratory Characteristics

During the study 65 women on anticoagulation were interviewed of whom 57 were eligible for inclusion (Figure 1). The baseline demographics and clinical characteristics of the study participants are described in Table 1. The majority of the women (median [IQR] age of 39 [8] years) were of African ethnicity (n = 52, 91.2%) in keeping with the demographics of the population served by CMJAH. VTE (n = 31, 54.4%) was the most common indication for anticoagulation, followed by valvular heart disease (n = 24, 42.1%). At enrolment, the median duration of anticoagulation was 15.5 [78.0] months. Fifteen (26.3%) women were living with HIV, consistent with the national rates of infection. There were 35 (61.4%) participants on concomitant medications. No participants were receiving concomitant antiplatelet therapy. There were 27 (90.0%) participants diagnosed with iron deficiency on iron studies, performed in 30 participants (Table 2).

Menstrual Cycle Characteristics and Impact on Quality of Life

The median cycle length was 6 [4] days on anticoagulation as compared to 5 [2] days prior to commencing anticoagulation ($p < 0.001$). The median total estimated menstrual blood loss was 120.0 [160.0] ml and the median PBAC score was 155.0

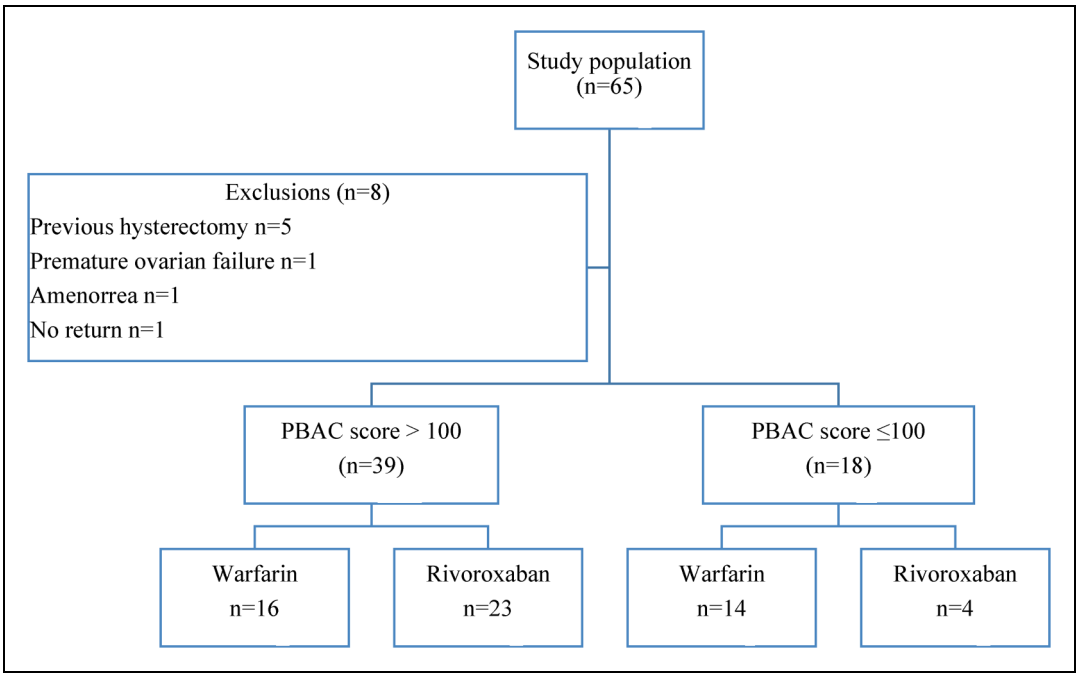


Figure 1. Flow diagram of study participants.

Table 1. Baseline Characteristics of Study Population.

Demographics	n = 57
Age at study entry (years), median [IQR]	39.00 [8.00]
Ethnicity	
African (n,%)	52 (91.22%)
Non- African (n,%)	5 (8.77%)
Characteristics	
Anticoagulant	
Warfarin (n,%)	30 (52.63%)
Rivaroxaban (n,%)	27 (47.37%)
Indication for anticoagulation	
Venous thrombo-embolic disease (n,%)	31 (54.39%)
Valvular heart disease (n,%)	24 (42.10%)
Non- valvular heart disease (n,%)	2 (3.51%)
Duration of anticoagulation (months), median [IQR]	15.50 [78.00]
Co-morbidities	
Cardiac conditions (n,%)	6 (10.5%)
Autoimmune conditions (n,%)	4 (7.02%)
Neurological conditions (n,%)	2 (3.50%)
HIV infected (n,%)	15 (26.32%)
Concomitant medications (n,%)[1]	35 (61.40%)

Key: IQR, Inter- quartile range, HIV, Human Immunodeficiency virus.
[1]Of the participants on warfarin, no participants were receiving CYP2C9 inhibitors.
Of the participants on Rivaroxaban, no participants were receiving CYP3A4 inducers.

