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Alice Ballerie * [a, b], Rémi Nguyen Van * [a], Karine Lacut[c], Hubert Galinat[d], Chloé Rousseau [e] Adeline Pontis[f], Fabienne Nédelec-Gac[f], Alain Lescoat [a,b], Nicolas Belhomme [a], Pierre Guéret[f], Guillaume Mahé[g], Francis Couturaud[c], Patrick Jégo [a, b], Isabelle Gouin-Thibault[f, b]

*: co-first author

[a]Department of Internal Medicine and Clinical Immunology, Rennes University Hospital, Rennes, France.
[b]Univ Rennes, Rennes University Hospital, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et Travail) - UMR_S 1085, Rennes, France
[c] Department of Internal Medecine and Chest Diseases, Brest University Hospital, Bretagne Occidentale University , EA 3878, CIC INSERM 1412, Brest, FCRIN INNOVTE, France.
[d] Hematology Laboratory, Brest University Hospital, Bretagne Occidentale University, EA 3878, Brest, France
[e] Clinical Investigation Center INSERM 1414, Department of clinical pharmacology, Rennes University Hospital, F-35033 France
[f] Hematology Laboratory, Rennes University Hospital, Rennes, France.
[g]Vascular Medicine Unit, Rennes University Hospital, INSERM CIC 1414, Clinical Investigation Center, Univ Rennes, M2S - EA 7470, F-35033, Rennes, France.

Running head: rivaroxaban and apixaban in obese VTE patients

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Corresponding author:
Isabelle Gouin-Thibault
Laboratory of Hematology,
Rennes University Hospital, Pontchaillou
2 rue Henri Le Guilloux
35033 RENNES CEDEX 09
33 2 99289563
isabelle.gouin@chu-rennes.fr

Highlights

- Prospective bi-centric study dedicated to DOAC levels in obese patients being treated for VTE and followed in a thrombosis clinic
- 22/146 patients (15%) had DOAC concentrations outside the on-therapy ranges
- Age≤63 y, use of rivaroxaban and time since last intake≤8h were associated with DOAC concentrations outside the on-therapy ranges
- 2 (1%) patients had recurrent VTE, none had major bleeding and 11 (8%) had minor bleeding

Abstract

Background

Direct oral anticoagulants (DOAC) use remains challenging in obese patients treated for Venous-Thrombo-Embolism (VTE) due to the paucity of prospective and dedicated studies.

Objective

To assess rivaroxaban and apixaban concentrations at different time-points after intake, in obese patients followed at a thrombosis center and treated for VTE; to define factors associated with DOAC levels outside the on-therapy ranges; and to evaluate bleeding and thrombosis rates during follow-up.

Methods

Observational prospective study in two French University hospitals.

Apixaban or rivaroxaban concentrations were measured after the first visit, regardless of last intake in obese patients receiving DOAC for VTE. Concentrations were compared to published reference values for non-obese patients. Demographic, clinical, biological and therapeutic data were collected. Univariate and multivariate analyses were performed to identify factors associated to DOAC concentrations outside the on-therapy ranges.

Results

Out of the 146 patients included, 22 (15%) had DOAC concentrations outside the on-therapy ranges, mainly in the rivaroxaban group (n=17).

Age≤63 years, use of rivaroxaban and time since last intake≤8h were associated with DOAC concentrations outside the on-therapy ranges, in multivariable analysis.

During the median follow-up of 16 months, two (1%) patients receiving apixaban had recurrent VTE. No patient had major bleeding, 11 (8%) patients had minor bleeding.

Conclusion

In this specific prospective bi-centric study dedicated to VTE obese patients**,** use of DOACs at fixed doses led to concentrations similar to those of non-obese patients in a high proportion of patients, without any effect of the BMI, and with risk-benefit profile comparable to non-obese patients.

