Thrombosis Research 136 (2015) 749–753

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Abnormal uterine bleeding in VTE patients treated with rivaroxaban compared to vitamin K antagonists

Nico De Crem [a], Kathelijne Peerlinck [b], Thomas Vanassche [b], Kristine Vanheule [b], Barbara Debaveye [b], Saskia Middeldorp [c], Peter Verhamme [b], Marijke Peetermans [a,*]

[a] University Hospital Leuven, Department of Internal Medicine, Herestraat 49, Leuven, Belgium
[b] University Hospital Leuven, Department of Cardiovascular Medicine, Herestraat 49, Leuven, Belgium
[c] Academic Medical Center Amsterdam, Department of Vascular Medicine, Meibergdreef 9, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 9 June 2015
Received in revised form 28 July 2015
Accepted 28 July 2015
Available online 4 August 2015

Keywords:
Venous thromboembolism
Anticoagulants
Menstruation
Abnormal uterine bleeding
Rivaroxaban
Vitamin K antagonist

ABSTRACT

Introduction: Rivaroxaban is a convenient oral anticoagulant for patients with venous thromboembolism (VTE). The impact of rivaroxaban and vitamin K antagonists (VKAs) on abnormal uterine bleeding (AUB) in real life has not been previously explored.
Materials and methods: We performed a single-center retrospective study on AUB in female VTE patients of reproductive age who were treated with either rivaroxaban or VKAs.
Results: Questionnaire results were available for 52 patients in each treatment group.
Approximately two thirds of all women reported AUB after initiation of anticoagulant therapy. Patients using rivaroxaban were more likely to experience prolonged (>8 days) menstrual bleeding (27 % *vs.* 8.3%, P = 0.017). Rivaroxaban treatment increased the duration of menstrual bleeding from median 5 (IQR 3.5-6.0) days before start of treatment to 6 (IQR 4.1-8.9) days (P < 0.001). VKA treatment did not lead to significant prolongation of the menstrual period.
Patients on rivaroxaban more frequently reported an unscheduled contact with a physician for AUB than women using VKAs (41% *vs.* 25%, P = 0.096). They also reported increased need for menorrhagia-related medical or surgical intervention (25% *vs.* 7.7%, P = 0.032) and had more adaptations of anticoagulant therapy (15% *vs.* 1.9%, P = 0.031).
Conclusion: AUB is frequent after initiation of anticoagulant therapy for acute symptomatic VTE. Compared to VKAs, rivaroxaban was associated with prolonged menstrual bleeding and more medical interventions and adaptation of anticoagulant treatment for AUB. These data can guide proactive discussion with patients starting anticoagulant therapy.

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1. Introduction

Venous thromboembolism (VTE) is a frequent disorder, affecting 1–10 per 10,000 women of reproductive age per year [1,2]. The two main clinical presentations are deep-vein thrombosis (DVT) and pulmonary embolism (PE). Therapy typically consists of initial treatment with low-molecular-weight heparins (LMWHs) followed by vitamin K antagonists (VKAs) for a period of at least 3 months. The need for long-term secondary prevention depends on the presence or absence of modifiable or non-modifiable risk factors [3]. Recently, direct-acting oral anticoagulants (DOACs) offer an alternative convenient treatment for patients with VTE. These drugs act through direct inhibition of thrombin (dabigatran) or activated factor X (rivaroxaban, apixaban, edoxaban). Phase III trials have demonstrated that DOACs were as effective as VKAs while associated with less major bleeding. DOACs offer an important advantage because laboratory monitoring and subsequent dose adjustment are not necessary, contrary to therapy with VKAs [4].

