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ORIGINAL ARTICLE

How do anticoagulants impact menstrual bleeding and quality of life? - The PERIOD study

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Abstract

Background: There is increasing recognition that menstruating women prescribed anticoagulants experience heavy menstrual bleeding.

Objectives: The aim of this study is to report the extent of bleeding in menstruating women after commencing anticoagulants and the impact it has on their quality of life.

Methods: Women aged 18 to 50, initiated on anticoagulant therapy, were approached to take part in the study. In parallel, a control group of women was also recruited. Women were asked to complete the menstrual bleeding questionnaire and a pictorial blood assessment chart (PBAC) during their next 2 menstrual cycles. Differences between the control and anticoagulated group were compared. Significance was considered at $< .05$. Ethics committee approval: REC reference: 19/SW/0211.

Results: Fifty-seven women in the anticoagulation and 109 women in the control group returned their questionnaires. Women in the anticoagulated group reported an increase in the median length of their menstrual cycle from 5 to 6 days after commencing anticoagulation, compared to 5 days for women in the control group ($P < .05$). Anticoagulated women reported significantly higher PBAC scores as compared to the control group ($P < .05$), with two-thirds of women in the anticoagulation group reporting heavy menstrual bleeding. Women in the anticoagulation group reported worsening quality of life scores following the initiation of anticoagulation, compared with women in the control group ($P < .05$).

Conclusion: Heavy menstrual bleeding occurred in two-thirds of women commencing anticoagulants, who completed a PBAC, which had negative impact on their quality of life. Clinicians commencing anticoagulation therapy should be mindful of this, and recognized measures should be taken to help minimize this problem for menstruating individuals.

KEYWORDS
anticoagulants, heavy menstrual bleeding, menorrhagia, quality of life, venous thromboembolism, women

Essentials

- Little research exists which understands the impact of anticoagulants on menstruating women.
- Quality of life and menstrual bleeding was compared between anticoagulated and control women.
- Anticoagulated women bled more and had worse quality of life scores, compared to a control group.
- This problem should be minimized for menstruating women commencing anticoagulants.

1 | BACKGROUND

Research demonstrates that during menstruation, 38% of all women report not being able to perform their regular daily activities, [1–2] with some women diagnosed with a bleeding disorder who experience heavy menstrual bleeding (HMB) reporting that on the days of heavy bleeding, they avoid leaving home [3]. Given this, one would anticipate numerous reports of HMB reported in women prescribed *traditional* anticoagulants, such as vitamin K antagonists (VKA) and low molecular weight heparin (LMWH); particularly given the incidence of venous thromboembolism (VTE) is greater in women than in men during the child-bearing years [4]. However, prior to the direct oral anticoagulant (DOACs) era, little published research exists reporting on this. Indeed, the studies of note comprise of 4; Fihn et al., [5] conducted a retrospective study of 900 patients from 5 anticoagulation clinics in the USA, and reported that the risk of bleeding was 1.9 times greater (95% CI 1.3-3.0) in women. In this study, the excess bleeding was almost exclusively vaginal or uterine bleeding. This was followed by Kuijer et al.'s [6] work, which reported that female gender was an independent predictor of bleeding for patients prescribed anticoagulants in the setting of VTE, with the duration of menstrual bleeding reported to increase. A Swedish study of 90 women between the ages of 15 to 49 prescribed oral anticoagulation reported the mean duration of menstrual bleeding increased from 5.6 to 6.1 days and the proportion of women reporting menorrhagia that had an impact on their quality of life increased from 44% to 71% [7]. Finally, Huq et al. [8] assessed the changes in menstrual blood loss and pattern in women prescribed anticoagulant treatment. Fifty-three women participated in the study and the mean duration of menstruation increased from 5 days (before) to 7 days after commencement of treatment. Thirty-one of the 47 women who completed a bleeding assessment chart reported menorrhagia [8].

The arrival of the DOACs into clinical practice has made anticoagulation treatment easier; they can be taken orally and have predictable pharmacokinetic profiles meaning monitoring is not usually required. Following their widespread use in clinical practice outside the confines of a clinical trial, the first reports of HMB began to emerge [9,10]. These early reports and those which have subsequently reported, [11–18] prompted post-hoc analysis of the DOAC phase III VTE clinical trials, which has confirmed this issue [19–22].