Key words: obesity, venous thromboembolism, hemorrhage, apixaban, rivaroxaban

INTRODUCTION

The prevalence of obesity, defined as a Body Mass Index (BMI) between 30 kg/m^2 and 40 kg/m^2, and 'extreme obesity' as a BMI of >40 kg/m^2, is dramatically increasing. Patients with excessive BMI have a higher risk of Venous Thrombo-Embolism (VTE) and of recurrent VTE following withdrawal of anticoagulation therapy.[1]

The advent of direct oral anticoagulants (DOAC) is a major breakthrough in the management of patients with VTE. Among them, apixaban and rivaroxaban, which specifically target factor Xa, have been approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for prevention of their recurrence[2–4]. In comparison with vitamin K antagonists, DOAC have a more predictable anticoagulant activity, less drug-drug interactions and are associated with a lower incidence of intracranial hemorrhage[5]. DOAC are an attractive alternative to vitamin K antagonists in obese patients who are prone to long-term treatment for unprovoked VTE and experience venipuncture difficulties. Pharmacokinetics (PK) characteristics of apixaban and rivaroxaban in non-obese subjects have been thoroughly studied [6,7]. PK parameters can be altered in obese patients but the effect varies widely among drugs and has not been clearly defined with DOAC[8]. Data on healthy subjects showed that high body weight group (≥ 120 kg) had approximately 31% and 23% lower apixaban maximum concentrations and exposure than the reference body weight group (65-85 kg)[9], while maximum concentrations of rivaroxaban were unaffected in subjects >120 kg as compared to normal weight subjects (70-80 kg)[10].

In 2016, due to the limited available PK and specific clinical data, especially in "extreme" obese patients, the International Society on Thrombosis and Hemostasis (ISTH) raised the concern for DOAC under-dosing in patients with BMI >40 kg/m^2 or weight >120 kg. ISTH guidelines suggested to check whether drug-specific peak and trough levels in this population fall within the expected range of non-obese patients and to change to vitamin K antagonists if levels fall below the expected range [11]. Thereafter, the few studies that reported data on DOAC concentrations in patients with BMI over 30 kg/m^2 included either a very limited number of obese patients, or were retrospective cohorts with potential inaccuracy in timing of peak and trough levels, or included heterogeneous patient populations with various indications and did not include data on clinical outcomes [12–14]. The accuracy in the time between blood sample and drug intake is important for making clinically relevant interpretation of results. Moreover, the time of DOAC maximum concentration is not well defined and may differ from one patient to another [15]. The other available data on obese

patients are based on post hoc analyses of randomized trials, registries, retrospective studies or healthcare claims databases. These studies showed minor effects of obesity on DOAC PK and reported similar efficacy and safety of DOACs across the different weight groups, and *versus* vitamin K antagonists, suggesting DOAC efficacy and safety in obese patients[16–26]. However, these conclusions may be tempered as the lack of prospective and specific studies in this population, and the high number of studies integrating healthcare claim databases, represent limitations.

In this context, we conducted a prospective observational real-life two-center study with the following objectives: to assess rivaroxaban and apixaban concentrations measured at different time-points after intake, in obese patients treated for VTE, and to compare these concentrations to reference values available in the literature for non-obese patients; to define risk factors of DOAC concentrations outside the on-therapy ranges; and to evaluate bleeding and thrombosis rates during follow-up.

MATERIAL AND METHODS

Study design, population and data collection

This is an observational prospective longitudinal study in two French University hospitals.
Consecutive adult obese patients (BMI≥30 kg/m^2) receiving apixaban or rivaroxaban for VTE treatment and followed in the outpatient thrombosis clinics of Rennes and Brest University Hospitals between August 2017 and January 2019, were included in this study. The two thrombosis centers are multidisciplinary groups dedicated to the treatment and follow-up of patients with venous thromboembolism events. The patients are usually seen one month and 6 months after diagnosis and then once a year when the treatment is prolonged. Any obese patient with VTE followed by the thrombosis center could be included in the study, whatever the time since the initiation of anticoagulation.
Apixaban or rivaroxaban plasma concentrations were measured in all patients just after the inclusion visit, whatever the time since last intake, as part of routine care. The exact time between DOAC intake and blood sampling was strictly recorded, as well as DOAC dose.
For each patient, demographic, clinical, biological and therapeutic data were collected from computerized medical records:

- gender, age, weight, BMI, creatinine, creatinine clearance (calculated using the Cockcroft and Gault formula), liver disease defined as chronic alcoholism,

steatosis or moderate disturbance of liver function; these tests were performed at the inclusion visit as part of the monitoring of the obese patients

- date and type of the index VTE event, personal and family history of VTE, VTE risk factors: cancer, thrombophilia (antithrombin, protein S, protein C deficiency, factor V and II mutations, antiphopholipid syndrome), myeloproliferative neoplasm
- duration of treatment since initiation, concomitant medications that could potentially interact with apixaban and rivaroxaban transport or metabolism, *i.e.* P-glycoprotein and CYP450 inhibitors or inductors (antifungal agents, HIV protease inhibitors, antibiotics, tacrolimus, cyclosporine, carbamazepine, rifampicin, St John's Wort)
- After inclusion visit the following outcomes were recorded until the end of the study: bleeding (all types), major bleeding according to ISTH definition[27] and confirmed VTE recurrence including deep vein thrombosis and pulmonary embolism.

The study was approved by the local ethics committee. All patients were informed and did not object to the inclusion.

Apixaban and rivaroxaban concentration measurements

Blood was collected into 109mM citrate tubes and was centrifuged within 2h to obtain plasma for testing.

Plasma apixaban and rivaroxaban concentrations were measured using the commercial assay STA-Liquid-anti-Xa®, with specific controls and calibrators on a STA-R Evolution® analyser (Stago) in each center, as proposed in the international recommendations on DOAC measurements [28] . These specific methods enable the accurate measurement of drugs over a wide range of concentrations up to 500 ng/mL and over 500 ng/mL after plasma dilution. The lower limit of quantification was of 20 ng/mL.

Statistical analysis

Each apixaban or rivaroxaban value was categorized, according to the time since last intake that was precisely recorded, as being within, above, or below processing ranges..

For that, each DOAC value was compared to the concentration-time profiles (mean values with 90% prediction intervals of the 5^{th}-95^{th} percentiles) at steady state for apixaban and

rivaroxaban in non-obese patients treated for VTE in clinical studies[6,7]. On-therapy ranges were therefore defined as the 5^{th}-95^{th} percentiles of observed concentrations, provided for hours 1, 2, 3, 4, 5, 6, 9, 12, 18 and 24h after rivaroxaban 20 mg once daily intake or obtained from the concentration-time profile for apixaban 5 mg or 2.5 mg twice daily [6,7].

Descriptive statistics were reported as median (min-max) for continuous data, and as number (percentage) of situations for categorical data.

We constructed a receiver operating characteristic (ROC) curve, to define a threshold for age, BMI and time since last intake with the best sensitivity and specificity discriminating between DOAC values within and outside the on-therapy ranges of DOAC.

We computed univariate logistic regression to select risks factors of DOAC values outside the on-therapy ranges. The quantitative variables tested were age, BMI, creatinine, creatinine clearance, duration of anticoagulation since initiation, time since last intake, whereas the qualitative variables were gender, age ≤ 63 years, categories of BMI or BMI ≥ 37.6 kg/m^2, liver disease, DOAC type, time since last intake ≤ 8h, concomitant intake of interfering drugs. The multivariate model was obtained by backward stepwise regression. Variables entered in the stepwise regression had a p-value lower than 0.20 in the univariate analysis.

All statistical analyses were performed with SAS software V9.4 (SAS Institute, Cary, N.C., USA). A p-value lower than 0.05 was considered statistically significant.

RESULTS

Clinical and therapeutic characteristics

Baseline characteristics of the 146 obese patients receiving apixaban or rivaroxaban for VTE included in this study are summarized in Table 1. Twenty-seven (18%) patients were from Brest University hospital and 119 (82%) from Rennes University Hospital. BMI ranged from 30.1 to 54 kg/m^2, with 20% patients having a BMI ≥ 40kg/m^2. Most of patients were treated for PE, mainly unprovoked thromboembolism events. No patient had cirrhosis or severe renal impairment (creatinine clearance < 30 mL/min using the Cockcroft and Gault formula), only two patients had a creatinine clearance < 50 mL/min. Half of them received rivaroxaban 20 mg once a day and half, apixaban either 5 mg or 2.5 mg twice a day. Only 4 patients (3%) had comedications that could interact with DOAC metabolism or absorption. No patient was taking aspirin or anti-P2Y12 drug.