Rivaroxaban has been licensed for the treatment and secondary prevention of VTE and was reimbursed for VTE in Belgium in January 2013. Its efficacy and safety have been proven in the EINSTEIN-DVT and -PE studies that showed non-inferiority for recurrent VTE and a significant reduction in major bleeding rate [5–7]. In the setting of non-valvular atrial fibrillation, there was a shift in bleeding pattern, with fewer intracranial hemorrhages and higher gastrointestinal bleeding rates amongst the patients treated with rivaroxaban compared to warfarin [8,9]. A different bleeding pattern may also be present for urogenital bleedings. Currently, there are no specific data regarding the effect of rivaroxaban

Abbreviations: AUB, abnormal uterine bleeding; BMI, body mass index; DVT, deep-vein thrombosis; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LMWH, low-molecular-weight heparin; DOAC, direct-acting oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

* Corresponding author at: Herestraat 49 box 911, B- 3000 Leuven, Belgium.
E-mail address: marijke.peetermans@med.kuleuven.be (M. Peetermans).

http://dx.doi.org/10.1016/j.thromres.2015.07.030
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on abnormal uterine bleeding (AUB). The objective of our study was to evaluate the impact of rivaroxaban compared to VKAs on AUB in women with acute symptomatic VTE.

2. Materials and Methods

We conducted a single-center retrospective study at the University Hospital of Leuven, Belgium. The study was approved by the institutional review board. All women between the age of 14 and 55 years who were enrolled in the VTE care program from September 2007 until September 2014 were evaluated for eligibility. Patients who did not have an acute symptomatic VTE, but suffered from asymptomatic thrombosis, thrombophilia or superficial thrombophlebitis were excluded from the study, as well as those who were treated with an anticoagulant other than rivaroxaban or VKAs. One hundred nineteen patients gave written informed consent for review of their medical records and filled out a questionnaire appropriately. The questionnaire is available in the Supplementary Appendix.

We collected information on baseline biometric parameters and VTE risk factors at the time of the index VTE. Recent immobilization was defined as being bedridden during more than half of the time for a duration of at least three consecutive days in the past four weeks or as having a recent self-reported significant reduction in physical movement. Use of estrogen included use of estrogen containing combined contraceptives, selective estrogen receptor modulators and in vitro fertilization therapy. The puerperium was defined as a period of 8 weeks starting from delivery. Malignancy was defined as active malignancy or having had treatment within a period of six months prior to the diagnosis of VTE [10,11]. Thrombophilia included proven resistance to activated protein C, protein S and protein C deficiency, antithrombin deficiency, prothrombin G20210A mutation, elevated factor VIII, the presence of a lupus anticoagulant and/or anticardiolipin antibodies. A positive familial history of VTE was defined as a history of PE or DVT in a first or second degree relative.

We defined AUB according to the recommendations of the International Federation of Gynecology and Obstetrics (FIGO) as prolonged menstrual bleeding (more than 8 days in duration on a regular basis), intermenstrual bleeding, heavy menstrual bleeding (passage of blood clots) or menstrual blood loss causing anemia or requiring unscheduled contact with a medical practitioner, medical or surgical intervention or adaptation of anticoagulant therapy [12]. We also assessed if the change in menstrual bleeding pattern interfered with activities of daily life.

We assessed the presence of anemia as well as other manifestations of increased bleeding tendency, e.g. epistaxis, ecchymoses, hematuria and gastrointestinal blood loss. Anemia was defined according to the World Health Organization definition as a serum haemoglobin level of less than 12 mg/dL or, in the absence of an available in-hospital laboratory analysis, as self-reported anemia or need for transfusion [13]. Iron deficiency was concluded upon iron replacement therapy.

Data on unscheduled contact(s) with a medical practitioner, medical or surgical intervention or adaptation of anticoagulant treatment because of menstrual bleeding were collected. We defined an unscheduled contact as a consultation with a physician or a hospitalization specifically for AUB. A medical or surgical intervention was defined as change of oral hormonal or contraceptive therapy (e.g. implantation of an intrauterine device), endometrial ablation/embolization or hysterectomy.