When anticoagulants are started for menstruating women, they are usually prescribed to manage an acute condition, such as VTE, where it is important to maintain a therapeutic concentration of anticoagulation to manage the event, while minimizing the risk of bleeding. When HMB manifests in women prescribed anticoagulants, this balance is upset and at its extreme, may lead to the patient missing significant days off-anticoagulation, either on the advice of their clinician or a decision taken by the patient themselves, risking recurrence [13]. Although now it is increasingly accepted in the thrombosis community that HMB is a real problem for menstruating women prescribed anticoagulants, little research has been conducted to understand the impact of anticoagulant therapy on women's menstrual cycles from a bleeding and quality of life perspective. It is important to understand this, so that when anticoagulants are given to premenopausal women, this is fully considered and HMB is minimized, where possible.

The aim of our study is to report on the extent of bleeding in menstruating women prescribed anticoagulation therapy and the impact this has on their quality of life, in comparison to a control group of women.

2 | METHODS

We conducted a prospective cohort study. Women aged 18 to 50 years, prescribed anticoagulant therapy (either DOACs, VKA, or LMWH), for any indication were approached to take part by provision of the study information leaflet at the time of initiation. The lead researcher (J.P.) subsequently contacted interested women by phone and explained the study and what it would entail. If they agreed to take part, following informed consent, women were emailed the online study link to enter their data, within the first 2 weeks of starting anticoagulation therapy. Subjects were recruited from the anticoagulation clinics at King's College Hospital, NHS Foundation Trust, a 1500 bedded teaching hospital. The anticoagulation clinics (Denmark Hill and Princess Royal) serve an ethnically and socio-economically diverse population in Southeast London, UK.

In parallel, a control group of women, aged 18 to 50 years were also recruited through local advertisement in the King's College London research volunteer recruitment circular, which is emailed to all members of the University community every 2 weeks with brief details of each study. Women who expressed an interest to take part, contacted a member of the research team (O.N.) who then called the control volunteer, explained the study and what it would entail; and if they agreed to take part, the online study link was shared with the eligible volunteers to enter their data.

All women who agreed to take part were asked to complete 2 validated instruments during their next 2 consecutive menstrual cycles, following recruitment: (1) the menstrual bleeding questionnaire (MBQ)

[23] and (2) the pictorial blood assessment chart (PBAC). The MBQ is a bleeding-specific symptom and quality of life instrument that measures the impact of HMB, comprising 20 items. The responses are summed to obtain a total score and multiplied by 1.32 to scale, with a score of 0 indicating least impact possible and 100, worse impact possible. The PBAC allows for an objective recording of blood loss. The PBAC tool utilized was the chart developed by Higham et al. [24] and further refined by Wyatt et al. [25], with a PBAC score >100 indicating HMB [26].

2.1 | Inclusion/exclusion criteria

For the anticoagulation group, all premenopausal women, new on anticoagulation therapy, aged between 18 to 50 years, who were not pregnant and able to read and speak English were eligible to take part in the study, even if they did not report regular menses. Women who were not experiencing regular periods, eg, patients who had their periods suppressed, were still included, to assess if anticoagulant therapy caused any *breakthrough* bleeding.

For the control group, the following recruitment exclusions were applied by the recruiting gynecologist (O.N.) when consenting women: known inherited bleeding disorder, known uterine fibroid disease, women on the progestogen only pill, pregnant women, unable to provide informed consent, unable to read or speak English in order to consent and self-complete the questionnaires, those women prescribed medications known to impact uterine haemostasis, eg, anti-platelets, women with an intra-uterine device (IUD) in situ, women prescribed the combined oral contraceptive pill, women being treated for HMB, and women with menorrhagia secondary to known adenomyosis.

2.2 | Data collection

For all recruited anticoagulated and control women, their age, their ethnicity, the usual length of their menstrual cycle (prior to taking part in the study), age at menarche, any hormonal contraception use (anticoagulated group), and the type of sanitary products (tampons, sanitary towels, or both) used during their menstrual cycle was captured by consultation at the time of consent. Recruited women were then emailed the online link to the study instrument, hosted on JISC online surveys, with a unique username and password, which allowed them to login to record their blood loss and report their experience, according to the 2 validated instruments, during 2 consecutive cycles. In addition, at the time of recruitment, a brief instruction sheet was emailed / posted to volunteers, which further explained how to complete the PBAC tool. Through medical chart review, women in the anticoagulation group also had details on the indication for anticoagulation, which anticoagulation agent was prescribed and routine bloods (renal function, full blood count) at time of diagnosis, recorded.