Table 2. Laboratory Characteristics on Anticoagulation.

Laboratory Characteristics	
Haemoglobin (g/L), mean ± SD (ref: 116–164)	111.18 ± 21.57
Mean cell volume (fL), mean ± SD (ref: 78.9–98.5)	85.91 ± 8.66
Mean corpuscular haemoglobin concentration (g/dL), median [IQR] (ref: 32.7–34.9)	31.60 [2.50]
Serum iron[1] (µmol/L), mean ± SD (ref: 9–30.4)	8.67 ± 5.46
Transferrin[1] (g/L), median [IQR] (ref: 2.5–3.8)	3.80 [8.10]
% saturation[1], median [IQR] (ref: 15–50)	3.75 [9.10]
Ferritin[1] (µg/l), median [IQR] (ref: 15–150)	34.50 [28.00]
Estimated glomerular filtration rate (mL/min), mean ± SD (ref: 71–121)	59.88 ± 0.71
International normalised ratio on warfarin, mean ± SD	
Range 2.0–3.0	2.51 ± 0.83
Range 2.5–3.5	2.43 ± 0.78

Key: IQR, Inter- quartile range, SD, standard deviation.
[1]in 30 participants.

[200.0] in the study population. In participants with iron deficiency (n = 27), the median PBAC score was 171.0 [221.0]. Thirty-nine (68.4%, 95% CI 0.55–0.79) women experienced heavy menstrual bleeding, defined as a PBAC score of >100. Median cycle length on anticoagulation and the MBQ score were significantly higher among women with a PBAC score of >100 (Table 3). The PBAC score correlated positively with the MBQ score ($r = 0.547$, $p < 0.001$). No significant difference in median PBAC scores was observed with anticoagulation

Table 3. Characteristics of Participants with Pictorial Blood Loss Assessment Chart Scores > 100 and ≤ 100.

Variable	PBAC > 100 n = 39	PBAC ≤100 n = 18	p value
Age (years), median [IQR]	39.00 [7.00]	40.50 [10.00]	0.916
Menstrual cycle length before anticoagulation (days), median [IQR]	5.00 [3.00]	4.00 [1.00]	0.153
Menstrual cycle length on anticoagulation (days), median [IQR]	7.00 [5.00]	5.00 [2.00]	0.002
Duration on anticoagulation (months), median [IQR]	15.00 [70.00]	60.00 [126.00]	0.196
MBQ Score, median [IQR]	26.00 [22.00]	9.50 [13.00]	<0.001
Haemoglobin (g/L), mean ± SD	111.23 ± 23.21	110.23 ± 18.23	0.874
% saturation, median [IQR]	3.75 [16.40]	3.72 [3.10]	0.895
Ferritin (µg/l), median [IQR]	34.00 [29.00]	40.00 [35.00]	0.333

Key: IQR, Inter- quartile range, SD, standard deviation, MBQ, menstrual bleeding questionnaire, PBAC, pictorial blood loss assessment chart.

categorised according to duration of treatment of ≤ 6 months and >6 months ($p = 0.198$).

Median total estimated menstrual blood loss, PBAC scores and MBQ scores were higher among participants on Rivaroxaban as compared to Warfarin ($p < 0.001$) (Table 4). Median cycle length on Rivaroxaban was 9.00 [6.00] days as compared to 5.00 [1.00] days on Warfarin ($p < 0.001$). Twenty-three (85.2%) of the participants on Rivaroxaban and 16 (53.3%) of the participants on Warfarin had PBAC scores of >100 ($p < 0.010$). There was no difference in haemoglobin levels and iron studies according to anticoagulant groups. Iron deficiency was diagnosed in 12 (40.0%) participants on Rivaroxaban for a median of 8.5 [12.0] months and 15 (50.0%) participants on Warfarin for a median of 84.0 [86] months.