Rivaroxaban and apixaban concentrations

The DOAC concentrations for each molecule and dosage as well as the time between intake and sampling are reported Table 2 - Figure 1.

Out of the 146 patients, 22 (15%) had DOAC concentrations outside the on-therapy ranges mainly in the rivaroxaban group, *i.e.* 22% of patients treated with rivaroxaban 20 mg and 8.5% of patients treated with apixaban 5 mg twice daily and 1 patient receiving apixaban 2.5 mg twice daily (Table 2).

Out of the 22 concentrations out of range, 19 (86%) were below the on-therapy ranges in patients with a BMI varying from 31 to 42 kg/m^2. In these patients, the median [min-max] time between intake and sampling was of 4.75 h [2.5 – 19.5] and 4 h [1.5 – 8] in patients treated with rivaroxaban 20 mg and apixaban 5 mg, respectively and was of 3.5h in the patient receiving 2.5 mg apixaban.

The three patients with concentrations higher than the on-therapy ranges, were receiving rivaroxaban and had a BMI of 35.9, 46.9 and 42.9 kg/m^2. The time between intake and sampling in these patients was of 4, 8 and 9h.

Risk factors of DOAC concentrations outside the on-therapy ranges

The ROC curve analysis demonstrated that, to predict DOAC values outside the on-therapy ranges, age ≤ 63 years had a specificity of 52% (95% CI: 44-61) and a sensitivity of 73% (95% CI: 54-91); a time since last intake ≤ 8 hours had a specificity of 31% (95% CI: 23-40) and a sensitivity of 86% (95% CI: 72-100) and BMI ≥ 37.6 kg/m^2 had a specificity of 73% (95% CI: 66-81) and a sensitivity of 41% (95% CI: 20-61).

The results of the univariate analysis are reported in Table 3. Multivariable analysis highlighted three independent parameters associated with DOAC concentrations outside the on-therapy ranges (Table 3): age ≤ 63 years, use of rivaroxaban and time since last intake ≤ 8h. Neither BMI nor creatinine clearance were associated with DOAC concentrations outside the on-therapy ranges.

Thrombosis and bleeding events during the follow-up

Follow-up duration ranged from 0.4 to 132 months with a median of 16 months (Table 2). During follow-up, two patients (1%) (Age: 31 and 45 years, BMI: 36.7 and 32 kg/m^2), receiving apixaban treatment (one, 5 mg and one, 2.5 mg, twice a day) for PE and DVT, had recurrent VTE, 5 and 13 months after DOAC measurements that were within the on-therapy ranges. The patient on apixaban 2.5 mg twice daily, had received full dose apixaban for 6 months.

No patient had major bleeding and 11 (8%) with a BMI ranging from 32.7 to 46.9 kg/m^2 (median age, [min, max]: 53 years [27-84]) had non-major bleeding that could be related to anticoagulant therapy (minor hemorrhoidal bleeding, menorrhagias, non-severe epistaxis, hematurias, tooth brushing gingivoragias, low-abundance hemoptysis whose etiological checkup was negative and without subsequent recurrence). Among these patients, one (1%) with a BMI of 46.9 kg/m^2, had a rivaroxaban concentration slightly above the on-therapy ranges (453 ng/mL, 4h after intake, for an on-therapy ranges of 161-369 ng/mL); all others had DOAC concentrations within the expected value.

DISCUSSION

In this study, we showed that among 146 obese patients with a wide range of BMI, treated with rivaroxaban and apixaban, 124 (85%) had DOAC concentrations similar to those of non-obese patients and, 2 (1%) patients developed recurrent thrombosis during follow-up.

One strength of this work is the accuracy of the reported time between DOAC intake and sampling that was prospectively recorded. It is of the utmost importance, especially since we measured concentrations at different time-points after intake and compared them to the corresponding concentrations in non-obese patients from the literature. This approach is more relevant than measuring concentrations at "peak time", since it may vary from patient to patient.