Women were sent an email reminder 2 months after recruitment and a further 2 reminders following this, at 1 monthly intervals, if a questionnaire had not been returned. Once a completed questionnaire had been returned, volunteers across both the anticoagulated and control group were sent a £10 retail e-gift card, as a thank you for their participation and time.

TABLE 1 Indication for anticoagulation and anticoagulants prescribed

Characteristic	*n* = 57
Mean weight, kg, (SD)	79.6 (23.0)
Indication for anticoagulation, *n* (%)	
PE	24 (42)
Distal DVT	15 (25)
Proximal DVT	4 (7)
DVT and PE	3 (5)
Upper limb DVT	3 (5)
Mechanical heart valve replacement	2 (4)
Sagittal sinus thrombosis	2 (4)
Portal vein thrombosis	1 (2)
Nephrotic syndrome	1 (2)
Vertebral artery dissection	1 (2)
Arterial thrombosis	1 (2)
Anticoagulant commenced, *n* (%)	
Rivaroxaban	24 (42)
Apixaban	17 (30)
Warfarin (2-3)	8 (13)
Enoxaparin	5 (9)
Edoxaban	2 (4)
Warfarin (2.5-3.5)	1 (2)
Relevant baseline bloods, mean (SD)	
Hb, g/L	123 (22)
HCT, %	38 (6)
MCV, fL	90 (9)
Serum creatinine, umol/L	67 (16)
Calculated CrCl*, mL/min	130 (41)
Duration of anticoagulation, months, *n* (%)	
3	25 (44)
6	6 (10)
12	4 (7)
Long-term	22 (39)

CrCl, creatinine clearance; DVT, deep vein thrombosis; Hb, hemoglobin; HCT, hematocrit; MCV, mean cell volume; PE, pulmonary embolism.
*calculated using the Cockcroft-Gault equation [27]

2.3 | Data analysis

Data was coded and entered onto the IBM SPSS Statistics version 28.0.1.1 and analyzed. Figures were drawn in Sigma Plot version 14.0.

TABLE 2 Summary of the demographic information in both groups

Characteristic	Anticoagulant group *n* = 57	Control group *n* = 109	*P* value
Age, y; mean (SD)	37.2 (8.6)	28.5 (7.5)	< .001
Ethnicity, *n* (%)			< .001
White	34 (60)	63 (58)	
Black	14 (25)	4 (4)	
South Asian	3 (5)	22 (20)	
East Asian	2 (3)	13 (12)	
Mixed race	3 (5)	7 (6)	
Other	1 (2)	0 (0)	
Age, y, at menarche; mean (SD)	12.8 (1.6)	12.4 (1.3)	0.05
Length of cycle*, d; median (min-max)	5 (0-10)	5 (3-8)	0.81
Use of moon cup during periods, *n* (%)	5 (9)	16 (15)	-

*Length of menstrual cycle reported by women prior to completing the questionnaires.

The total PBAC score for each volunteer for cycles 1 and 2 was computed. Women's quality of life was assessed through the MBQ and the scaled score computed. Differences in scores between the anticoagulated and control groups were compared. The PBAC and the quality-of-life scores were additionally correlated. Finally, differences in the PBAC and quality of life scores were compared between cycle 1 and cycle 2, in both groups of women.

Continuous variables are reported as mean and SD or median and IQR for normal and non-normal data, respectively. Chi-squared test was used to compare categorical data between groups. As the data from the questionnaire and PBAC was non-normally distributed, comparisons between 2 groups were assessed by Mann-Whitney U-test. Correlations were assessed using Spearman's rho. Within subject comparisons between cycle 1 and cycle 2 was made using the Wilcoxon sign rank test. Significance was set at < .05.

The PERIOD study had ethics committee approval from the South-West Bristol ethics committee. REC reference: 19/SW/0211.

3 | RESULTS

During the study recruitment period (9/11/2020 to 1/4/2022), 94 women starting anticoagulant therapy agreed to take part in the study. Of these, 57 women returned questionnaires (64% response rate). Their mean age was 37.2 years (SD, 8.6; range, 18-49) and the women reported a median menstrual cycle length, preanticoagulation of 5 days (0-10 (min-max)). Table 1 outlines the indication for commencing anticoagulation, which anticoagulant was commenced and baseline bloods at the time of diagnosis in these 57 women.