On univariate analysis, the odds of heavy menstrual bleeding increased approximately 5-fold (OR 5.03, 95% CI 1.40–18.12, $p < 0.014$) with Rivaroxaban (Supplementary Table 1).

Figure 2 describes the PBAC and MBQ scores according to Warfarin INR range of 2–3 and 2.5–3.5 and Rivaroxaban dose of 10 mg and 20 mg. Median cycle length on Warfarin INR 2–3 and 2.5–3.5 was 6.00 [3.00] and 5.00 [2.00] days respectively. Median cycle length on Rivaroxaban 10 mg and 20 mg was 9.00 [4.00] and 10.00 [10.00] days respectively.

Median MBQ scores of impact on quality of life were significantly higher among participants on Rivaroxaban as compared to Warfarin for all 20 questions except question 19 on predictability of menstrual period start date (Supplementary Table 2). The key factors impacting on quality of life are described in Table 5. Employed women on Rivaroxaban (12, 50.0%) were more likely to miss days of work because of menstrual bleeding as compared to Warfarin (0, 0.0%) ($p < 0.001$). There were 2 (8.33%) women on Rivaroxaban who reported missing >13 days of work.

Table 4. Characteristics of Participants on Warfarin and Rivaroxaban.

Variable	Warfarin n = 30	Rivaroxaban n = 27	p value
Age (years), median [IQR]	38.50 [10.00]	39.00 [7.00]	0.471
Menstrual cycle length before anticoagulation (days), median [IQR]	5.00 [1.00]	5.00 [2.50]	0.418
Menstrual cycle length on anticoagulation (days), median [IQR]	5.00 [1.00]	9.00 [6.00]	<0.001
Duration on anticoagulation (months), median [IQR]	80.00 [114.00]	8.00 [10.50]	<0.001
Haemoglobin (g/L), mean ± SD	108.22 ± 18.60	114.02 ± 24.08	0.323
Serum iron (µmol/L), mean ± SD	8.77 ± 5.71	8.57 ± 5.41	0.922
% saturation (%), median [IQR]	4.00 [9.00]	3.43 [13.50]	0.868
Ferritin (µg/l), median [IQR]	30.00 [37.00]	39.00 [30.00]	0.934
Blood loss (ml), median [IQR]	83.20 [68.80]	193.60 [157.60]	<0.001
PBAC Score, median [IQR]	104.00 [86.00]	242.00 [197.00]	<0.001
MBQ score, median [IQR]	10.00 [13.00]	29.50 [13.50]	<0.001

Key: IQR, Inter- quartile range, SD, standard deviation, MBQ, menstrual bleeding questionnaire, PBAC, pictorial blood loss assessment chart.

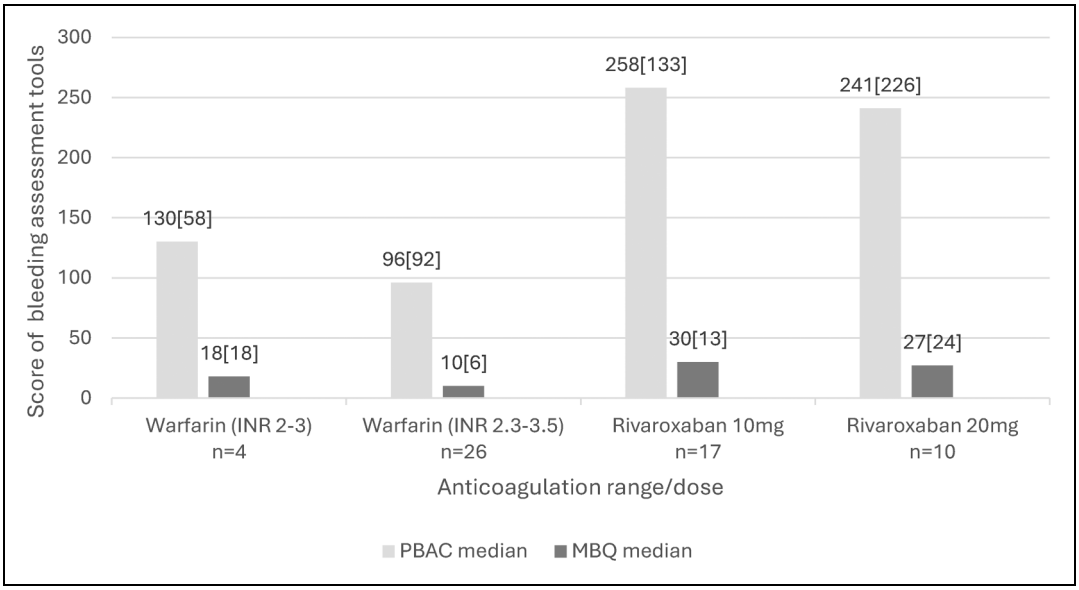


Figure 2. Median PBAC and menstrual bleeding questionnaire scores according to anticoagulant range/dose.