Moreover, in the 2016 ISTH guidelines, the on-therapy ranges for peak and through, rivaroxaban and apixaban concentrations were either mean and percentage coefficient of variation from data on healthy subjects (n<10), or range (5th–95th percentile) or mean ± SD from pooled data on patients treated for VTE and atrial fibrillation (AF) for rivaroxaban. As for apixaban, no data for VTE patients were reported [11]. In our study, we chose to use more accurate and specific data corresponding the 5th-95th percentiles of the time-profiles of rivaroxaban and apixaban observed concentrations in VTE clinical studies [6,7].

The large sample size, the wide prospective data collection and the homogeneity of our population of obese patients, all treated for VTE and followed in a thrombosis center, are other strengths of our study. Previous studies evaluating DOAC concentrations[13,14] were characterized by a limited sample size or heterogeneous indications for DOAC, including VTE and AF. Patients with VTE and AF differ in terms of clinical and demographical characteristics such as age, renal function or co-medications with potential impact on DOAC PK. In our study, patients (58.6 +15.9 years) had comparable age than patients included in DVT or PE trials[2–4], with no severe renal impairment and only two patients with creatinine

clearance below 50 mL/min, and a few patients (3%) had concomitant medications that could interact with DOAC metabolism or absorption. In our study, univariate and multivariable analyses were performed to identify risk factors of DOAC concentrations outside the on-therapy ranges in this specific population of obese patients treated for VTE, especially since patients included in this study had a wide range of BMI. Neither BMI nor creatinine clearance were a determinant of DOAC concentrations outside on-therapy ranges in our population. Similarly, Martin *et al*, using Pearson's correlations found no relationship between DOAC peak or trough concentrations and BMI or renal function (Cockcroft clearance) in 63 patients with AF and 53 patients with VTE[14].

Speed V *et al* developed a population PK model, using retrospective data of AF and VTE patients, to simulate rivaroxaban concentrations at the extremes of bodyweight[17]. They found that creatinine clearance calculated by Cockcroft-Gault formula was the most significant covariate influencing rivaroxaban exposure[17]. However, their patients were mainly AF patients thus potentially older (range: 16-96 years) and with more frequent renal impairment (creatinine clearance range: 16-259 mL/min) than in our population. Moreover, they use lean bodyweight as the weight descriptor instead of total body weight, in Cockcroft-Gault formula.

We found that rivaroxaban (as compared to apixaban) and time since last intake ≤ 8h were independent predictors of DOAC concentrations outside the on-therapy ranges. One hypothesis for the predictor, time ≤ 8h, is the complex and variable absorption of rivaroxaban potentially related to a prolonged absorption phase and an enteroenteric recycling with subsequent inter-individual variability in rivaroxaban PK, within the first hours after intake [15,29]. Indeed, in PK studies, at least two peak rivaroxaban concentrations were found [15,29]. Absorption is usually not affected by obesity[8], but whether obesity may influence such a complex absorption is not known. Moreover, the variations in concentration-time profiles and the peak-to-trough ratio are greater with rivaroxaban once-daily than with apixaban twice daily[30], potentially contributing to the higher number of values outside the on-therapy ranges in rivaroxaban-treated patients. In accordance with our results, Martin *et al.* found a high proportion of peak concentrations (15/36; 42%) below the on-therapy ranges with rivaroxaban and none among the 8 peak apixaban concentrations [14]. Similarly, Piran *et al*. found that among 21 patients with a body weight over 120 kg and treated with rivaroxaban for various indications, 6 (28%) had concentrations outside the on-therapy ranges and none with apixaban[13]. All together, these results highlight the difficulty of interpreting concentrations and especially peak values, in patients treated with rivaroxaban and are in line

with the up-dated ISTH guidelines for obese patients, which suggest not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decision[31].