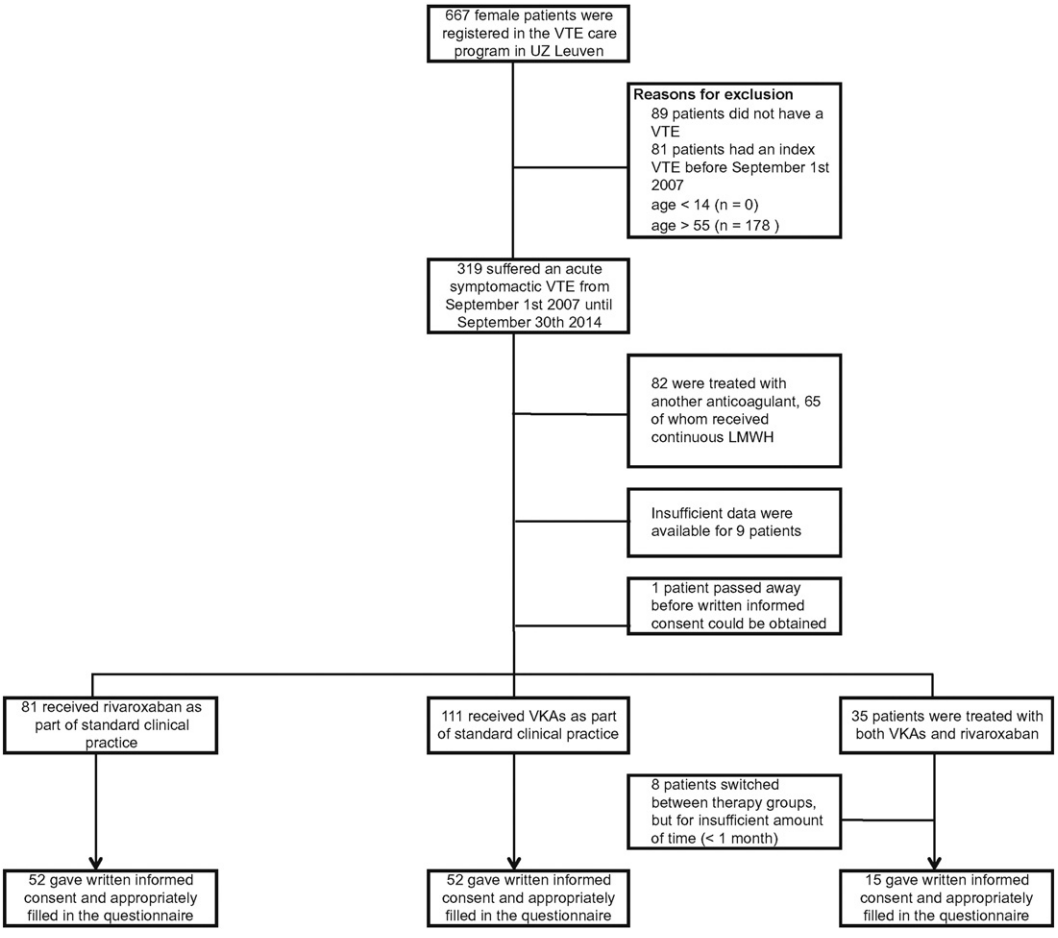

Fig. 1. Study population. VTE denotes venous thromboembolism, LMWH = low-molecular-weight heparins, VKA = vitamin K antagonists.

Adaptation of anticoagulant treatment included temporary interruption (>3 days) or dose reduction (>3 days) or change of anticoagulant therapy.

Statistical analysis was performed using GraphPad Prism 6 (Version 6.05, GraphPad Software, San Diego, USA). For comparison of the duration of menstrual bleeding before *vs.* after initiation of anticoagulant therapy, Wilcoxon matched pairs test was used. Data of rivaroxaban and VKA-treated patients were analysed with unpaired t-test or non-parametric Mann–Whitney test. For dichotomous data, groups were compared using Fisher's exact tests.

3. Results

Patient enrollment and disposition is shown in Fig. 1.