Table 5. Menstrual Bleeding Questionnaire Factors Impacting on Women's Quality of Life, According to Warfarin and Rivaroxaban.

Factor	Total n = 57	Warfarin n = 30	Rivaroxaban n = 27	p value
Changing sanitary products at night, during sleep (MBQ Q5 score ≥1) (n, %)	23 (40.35%)	7 (23.33%)	16 (59.26%)	0.006
Passing of blood clots staining clothing (MBQ Q7 score ≥1) (n, %)	37 (64.91%)	13 (43.33%)	24 (88.89%)	<0.001
Pain related to menstrual period (MBQ Q8 score ≥1) (n, %)	27 (47.37%)	8 (26.67%)	19 (70.37%)	0.001
Difficulty with work because of menstrual bleeding (MBQ Q10 score ≥1) (n, %)	21 (36.84%)	5 (16.67%)	16 (59.26%)	0.002
No. of days avoiding family activities (MBQ Q12 score ≥1) (n, %)	22 (38.60%)	5 (16.67%)	17 (62.96%)	0.003
No. of days avoiding social activities (MBQ Q14 score ≥1) (n, %)	16 (28.07%)	5 (16.67%)	11 (40.74%)	0.141
Extreme concern about blood staining clothes (MBQ Q18, scale 0–10), median [IQR]	2.00 [6.80]	2.00 [2.00]	7.00 [7.00]	<0.001
Not being able to predict at all when period will end (MBQ Q20 score >1)	21 (36.84%)	5 (16.67%)	16 (59.26%)	0.001

Key: IQR, Inter- quartile range, MBQ, menstrual bleeding questionnaire.

Management

On record review, contraception included barrier methods (n = 26, 45.6%), intra-uterine contraceptives, (n = 5, 8.8%), subdermal implants (n = 5, 8.8%), contraceptive injection, (n = 5, 8.8%), and combined oral contraceptive (n = 5, 8.8%).

Twenty-nine (74.4%) participants on anticoagulation received management for heavy menstrual bleeding including

Table 6. Management of Heavy Menstrual Bleeding.

Treatment of HMB	Number n = 29
Oral iron supplements (n, %)	23 (79.31%)
Intravenous iron infusion (n, %)	3 (10.34%)
Red cell transfusion (n, %)	3 (10.34%)
Tranexamic acid (n,%)	2 (6.90%)
Change of anticoagulant (n, %)	8 (27.58%)
Dose reduction of anticoagulation (n, %)	4 (13.79%)
Referral to gynaecology (n, %)	4 (13.79%)
Hospital admission (n, %)	3 (10.34%)

Key: HMB, heavy menstrual bleeding.

its complication of iron deficiency (Table 6). The majority of participants with heavy menstrual bleeding were managed as out-patients and 3 (10.3%) required hospitalisation for red cell transfusions and/or tranexamic acid. In 8 (27.6%) women the anticoagulant was changed from Rivaroxaban to Warfarin (n = 5) or Apixaban (n = 3); following which 6 (75.0%) reported an improvement of symptoms. In a further 4 (13.8%) the dose of Rivaroxaban was reduced and anti-Xa levels monitored. This resulted in an improvement of symptoms in half. In 4 (13.8%) women referred to gynaecology for the management of heavy menstrual bleeding, symptoms were controlled with hormonal contraception alone.