Age ≤ 63 years was an independent risk factor of values outside the on-therapy ranges in our study. In the population PK of apixaban, in non-obese subjects treated for VTE, age had less than 25% impact on apixaban exposure[6] and moderately affected rivaroxaban PK profile[7]. However, young age (< 60 years compared to 75 years) has been reported as a predictor of non-adherence to DOAC treatment[32]. Non-adherence or poor adherence to treatment of younger patients in our study may have contributed to values outside the on-therapy ranges. Another hypothesis could also be a more efficient drug clearance with better end organ function for younger patients.

Over the mean follow-up of 17 months, two patients with BMI < 40 kg/m^2 developed recurrent DVT or PE, which is consistent with the expected number of recurrence based on data from randomized controlled trials[4]. Hemorrhagic complications were all minor and their rate was comparable to non-obese population[2,4].

One limitation of our study is that it was not designed to assess clinical outcomes. However, the length of follow-up, in a thrombosis center, allowed us to provide information on the safety and efficacy of DOAC in our population. Another limitation is that DOAC concentrations were not measured when the recurrent or hemorrhagic events occurred. Therefore, the relationship between DOAC concentrations and clinical outcomes is difficult to establish. Nevertheless, the DOAC concentration measurements were only aimed at evaluating the response of obese patients to a fixed dose of DOAC, in comparison with non-obese patients.

Finally, our work is the largest study focusing on DOAC concentrations, with a clinical follow-up, in obese patients treated for VTE, so far. We found that DOAC use in obese patients treated for VTE, at fixed doses led to concentrations similar to those of non-obese patients in a high proportion of patients, without any effect of the BMI, and with similar risk-benefit profile comparable to non-obese patients. Guidelines from the ISTH were developed to provide practical guidance for clinicians regarding DOAC use in obese patients, suggesting DOAC concentration measurement in obese patients to manage anticoagulation [11]. Overall, our results, in accordance with others, raise the question of the relevance of measuring DOAC concentrations in obese patients to manage anticoagulation. A prospective study, focusing on obese patients and providing robust PK data in comparison to non-obese

subjects, would be useful to definitively draw conclusions on the PK profiles of DOAC in this population.

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CONFLICT OF INTEREST

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All other authors declare no conflicts of interest.

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FIGURE LEGEND

Figure 1: DOAC concentrations according to the time since last intake

TABLES AND FIGURE

Table 1: Baseline characteristics of the 146 obese patients receiving apixaban or rivaroxaban for VTE

Clinical characteristics	**n=146**	
Gender (women)	70	(48)
Age (years)*	61	(19-86)
Weight (kg)*	100	(73-178)
BMI (kg/m^2)*	34.5	(30-54)
BMI 30-34.9 kg/m^2	79	(54)
BMI 35-39.9 kg/m^2	38	(26)
BMI $\geq$40	29	(20)
Creatinine (µmol/L)*	77	(44-155)
Creatinine clearance (mL/min)* #	125	(40-328)
Liver disease	7	(5)
VTE characteristics	**n=146**	
Pulmonary embolism with or without deep-vein thrombosis	115	(79)
Deep-vein thrombosis only	31	(21)
History of venous thromboembolism before index event	72	(50)
Unprovoked VTE	116	(80)
Active cancer	3	(0.9)
Antiphospholipid syndrome	11	(8)
Hereditary thrombophilia	20	(14)
First-degree family history of VTE	44	(33)
Myeloproliferative neoplasm	1	(1)
DOAC characteristics	**n=146**	
Anticoagulation duration between VTE and inclusion (months)*	6	(0.5-81)
Apixaban 5mg twice daily	47	(32)
Apixaban 2.5 mg twice daily	22	(15)
Rivaroxaban 20mg once daily	74	(51)
Rivaroxaban 10 mg once daily	1	(0.7)
Rivaroxaban 15 mg twice daily	2	(1.3)
Relevant comedications that could interact with DOAC	4	(3)

Qualitative variables are expressed as n (%) and quantitative variables* are expressed as median (min-max).
VTE: Venous ThromboEmbolism events
BMI: Body Mass Index
DOAC: Direct Oral AntiCoagulants
Creatinine clearance is calculated using the Cockcroft and Gault formula.