Three hundred nineteen female patients of reproductive age (14–55 years old) suffered from a VTE during the study period. Of those, 111 patients received VKAs as part of standard clinical practice, as compared to 81 patients who were treated with rivaroxaban. A small group of patients (n = 35) received both VKAs and rivaroxaban during the course of VTE treatment. However, 8 patients switched between therapy groups for an insufficient amount of time (less than one month) to allow for comparison of the effect of both therapies on menstrual bleeding pattern and were excluded from the study. Written informed consent was obtained in 52 VKA-treated patients, 52 rivaroxaban-treated patients and 16 patients who had received both. 1 patient who switched between therapies was not included in the statistical analysis due to inappropriately filling out of the questionnaire. Patient characteristics are shown in Table 1. There was no significant difference in both therapy groups in biometric parameters. Patients treated with rivaroxaban were more likely to have a DVT (63% *vs.* 35%, P = 0.006) and less likely to have an index VTE other than DVT or PE as compared to the VKA group (0.0% *vs.* 15%, P = 0.006). Patients using rivaroxaban were less frequently using estrogen containing therapy at the time of the index VTE as compared to VKA-treated patients (63% *vs.* 85%, P = 0.024). Other VTE risk factors were well balanced between both therapy groups.

The results of the retrospective database and questionnaire analysis are shown in Table 2.

Approximately two thirds of rivaroxaban-treated (73%) and VKA-treated patients (67%) suffered from AUB. Initiation of anticoagulant therapy with rivaroxaban was associated with increased rates of prolonged menstrual bleeding (27% after *vs.* 4.1% before the start of treatment, P = 0.002), intermenstrual bleeding (41% *vs.* 12%, P < 0.001) and an increased average menstrual bleeding time (6 (4.1-8.9) days *vs.* 5 (3.5-6.0) days, median (IQR), P < 0.001) (Fig. 2). Start of VKA treatment increased intermenstrual bleeding rates (26% *vs.* 7.8%, P = 0.018) but had no significant effect on the duration of menstrual blood loss or on prolonged bleeding rates (Fig. 2). As compared to VKA-treated patients, rivaroxaban-treated patients reported more prolonged menstrual bleeding (27% *vs.* 8.3%, P = 0.017) after initiation of anticoagulant therapy (Fig. 2). Patients treated with VKAs reported more bleeding other than AUB as compared to patients treated with rivaroxaban (P < 0.001), mainly because of an increase in ecchymoses. No difference in the presence of anemia between both treatment groups was observed.

Patients on rivaroxaban reported more unscheduled contacts with a medical practitioner compared to patients on VKAs (41% *vs.* 25%, P = 0.096), more medical or surgical interventions (25% *vs.* 7.7%, P = 0.032) and more adaptation of anticoagulant treatment (15% *vs.* 1.9%, P = 0.031) because of AUB (Table 2).

The patients who received both therapies during the course of VTE treatment were analyzed separately and the same trends were noted in this group of patients *(data not shown)*.

4. Discussion

We conducted a single-center retrospective study to evaluate the impact of rivaroxaban and VKAs on AUB. Approximately two thirds of patients reported AUB. Use of rivaroxaban was associated with a

Table 1
Patient characteristics.