Discussion

This single-centre study provides important insights into the impact of heavy menstrual bleeding on quality of life, as determined by validated PBAC and MBQ tools. The findings of this study confirm that in South African women in the reproductive age group on anticoagulant therapy, heavy menstrual bleeding is an important side effect. Approximately two-thirds of women who received anticoagulant treatment for a range of conditions including VTE, valvular and non-valvular heart disease experienced heavy menstrual bleeding. These rates are consistent with earlier studies in different ethnic groups. In the international TEAM-VTE study performed across eight countries in Europe, rates of heavy menstrual bleeding of 66.0%, 95% CI 0.6–0.8 were reported among 98 anticoagulated women.[11]

In the current study the median PBAC score was 155.0 [200.0] in women on anticoagulation for a median duration of 15.5 [78.0] months. This finding is comparable with an earlier study of women on long-term warfarin which reported a median PBAC score of 210.0 (range 14.0-1010.0).[17] In contrast, the more recent, TEAM-VTE study reported a lower median PBAC score following initiation of anticoagulation of 95.0 [221.0] for the first cycle.[11] Moreover, the authors observed a non-significant decline in the rates of heavy menstrual bleeding over the follow-up six-month period. Future studies are indicated over consecutive menstrual cycles to assess the impact of anticoagulation beyond six-months on heavy menstrual bleeding and its impact on quality of life.

Importantly, heavy menstrual bleeding was associated with a considerable negative impact on quality of life including changing sanitary products at night, passing of blood clots staining clothing, pain, difficulty with work, avoiding family and social activities, extreme concern about blood staining clothes and not being able to predict when the menstrual cycle will end. Mental and social well-being are important aspects of total health care. It is thus essential for clinicians to take a menstrual history and provide adequate counselling when prescribing and monitoring anticoagulant therapy. The high PBAC and MBQ completion rates in this study suggest that these are useful validated tools which take into consideration cultural differences.

Consistent with earlier observations, the rates of heavy menstrual bleeding and its negative impact on quality of life were most pronounced among women receiving Rivaroxaban.[8,11] While the mechanism has not been described, it is possible that factor Xa inhibitors induce bleeding by compromising uterine mucosal integrity similar to the effect on the gastrointestinal mucosa. Rivaroxaban was associated with a 5-fold increased risk of heavy menstrual bleeding, with prolongation of the menstrual cycle and an increased need for modification of anticoagulant treatment as compared to Warfarin. This study consisted of a large subgroup of women on Warfarin (52.6%) in contrast to studies from high income countries. This study describes the heavy menstrual bleeding characteristics of 24 (42.1%) women with valvular heart disease who required an INR of 2.5–3.5, which were similar to earlier studies on Warfarin.[12,17] The increasing use of DOACs in our setting, owing to the lower risk profile and ease of use, requires careful consideration in women in the reproductive age group. Moreover, owing to the reduced monitoring requirements of Rivaroxaban, symptoms and complications of heavy menstrual bleeding may be identified later as compared to Warfarin. In 12 (30.8%) women with heavy menstrual bleeding Rivaroxaban treatment was modified by reducing the dose or switching to Warfarin or Apixaban. The results of the EINSTEIN-CHOICE sub-study, suggest that in women with heavy menstrual bleeding, the dose of Rivaroxaban can be safely reduced to 10 mg daily for extended treatment of VTE after completion of 6 to 12 months of anticoagulation.[23] Rivaroxaban 10 mg was associated with a decrease in cycle length and heavy menstrual bleeding duration as compared to 20 mg. With the availability of several anticoagulant agents, switching agents is another reliable option.[6] The ongoing heavy MEnstrual bleeding in premenopausal women treated with DirEct oral Anticoagulants (MEDEA) trial is a Dutch multicentre, randomized trial in women with heavy menstrual bleeding on factor Xa inhibitor treatment. The study is currently randomising women to either switch to dabigatran, continue on the factor Xa inhibitor with the addition of an antifibrinolytic agent or to continue on the factor Xa inhibitor with no intervention.[24] In particular, the anti-fibrinolytic agent tranexamic acid has not been shown to increase the risk of thrombosis and has been associated with a decrease in heavy menstrual bleeding.[25] Recent phase 2 trials of Factor XI inhibitors have reported a reduction in major or clinically relevant non-major bleeding compared to prophylactic LMWH in orthopaedic patients and DOAC in non-valvular atrial fibrillation. These promising early results have led to the initiation of phase 3 trials with safety results awaited.[26,27]

Women who present with anticoagulant associated heavy menstrual bleeding require an individualised management approach in consultation with gynaecology. Treatment options in pre-menopausal women also include prescribing hormone contraception and uterine surgical interventions.[16,28] Medical management for heavy menstrual bleeding was initiated in 74.4% (n = 29) of which 13.8% (n = 4) were referred to gynaecology for hormonal contraception. Levonorgestrel intrauterine systems are safe and effective and have been associated with blood loss reduction by 80%, improved compliance and low side effect profiles and as such are the preferred modality.[29] They result in amenorrhea in 50% of women. The etonogestrel subdermal implant results in amenorrhea in approximately 20% of women and depot-medroxyprogesterone acetate results in amenorrhea in greater than 50% of women. Furthermore, the combined oral contraceptive is an alternative which has not been associated with a significantly increased risk of recurrent thrombosis in women on anticoagulation therapy.[13]