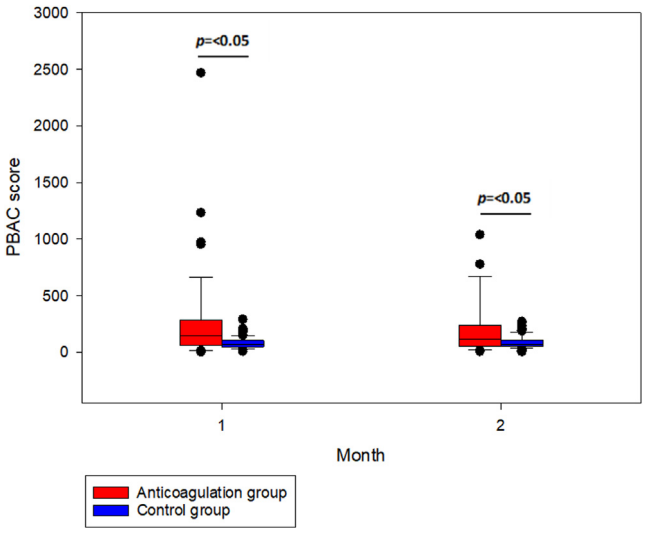

FIGURE 1 Anticoagulation group vs control group PBAC scores during both cycles. PBAC, pictorial blood assessment chart

Nineteen women (33%) were on some form of contraceptive therapy prior to starting anticoagulation therapy. Four women had levonorgestrel IUD's in situ; 5 women were on the combined oral contraceptive pill, of whom 3 stopped at the time of diagnosis; 4 women were on the progesterone only pill, of whom 1 stopped at diagnosis; 3 women were on the norelgestromin and ethinyl estradiol contraceptive patch, of whom 1 stopped at diagnosis; 2 women had the progesterone implant in place and 1 further woman was having the progesterone depot injection every 3 months. Nine (16%) of the women in the anticoagulant group had a prior gynecology history of note, at the time of diagnosis; 5 had a recorded history of HMB, 1 had a recent termination of pregnancy, 1 patient had adenomyosis and endometriosis, 1 woman had previously diagnosed fibroids, and 1 woman had a history of HMB with previously diagnosed fibroids.

In the control group, 147 women consented to take part following 2 rounds of advertisements, of whom 109 returned questionnaires (74% response rate). Table 2 outlines the demographic information on the control group of women in comparison to the anticoagulated group.

3.1 | Menstrual cycle length and pictorial blood loss assessment charts

Seven women in the anticoagulated group reported no bleeding during a consecutive 2-month period. This was due to a diagnosis of cancer (3 women) and receiving chemotherapy, 3 women reported no bleeding due to the Mirena coil® and 1 woman having unpredictable cycles. None of these 7 women in the anticoagulated group, reported breakthrough bleeding during the first 2 months following commencement of anticoagulation.

The remaining 50 women in the anticoagulated group reported a significantly longer median menstrual cycle length, following the

TABLE 3 Quality of life scores across the 2 groups

Scaled menstrual bleeding quality of life questionnaire score, median (IQR)	Anticoagulated group (n = 57)	Control group (n = 109)	P value
Cycle 1	26 (16-41)	19 (15-25)	.001
Cycle 2	25 (15-35)	17 (13-21)	.001

commencement of anticoagulation compared to the control group: 6 days vs 5 days for cycle 1 (P = .02) and cycle 2 (P = .001).

The median PBAC scores were significantly higher in the anticoagulated group compared to the control group, during both cycles as illustrated in Figure 1.

Thirty-two women (64%) in the anticoagulated group reported a PBAC score > 100 during cycle 1, indicating HMB, compared to 37 women (34%) in the control group. For cycle 2, 30 women in the anticoagulated group (60%) report a PBAC score > 100 compared to 31 women (28%) in the control group.

No significant differences were found within groups between cycles 1 and 2 for the PBAC scores or cycle length.

3.2 | Quality of life

Table 3 outlines the MBQ quality-of-life scores reported by the women for the 2 cycles, with the anticoagulant group compared to the control group.