Parameter	Patients treated with rivaroxaban (N = 52)	Patients treated with VKAs (N = 52)	P-value
Patient characteristics			
Median age at time of index thrombosis (IQR) - yr	38 (23–43)	29 (24–49)	NS
Median BMI at time of index thrombosis (IQR) - kg/m^2	24 (21–30)	25 (21–28)	NS
Disease characteristics			
Indication for anticoagulation -no. (%)			
Deep-vein thrombosis	33 (63%)	18 (35%)	**0.006**
Pulmonary embolism	9 (17%)	14 (27%)	NS
Combined deep-vein thrombosis and pulmonary embolism	10 (19%)	12 (23%)	NS
Other VTE *	0 (0.0%)	8 (15%)	**0.006**
Risk factors for VTE			
Recent immobilization or surgery	18 (35%)	18 (35%)	NS
Use of estrogen	33 (63%)	44 (85%)	**0.024**
Overweight or obesity	22 (42%)	25 (48%)	NS
Pregnancy/puerperium	2 (3.8%)	2 (3.8%)	NS
Malignancy-associated	2 (3.8%)	0 (0.0%)	NS
Active smoking	6 (12%)	8 (15%)	NS
Thrombophilia	17 (33%)	26 (50%)	NS
Hereditary	16 (31%)	23 (44%)	NS
Antiphospholipid antibodies	2 (3.8%)	4 (7.7%)	NS
Previous VTE	14 (27%)	11 (21%)	NS
Positive family history of VTE	12 (23%)	19 (37%)	NS

VKAs denotes vitamin K antagonists, IQR = interquartile range, BMI = body mass index, VTE = venous thromboembolism.

* Of whom 7 had a cerebral venous sinus thrombosis and 1 had a portal vein thrombosis.

Table 2
Study outcomes.

Outcome	Patients treated with rivaroxaban	Patients treated with VKAs	P-value
Total of AUB according to study definition - no. (%)	38/52 (73%)	35/52 (67%)	NS
Menstrual disturbances: objective parameters - no. (%)	28/52 (54%)	26/52 (50%)	NS
Prolonged bleeding (>8 days)	13/48 (27%)	4/48 (8.3%)	**0.017**
Intermenstrual bleeding	21/51 (41%)	13/50 (26%)	NS
Blood clots during menstruation	16/48 (33%)	17/49 (35%)	NS
Menstrual disturbances: subjective parameters - no. (%)	30/52 (58%)	29/51 (57%)	NS
Prolongation of bleeding	22/52 (42%)	19/51 (45%)	NS
Increased intensity	27/52 (52%)	24/51 (47%)	NS
Interference with daily life	6/52 (12%)	9/51 (18%)	NS
Anemia/iron deficiency - no. (%)	11/52 (21%)	12/52 (23%)	NS
Treated with iron suppletion	6/51 (12%)	7/51 (14%)	NS
Treated with transfusion	1/51 (2.0%)	1/52 (1.9%)	NS
Unscheduled contact with a medical practitioner - no. (%)	21/51 (41%)	13/52 (25%)	0.096
Consultation of a medical practitioner	21/51 (41%)	13/52 (25%)	0.096
Hospitalization	1/51 (2.0%)	1/52 (1.9%)	NS
Medical or surgical intervention - no. (%)	13/52 (25%)	4/52 (7.7%)	**0.032**
Change of contraceptive therapy	12/52 (23%)	4/52 (7.7%)	0.055
Endometrial ablation or embolization	1/52 (1.9%)	1/52 (1.9%)	NS
Hysterectomy	1/52 (1.9%)	0/52 (0.0%)	NS
Adaptation of anticoagulant therapy - no. (%)	8/52 (15%)	1/52 (1.9%)	**0.031**
Temporary interruption or dose reduction of anticoagulant therapy (>3 days)	5/52 (9.6%)	1/52 (1.9%)	NS
Change of anticoagulant therapy	5/52 (9.6%)	1/52 (1.9%)	NS

*VKAs denotes vitamin K antagonists, AUB = abnormal uterine bleeding.

prolongation of menstrual bleeding and an increased need for medical or surgical intervention and for adaptation of anticoagulant treatment due to AUB as compared to VKAs. Therapy with rivaroxaban also significantly increased the average duration of menstrual bleeding and the occurrence of intermenstrual bleeding.