Our results must however be interpreted in light of certain limitations. First, the PBAC and MBQ were assessed over one menstrual cycle. Nonetheless, the PERIOD study which assessed PBAC and MBQ scores over two cycles did not show a significant difference between cycles one and two.[8] Second, subgroup analysis according to the range of INR and dose of Rivaroxaban could not be assessed owing to the small number of participants in particular with an INR range of 2.0–3.0. Third, iron studies were available in only half of the study participants which can be attributed to the underreporting of symptoms of heavy menstrual bleeding. Also, laboratory parameters before the start of anticoagulant therapy were not collected. Fourth, cycle length prior to starting anticoagulation was determined retrospectively. Recall bias, in particular for patients on treatment for > 6 months (n = 42, 73.7%), could have resulted in an inaccurate assessment of prior cycle length. Nonetheless previous studies performed at initiation of anticoagulation, showed similar median cycle lengths.[7,8] Finally, the study employed the semi-quantitative (PBAC) assessment to quantify menstrual blood loss. The PBAC, however, is widely used in clinical studies and has been associated with a sensitivity of 58–99% and a specificity 75–89% for scores above 100 for heavy menstrual bleeding.[30]

Conclusion

In conclusion, this study adds to the evidence that heavy menstrual bleeding is a frequent complication during anticoagulation therapy, which was associated with a considerable negative impact on quality of life. This was most significant for women on Rivaroxaban as compared to Warfarin. The majority of participants with heavy menstrual bleeding were managed medically as out-patients. It is thus important for anticoagulation clinics to incorporate into daily practice counselling the possible changes in the menstrual cycle length and bleeding, monitoring and appropriate treatment for heavy menstrual bleeding and iron deficiency. Owing to the observational study design and small number of participants on subgroup analysis according to anticoagulant ranges/doses, the results of ongoing randomized trials are awaited to assess the optimal interventions for heavy menstrual bleeding in this group of patients.

Acknowledgements

The authors would like to express their gratitude to the patients for participating and Sisters Masebe and Sithole at the anticoagulation clinic.

Author Contributions

Conceptualization: N Hassan
Supervision: E Schapkaitz, H Rhemtula, N Ncete
Writing – original draft: N Hassan
Review & editing: E Schapkaitz, H Rhemtula, N Ncete

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Elise Schapkaitz https://orcid.org/0000-0002-1534-2930

Supplemental Material

Supplemental material for this article is available online.

References

1. James AH. Heavy menstrual bleeding: Work-up and management. *Hematology Am Soc Hematol Educ Program*. 2016 Dec 2;2016(1):236-242. doi:10.1182/asheducation-2016.1.236
2. Munro MG, Critchley HO, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO Classification system (PALM-COEIN) for causes of abnormal uterine bleeding innongravid women of reproductive age. *Int J Gynaecol Obstet*. 2011;113(1):3-13.
3. DeLoughery E, Bannow BS. Anticoagulant therapy for women: Implications for menstruation, pregnancy, and lactation. *Hematology*. 2022 Dec 9;2022(1):467-473. doi:10.1182/hematology.2022000401
4. National Guideline A. National Institute for Health and Care Excellence: Clinical Guidelines. In Heavy Menstrual Bleeding (update) National Institute for Health and Care Excellence (UK). Copyright (c) NICE 2018, 2018.
5. Brekelmans MP, Scheres LJ, Bleker SM, et al. Abnormal vaginal bleeding in women with venous thromboembolism treated with apixaban or warfarin. *Thromb Haemost*. 2017;117(4):809-815. doi:10.1160/TH16-11-0874
6. Micaily I, Samuelson Bannow BT. VTE And anticoagulation in menstruating women. *Thromb Update*. 2021 Dec 1;5:100088.
7. De Crem N, Peerlinck K, Vanassche T, et al. Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists. *Thromb Res*. 2015;136(4):749-753.