Table 2: DOAC concentration characteristics and clinical outcomes during follow-up

DOAC concentrations	**n=146**	
Apixaban 5 mg twice daily		n=47
Delay since last intake (hours)*	5.5	(1.5-12)
Concentration (ng/mL)*	103	(23-300)
Apixaban 2.5 mg twice daily		n=22
Delay since last intake (hours)*	3	(1-6)
Concentration (ng/mL)*	58	(20-114)
Rivaroxaban 20 mg once daily		n=77
Delay since last intake (hours)*	7	(1-28)
Concentration (ng/mL)*	108	(20-453)
DOAC concentrations outside the on-therapy ranges	**n=22**	
DOAC concentration higher than expected value	3/146	(2)
Apixaban 5mg twice daily	0	
Apixaban 2.5mg twice daily	0	
Rivaroxaban 20 mg once daily	3/77	(3.9%)
DOAC concentration lower than expected value	19/146	(13)
Apixaban 5mg twice daily	4/47	(8.5)
Apixaban 2.5mg twice daily	1/22	(0.5)
Rivaroxaban 20mg once daily	14/77	(18)
Clinical outcomes	**n=146**	
Follow-up after DOAC measurement (months)*	16.4	(0.4-132)
Major bleeding	0	(0)
Non major bleeding	11	(7.5)
Recurrent VTE	2	(1.4)
Death from any cause	0	(0)

Qualitative variables are expressed as n (%) and quantitative variables* are expressed as median (min-max)
VTE: Venous ThromboEmbolism events

Table 3: Factors associated with DOAC concentrations outside the on-therapy ranges (univariate analysis)

Variables	n/N	OR [CI95%]	P
Clinical characteristics			
Gender (women)	7/70	0.57 [0.23 ; 1.46]	0.2419
Age (per 5 years)	22/146	0.90 [0.79 ; 1.04]	0.1569
Age ≤ 63 years	16/75	2.94 [1.08 ; 8.00]	**0.0351**
BMI kg/m^2	22/146	1.01 [0.93 ; 1.10]	0.7689
BMI 30-34.9	12/79	1.02 [0.41 ; 2.54]	0.9645
BMI 35-39.9	5/38	0.81 [0.28 ; 2.37]	0.7023
BMI ≥ 40	5/29	1.23 [0.41 ; 3.65]	0.7151
BMI ≥ 37.6	8/41	1.58 [0.61 ; 4.10]	0.3510
Creatinine (µmol/L)	22/146	1.08 [0.85 ; 1.37]	0.5400
Creatinine clearance (mL/min) (per 10mL/min)#	22/146	1.04 [0.96 ; 1.13]	0.3255
Liver disease	0/7	0.35 [0.02 ; 7.68]	0.5038
DOAC characteristics			
Duration of anticoagulation since initiation	22/146	0.98 [0.95 ; 1.02]	0.3328
Apixaban 5mg twice daily	4/47	0.42 [0.13 ; 1.32]	0.1360
Apixaban 2.5 mg twice daily	1/22	0.34 [0.06 ; 1.94]	0.2230
Rivaroxaban 20mg once daily	17/74	4.00 [1.39 ; 11.51]	**0.0103**
Delay since last intake	22/146	0.94 [0.86 ; 1.03]	0.1833
Delay since last intake ≤ 8h	19/104	2.91 [0.81 ; 10.40]	**0.1011**
Drugs interfering with DOAC	1/4	1.92 [0.19 ; 19.35]	0. 5798