Remarkably, 73% of rivaroxaban-treated and 67% of VKA-treated patients experienced AUB in our study. These high rates are comparable with data from two other retrospective studies on the impact of oral anticoagulation with VKA (mostly warfarin) on menstrual bleeding [14,15]. Both previous studies showed that women of reproductive age experienced prolonged and heavier menstrual bleeding whilst on anticoagulation. Our results confirm that in young women who initiate anticoagulant therapy, AUB remains an important side effect. AUB, although possibly underestimated by many clinicians, is especially relevant in the treatment of an acute symptomatic VTE of young female patients.

Increasing data emerge that bleeding patterns under DOAC therapy differ from those seen in VKA-treated patients. A recent meta-analysis that included the phase 3 trials comparing the use of dabigatran, rivaroxaban, apixaban or edoxaban with the use of VKAs found a 39% significant relative reduction in major bleeding and a 22% non-significant reduction in major gastrointestinal bleeding, albeit with substantial heterogeneity in the latter [4]. Higher gastrointestinal bleeding rates were observed amongst patients treated with rivaroxaban compared to VKAs in non-valvular atrial fibrillation [8,16,17], but not in VTE patients in the EINSTEIN-DVT and -PE trials [5,6]. Possible explanations for these findings are differences in pharmacological properties of the anticoagulants with a difference in non-absorbed fraction of DOACs, differences in dosing regimens and differences in study populations [9]. Our data indicate that other mucosal surfaces besides the gastrointestinal tractus can be more prone to bleeding while using rivaroxaban as well.

The nature of this retrospective study brings about several limitations. Our retrospective study is prone to selection bias. Patients who experience AUB according to our study definition are more likely to give written informed consent for analysis of their medical records and to fill out the questionnaire because of their awareness of the impact of oral anticoagulant treatment on menstrual bleeding. Therefore we can suspect an overestimation of the true effect of anticoagulant therapy on menstrual bleeding in this study. However, this potential selection bias would affect both VKA- as rivaroxaban-treated women.

Due to the later availability of rivaroxaban as compared to VKAs, patients receiving rivaroxaban are more likely to have more precise memories of the different aspects of menstrual bleeding before and after the start of anticoagulant therapy. We tried to account for this recall bias by excluding patients who had an index VTE before September 2007 in our study. Patients who switched between therapy groups were also not included in our results. The questionnaire results of these patients were considered to be more prone to imprecisions because of the importance of the association between the anticoagulant used and anticoagulation-related adverse events.

A significant number (n = 19 or 37% in the rivaroxaban group, n = 27 or 52% in the VKA group,) of patients had no in-hospital laboratory analysis available to assess the presence of anemia before and after the start of anticoagulant therapy. Therefore we used a definition of anemia as either a serum haemoglobin level of less than 12 mg/dL or self-reported anemia or need for transfusion. Anemia before the index VTE was also present in some patients (n = 3 in the rivaroxaban group, n = 1 in the VKA group) or unknown. In our study definition of AUB, we included only objective parameters to further reduce the risk of recall bias. We did not include heavy menstrual bleeding – i.e., menstrual bleeding that interferes with a woman's physical, emotional, social and material quality of life - in our study definition because of its subjective nature. This differs from the FIGO recommendations [12].

We can also suspect that a number of patients may already have had AUB before the start of anticoagulant therapy. However, we did not assess the presence of anemia, unscheduled contact with a medical practitioner, medical or surgical intervention or adaptation of anticoagulant treatment due to AUB before the start of anticoagulant therapy. Furthermore, the change of oral contraceptive or hormonal therapy at the time of index VTE – to eliminate estrogen use as a risk factor for VTE - also affects the menstrual bleeding pattern. Indeed, physicians often discontinue estrogen-containing drugs, as they are associated with an increased risk for VTE. However, a recent subanalysis of the EINSTEIN-DVT and -PE trials did not show an increased risk for recurrent VTE in women who continued estrogen-containing oral contraceptives while on anticoagulation [18]. Hence, a prospective validation of continued contraceptive use in women during anticoagulant therapy warrants further clinical evaluation.