8. Patel JP, Nzelu O, Roberts LN, Johns J, Ross J, Arya R. How do anticoagulants impact menstrual bleeding and quality of life? - The PERIOD study. *Res Pract Thromb Haemost*. 2023 Feb 7;2(2):100072.
9. Makam RCP, Hoaglin DC, McManus DD, et al. Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: Systematic review and meta-analysis. *PLoS One*. 2018 May 24;13(5):e0197583.
10. Myers B, Webster A. Heavy menstrual bleeding on Rivaroxaban – comparison with Apixaban. *Br J Haematol*. 2017 Mar 1;176(5): 833-835.
11. de Jong CMM, Blondon M, Ay C, et al. Incidence and impact of anticoagulation-associated abnormal menstrual bleeding in women after venous thromboembolism. *Blood*. 2022 Oct 20;140(16):1764-1773.
12. Ferreira M, Barsam S, Patel JP, et al. Heavy menstrual bleeding on rivaroxaban. *Br J Haematol*. 2016;173(2):314-315.
13. Martinelli I, Lensing AW, Middeldorp S, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. *Blood*. 2016;127(11):1417-1425.
14. Speed V, Patel JP, Arya R. Bleeding issues in women prescribed anticoagulation. *Thromb Update*. 2021 Dec 1;5:100068.
15. Karlsson TS, Marions LB, Edlund MG. Heavy menstrual bleeding significantly affects quality of life. *Acta Obstet Gynecol Scand*. 2014;93(1):52-57.
16. Fernandez-Jimenez MC, Moreno G, Wright I, Shih PC, Vaquero MP, Remacha AF. Iron deficiency in menstruating adult women: Much more than Anemia. *Womens Health Rep*. 2020 Dec 1;1(1):26-35.
17. Huq FY, Tvarkova K, Arafa A, Kadir RA. Menstrual problems and contraception in women of reproductive age receiving oral anticoagulation. *Contraception*. 2011;84(2):128-132.
18. Deiker M, BAloyi SM, Coetzee, Haupt L. The prevalence of bleeding disorders in women with regular heavy menstrual bleeding at a secondary gynaecology clinic in central South Africa. University of Free State- DSpace. http://hdl.handle.net/11660/11504
19. Matteson KA, Scott DM, Raker CA, Clark MA. The menstrual bleeding questionnaire: Development and validation of a comprehensive patient-reported outcome instrument for heavy menstrual bleeding. *BJOG : An International Journal of Obstetrics and Gynaecology*. 2015;122(5):681-689.
20. Spence M, de Repentigny K, Bowman M, Hopman W, Thibeault L, James P. Validation of the pictorial blood loss assessment chart using modern sanitary products. *Haemophilia*. 2021;27(5):632-635.
21. Higham JM, O'brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol*. 1990;97(8):734-739.
22. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352(10):1011-1023.
23. Boonyawat K, Lensing AWA, Prins MH, et al. Heavy menstrual bleeding in women on anticoagulant treatment for venous thromboembolism: Comparison of high- and low-dose rivaroxaban with aspirin. *Res Pract Thromb Haemost*. 2021 Feb 1;5(2):308-313.
24. Hamulyák EN, Wiegers HMG, Scheres LJJ, et al. Heavy menstrual bleeding on direct factor Xa inhibitors: Rationale and design of the MEDEA study. *Res Pract Thromb Haemost*. 2021;5(1):223-230.
25. Sundström A, Seaman H, Kieler H, Alfredsson L. The risk of venous thromboembolism associated with the use of tranexamic acid and other drugs used to treat menorrhagia: A case-control study using the General Practice Research Database. *BJOG*. 2009;116(1):91-97.
26. Piccini JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): A multicentre, randomised, double-blind, doubledummy, dose-finding phase 2 study. *Lancet*. 2022;399(10333):1383-1390.
27. Weitz JI, Bauersachs R, Becker B, et al. Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty: The FOXTROT randomized clinical trial. *JAMA*. 2020;323(2):130-139.
28. Scheres L, Brekelmans M, Ageno W, 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(12):1581-1589.
29. Chen S, Liu J, Peng S, Zheng Y. LNG-IUS vs. medical treatments for women with heavy menstrual bleeding: A systematic review and meta-analysis. *Front Med*. 2022;9:948709.
30. Magnay JL, O'Brien S, Gerlinger C, Seitz C. A systematic review of methods to measure menstrual blood loss. *BMC Womens Health*. 2018 Aug 22;18(1):142.