Women in the anticoagulant group were more likely to avoid social activities, report bleeding that would soak through to their outer clothing, more likely to have to get out of bed at night to change sanitary products and report the end date of their period being unpredictable (Table 4), compared to the control group of women. PBAC scores were more closely correlated with the quality-of-life scores in the anticoagulation group: cycle 1 (r = 0.82 [P < .001] and cycle 2 (r = 0.68 [P < .001]) compared to the control group: cycle 1 (r = 0.48 [P < .001] and cycle 2 (r = 0.51 [P < .001]). PBAC, pictorial blood assessment chart.

3.3 | Experience of the anticoagulated women

A wide range of anticoagulants were prescribed for the 57 women in the anticoagulant group and the majority of women in this group remained on the initial anticoagulant prescribed, which was most commonly rivaroxaban, followed by apixaban. A small number of women (n = 4, 7%) required a change of their anticoagulant to help with the management of the HMB experienced. This change was usually from rivaroxaban to apixaban (3 women) or rivaroxaban to enoxaparin followed by apixaban (1 woman). The median (min-max), PBAC scores for women prescribed the 3 most commonly prescribed anticoagulants in our anticoagulated cohort are outlined in Table 5.

4 | DISCUSSION

Our study compares menstrual bleeding rates in women commenced on anticoagulants, to a control group of women. The results confirm that for many anticoagulated women, bleeding increases during their menstrual cycle, which negatively impacts their quality of life and adds weight to the call that more needs to be done to support women, when prescribed anticoagulation therapy [28]. The strengths of our study include a relatively high questionnaire completion rate in both the anticoagulated and control groups, an ethnically diverse study population and recruitment and comparison with a control group.

Our findings show that HMB can become troublesome enough to warrant a change in the anticoagulant therapy, indeed this was the case in 4 women in our cohort. We also found that not all women were affected, suggesting that the effect is not a blanket effect, but does vary among women. In addition to increased bleeding, women in the anticoagulated group experienced longer cycles, as has previously been reported [6–8]. At the time of recruitment, both groups of women reported a median cycle length of 5 days prequestionnaire completion; this increased to 6 days when the PBAC chart was completed in the anticoagulated group and remained at 5 days for the control group. Our study also shows that the increased bleeding that women report, negatively impacts their quality of life, with the PBAC scores highly correlated with the quality of life scores in the anticoagulated group of women compared to the control group.

Our findings support the results of the recently published TEAM VTE study, which is the only other study, to the best of our knowledge, which has attempted to objectively assess this issue in anticoagulated women during the DOAC era [29]. The TEAM VTE study recruited 98 newly diagnosed VTE patients, asking them to complete a PBAC and the MBQ, over 3 to 6 months follow-up. Although they had 3 different definitions of what constituted HMB in their study, their headline finding is similar to ours: that two-thirds of women newly starting on anticoagulation therapy, experience HMB. In the TEAM VTE study, quality of life scores continued to decline with time. Although we only followed women for 2 consecutive menstrual cycles following commencement of anticoagulation, the scores between cycle 1 and cycle 2 in both groups were not significantly different. This suggests that if women likely to be continuing anticoagulation long-term (eg, unprovoked VTE, antiphospholipid syndrome, women with mechanical heart valves in situ) do suffer HMB with anticoagulation therapy, then this requires specific attention and intervention as this could be an ongoing feature, impacting significantly on their life. Although many of the studies to date focus on women newly commencing anticoagulants, women already prescribed anticoagulants, even those who have been on anticoagulants for many years, should not be forgotten. They may be suffering in silence and simple measures may make a big difference for them. In addition, there are recognized cultural differences on how women talk about their periods and in ethnically diverse populations, like that of SE London, clinicians should appreciate this, so all women are supported appropriately [30].