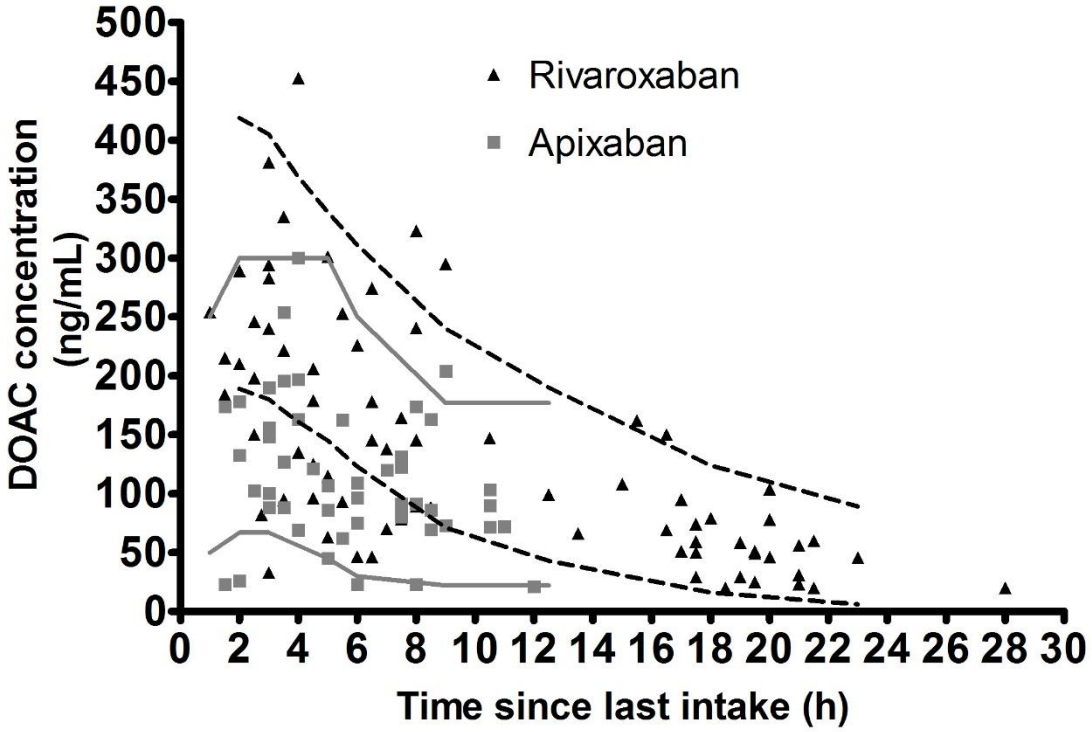
BMI: Body Mass Index
DOAC: Direct Oral AntiCoagulants
n: Number of patients with DOAC concentrations outside the on-therapy ranges
N: Number total of patients
Creatinine clearance is calculated using the Cockcroft and Gault formula.
OR: Odds Ratio; CI: Confidence Interval.
p-value lower than 0.20 (in bold) are variables entered in the stepwise regression.

Table 4: Factors associated with DOAC concentrations outside the on-therapy ranges (multivariate analysis)

Variables	OR [CI95%]	P
Age ≤ 63 years	3.43 [1.16 ; 10.10]	0.0255
DOAC (reference: apixaban 5mg twice daily)		0.0043
apixaban 2.5 mg twice daily	0.42 [0.04 ; 4,07]	
rivaroxaban 20mg once daily	5.48 [1.58 ; 18.95]	
Delay since last intake ≤ 8h	5.32 [1.37 ; 20.60]	0.0155

DOAC: Direct Oral AntiCoagulants
OR: Odds Ratio; CI: Confidence Interval.

Figure 1



Expected concentrations (5^{th}-95^{th} percentile) of apixaban 5 mg twice daily (solid gray line) and rivaroxaban 20 mg once daily (black dotted line) in patients treated for venous thromboembolism from Byon W et al. and Mueck W et al.[5, 6]
Black triangle: rivaroxaban concentrations
Gray square: apixaban concentrations

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

FC has received research grant support from Bristol-Myers Squibb/Pfizer and fees for board memberships or symposia from Bayer, Bristol-Myers Squibb/Pfizer and Astra Zeneca and having received travel support from Bayer, Bristol-Myers Squibb/Pfizer, Leo Pharma, and Actelion.
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Highlights

- Prospective bi-centric study dedicated to DOAC levels in obese patients being treated for VTE and followed in a thrombosis clinic
- 22/146 patients (15%) had DOAC concentrations outside the on-therapy ranges
- Age≤63 y, use of rivaroxaban and time since last intake≤8h were associated with DOAC concentrations outside the on-therapy ranges
- 2 (1%) patients had recurrent VTE, none had major bleeding and 11 (8%) had minor bleeding