In conclusion, our study shows that AUB is frequent after initiation of anticoagulation for acute symptomatic VTE. Compared to VKAs, the direct Xa inhibitor rivaroxaban is associated with prolonged menstrual bleeding and an increased need for medical or surgical interventions or adaptation of anticoagulant therapy for AUB. Our data can guide proactive discussion of physicians with patients who start anticoagulant therapy. However, prospective studies to evaluate the impact of DOACs on AUB in the setting of acute symptomatic VTE are needed to avoid the pitfalls associated with retrospective studies.

Authorship Details

NDC, TV, KP, PV and MP designed the study. NDC designed the questionnaire; NDC, KV and BD extracted data from patient files and

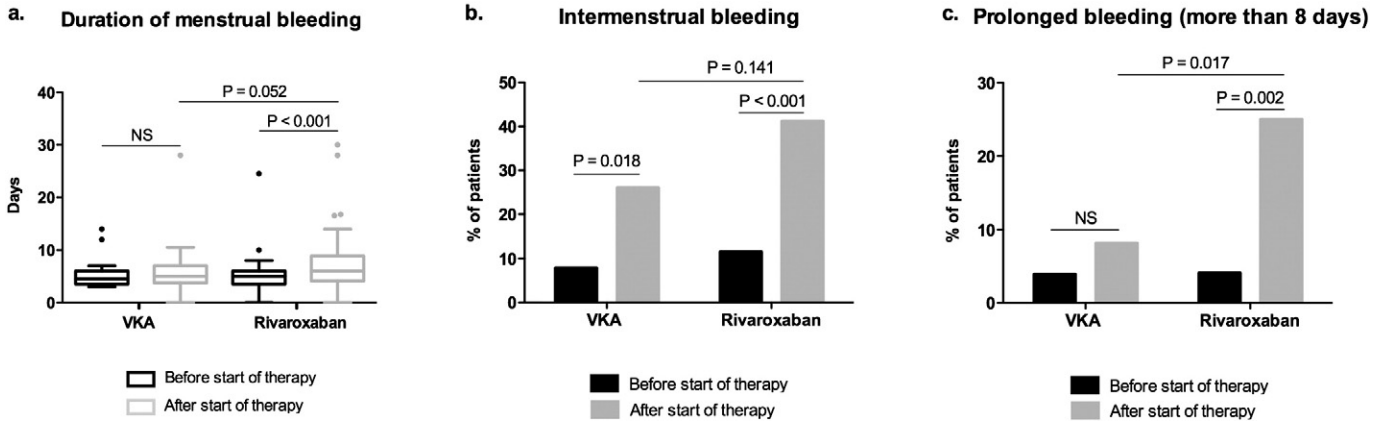

Fig. 2. Menstrual disturbances - objective parameters. a. Duration of menstrual bleeding; b. Intermenstrual bleeding; c. Prolonged menstrual bleeding (more than 8 days). VKA denotes vitamin K antagonists, NS = not significant.

analyzed the data. NDC wrote the manuscript. MP assisted in data analysis and interpretation. MP, SM and PV aided in manuscript preparation. All authors revised the manuscript and approved the final version to be submitted.

This work was supported by a grant of the Research Foundation Flanders (FWO-Vlaanderen, 11I0113N). MP is a fellow of the FWO, PV is a senior clinical investigator of the FWO. The funding source had no involvement in trial design, data collection/interpretation and manuscript preparation.

NDC, KP, TV, KV, BD and MP have no conflicts of interest with regard to this work. SM has received lecture fees and research support from Bayer, BMS/Pfizer, Glaxo-Smith-Kline, Aspen, Boehringer-Ingelheim and Daiichi-Sankyo. PV has received research support and honoraria for lectures and advisory boards from Bayer, Pfizer, Boehringer-Ingelheim, Daiichi-Sankyo, Sanofi-Aventis, Leo Pharma, and ISIS Pharmaceuticals. PV holds the Chair in Cardiovascular Medicine, funded by Bayer.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2015.07.030.

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