TABLE 4 Key factors impacting on women's quality of life, reported as % of women reporting

	Cycle 1		Cycle 2	
Reported item	Anticoagulation	Control	Anticoagulation	Control
Bleeding soaked through to outer clothes, %	54	22	44	25
Got out of bed to change sanitary products at night, %	54	28	46	28
Avoided social activities whether or not they were bleeding, %	35	29	30	21
End date of the period was not at all predictable, %	35	5	33	3

4.1 | Studies reporting on heavy menstrual bleeding with anticoagulants

Following the wider-spread use of DOACs into clinical practice, the issue of HMB has quite rightly gained prominence in the thrombosis community, with several reports from centers around the world consistently reporting on this issue [9–18]. These reports have been corroborated by post-hoc analysis of the DOAC VTE clinical trials [19–22], as well as real-world database studies [31–33]. Prior to the DOAC era, VKAs were also implicated with HMB [5–8]. Therefore, the issue of HMB should not be the sole consideration for women prescribed DOACs. Although women in our cohort prescribed VKA generally reported lower PBAC scores, compared to DOACs, this was not always the case. Therefore, women who remain or are started on VKA, for reasons of indication, or finance, deserve attention in this regard and should not be forgotten. In addition, with the recent licensing of rivaroxaban for VTE in children following the publication of the Einstein Jr study [34], girls who have reached menarche should also be supported and experience from the adult world should be shared with pediatric colleagues, so problems can be prevented from the outset for this population.

Our study had a wide range of anticoagulants prescribed, most commonly rivaroxaban, which is the first-line agent for VTE in our hospital, then apixaban and warfarin. Our study taken with our clinical experience and that reported in the literature suggests that rivaroxaban is commonly associated with HMB, more so than apixaban, dabigatran and warfarin. In our center, we very rarely prescribe dabigatran, but others report favorable experience with dabigatran in the setting of HMB and anticoagulation [17,20]. The mechanism behind the HMB observed with DOACs is not well understood; whether it is simply anticoagulation causing this or whether it is related to a mechanism at a molecular level is yet to be determined. Beyer-Westendorf and Marten suggest that increased bleeding observed with factor Xa inhibitors could be having a direct impact on coagulation factors or other proteins in the uterine wall [35]. They suggest that factor Xa inhibitors maybe synergistically acting with physiological anticoagulants required for shedding blood and endometrium cells during menstrual bleeding. A further hypothesis proposed by Beyer-Westendorf and Marten relates to a modulated fibrinolytic function of FXa, which is sequentially cleaved by plasmin. Covalent modification of the FXaα active site inhibits cleavage from FXaα to Xa33/13 by plasmin, leading to increased FXaβ levels. Carter et al. [36] have demonstrated that the plasma of patients taking rivaroxaban show enhanced fibrinolytic capacity, which correlated to increased FXaβ levels. One might also consider whether the pharmacokinetic properties of DOACs play a role in HMB. There are 2 studies underway which might provide an insight into this. The RAMBLE clinical trial (NCT02829957), is an open label trial, randomizing newly diagnosed women with VTE to treatment dose apixaban or rivaroxaban and comparing PBAC scores. Assuming the groups are well matched, this study will provide a valuable insight into which direct anti-Xa inhibitor is less likely to cause HMB. The other trial of note is the MEDEA trial, which is testing the hypothesis that a direct thrombin inhibitor, dabigatran is better in the setting of HMB than direct Xa inhibitors. This trial is an open label, pragmatic trial, which will randomize women with a PBAC score of >150 to one of 3 arms: (1) switch to dabigatran, (2) continue factor Xa inhibitor with the addition of tranexamic acid during the menstrual period, or (3) continue factor Xa inhibitor without intervention [37]. We look forward to seeing the results of these trials, which will undoubtedly help front-line clinicians with decision making.

TABLE 5 PBAC scores according to anticoagulation prescribed

Anticoagulant	Median PBAC score - Cycle 1 (min-max)	Median PBAC score - Cycle 2 (min-max)
Rivaroxaban, *n* = 24	186 (13-1232)	137 (14-1038)
Apixaban, *n* = 17	146 (2-972)	77 (6-1038)
Warfarin (2-3), *n* = 8	96 (17-155)	121 (51-188)

PBAC, pictorial blood assessment chart.

4.2 | Minimizing HMB for anticoagulated menstruating individuals

For menstruating individuals newly commencing anticoagulation, what can be done now in clinic? An important first step, is to ensure that all patients have their menstrual cycle history taken at the time of commencing anticoagulation. Taking such a history is important because if a patient presents with a history of HMB, then one anticipates that anticoagulants are more likely to exacerbate the problem and the choice of agent from the outset will be important in cases like these, where apixaban or dabigatran might be prescribed over rivaroxaban to circumvent a problem. Furthermore, when anticoagulation

is commenced for menstruating individuals, they should be counseled regarding the possibility of HMB and safety netted on what to do, should they experience HMB. Knowing who to contact in such circumstances should be conveyed and explaining that it is not normal for them to be changing sanitary products every 30 to 60 minutes. Finally, linked to the importance of taking a menstrual history, many patients are prescribed hormonal contraception, for example, to help regulate their periods. Some clinicians, at the time of diagnosis of VTE, discontinue hormonal contraception. This might do the patient a disservice, risking pregnancy or withdrawal bleeding and HMB at the time of the next cycle. As anticoagulation is being commenced to manage the VTE, no change is required in the immediate time-period. The decision to alter hormonal contraception can be taken in the fullness of time, depending on what decision is being taken on the duration of anticoagulation [38]. Those working outside of the haemostasis/thrombosis require particular education in this regard.

Clinicians charged with managing anticoagulation in this group of patients should be familiar with measures which might help manage HMB, should it occur, eg, tranexamic acid and when to employ, as has previously been described [28,39,40].

4.3 | Lived experience of women

The quality of life scores reported by women in our study, clearly demonstrate how this is negatively impacted upon, in the anticoagulated group of women relative to the control group. There was a 7- and 8-point difference in the scaled menstrual quality of life questionnaire score between the 2 groups, for cycle 1 and cycle 2 respectively. This is in keeping with the TEAM VTE study, which reported a 5-point difference in scores, when compared to the scores prior to starting anticoagulation in their cohort of women.

It is also important to remember that many women in our cohort were initiated on anticoagulation following an acute thrombotic event. A recently completed scoping review aiming to understand the physical, psychological and emotional impact of VTE from patients' perspectives, identified 7 major themes: (1) acute impacts: an unforeseen blow; (2) sustained psychological distress; (3) loss of self: life is changed; (4) challenges of thrombosis management; (5) balancing coping and control; (6) negative experience with the medical system; and (7) VTE in the context of other conditions. Clearly there is a lot that patients go through, following a VTE diagnosis and HMB would only add to this, particularly under the sub-theme of *burden of anticoagulation*, identified by the authors of this review. Clinicians should be mindful of this as it once again highlights the importance of trying to prevent HMB in the first place [41].

4.4 | Limitations

Our findings should be carefully considered in the context of their limitations. The anticoagulated and control groups were not matched, in terms of their PMH or use of hormonal contraception. Women with a history of HMB or users of hormonal contraception were excluded from the control group but were included in the anticoagulated group. This is an important confounder that should not be forgotten. Furthermore, the assumption is made that women were accurately recording their blood loss on the web-based system provided. A small number of women in both groups were using the menstrual cup during their cycles. These women recorded blood loss as milliliters in the PBAC chart. Our observation during the execution of our study was that the menstrual cup is increasingly being used, especially by the younger population and the current PBAC charts require updating to incorporate their increasing use. Furthermore, baseline menstrual cycle duration presented in Table 2 for both groups was reported retrospectively, so could have an element of recall bias. Finally, our control group were recruited from a central London based University population, which meant they were significantly younger in age compared to the anticoagulated group and ethnically more diverse, relative to the anticoagulated group. This could have impacted on the differences reported, particularly the age difference, where women over 30 are more likely to have myoma or endometriosis contributing to HMB.

5 | CONCLUSION

Heavy menstrual bleeding occurred in two-thirds of women newly starting anticoagulation therapy, who complete a PBAC, which negatively impacts on their quality of life. Clinicians prescribing anticoagulation therapy should be mindful of this, and recognized measures should be taken to help minimize this problem in menstruating women.

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AUTHOR CONTRIBUTIONS

J.P.P. contributed to the study design, recruited participants, collected, and analyzed the data and drafted the manuscript. O.N. recruited participants and reviewed and edited the manuscript. L.N.R. contributed to study design and reviewed and edited the manuscript. J.J. contributed to study design and reviewed and edited the manuscript. J.R. contributed to study design and reviewed and edited the manuscript. R.A. contributed to study design and reviewed and edited the manuscript.

RELATIONSHIP DISCLOSURE

L.N.R. has received speaker fees and travel grant from Bayer and an investigator-initiated research grant and travel grant from Sanofi. R.A. reports grants from Bayer; personal fees from Bayer and Sanofi and nonfinancial support from Bayer and Sanofi.

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