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Full Length Article

Validation of apixaban anti-factor Xa assay and impact of body weight

Suman M. Wasan[a,*], Natalie Feland[a], Russell Grant[b], Christopher E. Aston[c]

[a] Cardiovascular Section, Department of Medicine, University of Oklahoma Health Science Center, 800 Stanton L Young Blvd. AAT 5400, Oklahoma City, OK 72104, USA
[b] Labcorp of American Holdings, Center for Esoteric Testing, Burlington, NC, USA
[c] Department of Pediatrics, University of Oklahoma Health Science Center, USA

ABSTRACT

Background: Direct oral anticoagulants (DOACs) are widely used as therapies for venous thromboembolism and other cardiovascular diseases. However, routine coagulation monitoring is not required, but may be clinically indicated in high risk populations including obese patients.
Objectives: The aims of this study were two fold; to validate a chromogenic assay for anti-factor Xa measurement in patients taking apixaban, and correlate it with PT/INR and PTT, and to measure anti-factor Xa levels in patients who weighed > 120 kg.
Patients/methods: Patients who were taking apixaban had 3 blood samples drawn over a 4 h period. Apixaban levels were determined using an anti-factor Xa activity assay (STA-Liquid Anti-Xa) using STA-Apixaban Calibrator and STA-Apixaban Controls. The PT/INR was determined using standard methodology. Apix MS, using manufacturer provided apixaban standard, was performed on plasma.
Results and conclusions: 18 normal weight patients, 39 obese patients and 14 controls were enrolled. There was a strong correlation between apixaban anti-factor Xa activity compared to plasma Apix MS ($r = 0.95$). In patients > 120 kg, there was a statistically significant decreased rate of change in anti-factor Xa levels after ingestion. Further, the area under the curve for apixaban anti-factor Xa levels was significantly lower in patients over 120 kg. While INR correlated with apixaban MS and apixaban anti-factor Xa activity in both normal weight and obese patients, the association was not sufficiently strong to clinically manage patients, normal weight or obese. Given these findings, research is necessary to investigate the clinical utility of apixaban anti-factor Xa activity measurement in selected populations.

1. Introduction

Vitamin K antagonists, warfarin in the U.S., is no longer the only option for treatment of patients with atrial fibrillation and venous thromboembolism, accounting for > 3 million patients per year [1].

Since the direct oral anticoagulant medications (DOACs, including apixaban) exhibit more predictable pharmacokinetic and pharmacodynamic action than warfarin, routine coagulation monitoring is not required [2]. However, assessment of drug exposure and its anticoagulant effect may be helpful in certain clinical situations, such as detection of drug accumulation in acute renal/liver failure or overdose, assessing anticoagulant activity in patients with bleeding or thrombosis, planning the timing of urgent surgery or intervention, special patient characteristics such as obesity or gastrointestinal malabsorption, and determining the suitability for thrombolytic therapy for acute ischemic stroke or other peripheral vascular disease requiring revascularization [3,4].

This need in certain clinical situations raises the dilemma of currently no readily available rapid method to measure drug levels or degree of anti-factor Xa activity for apixaban. In addition, recent approval and availability of a competitive antidote that may be re-administered based on anti-factor Xa level necessitates this validated assay availability.

Activated partial thromboplastin time, thrombin time, and prothrombin time have been evaluated as surrogate measurements for apixaban and found to have poor correlation. Only high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) can be used to measure apixaban levels between 0.25 and 500 μg/L with excellent inter-assay accuracy, however, the clinical applicability is hampered by slow turn-around-time and limited availability. Anti-factor Xa activity assay technology now exists that, once validated, can be used by the clinical laboratory to perform apixaban anti-factor Xa measurement [5].

It has been recommended that apixaban specific calibrators and controls be employed to measure anti-factor Xa rather than low molecular weight heparin (LMWH) calibrators and controls due to variability. However, to date, these assays have only been studied in spiked plasma samples.

Importantly, in countries, both western and developing nations, with an obesity epidemic, there is a paucity of data regarding anti-factor Xa levels from clinical phase II and III trials in patients of elevated body weight especially over 120 kg. Studies in obese healthy volunteers have found up to a 30% reduction in medicinal apixaban blood levels [6]. The pharmacodynamic consequence is unknown since

* Corresponding author.
E-mail addresses: suman-wasan@ouhsc.edu (S.M. Wasan), Natalie-Feland@ouhsc.edu (N. Feland), Grantr@LabCorp.com (R. Grant), Chris-aston@ouhsc.edu (C.E. Aston).

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clinical studies in patients up to 100 kg weight have been favorable. Little is known regarding peak and trough anti-factor Xa levels in those with elevated body weight, especially in the morbidly obese, a growing proportion of the US population.

This was a two part clinical study aimed to address apixaban anti-factor Xa measurement validation in normal weight patients, and once validated, provide information on anti-factor Xa levels in obese patients. The aims of part 1 of the study were to correlate a chromogenic anti-factor Xa assay using the apixaban calibrators (STA®-Liquid Anti-Xa and STA®-Apixaban Calibrator and STA®-Apixaban Controls) with the serum drug levels via HPLC-MS/MS (Apix MS) in patients currently receiving apixaban, and secondly, to correlate the PT/PTT with the anti-factor Xa activity (Apix activity) and Apix MS. This first study was designed to assess the clinically available methods to analyze apixaban levels in patients.

The aims of part 2 of the study were to measure the levels of anti-factor Xa using STA®-Liquid Anti-Xa and STA®-Apixaban Calibrator and STA®-Apixaban Controls in patients currently receiving apixaban who have a body weight > 120 kg, and to measure the correlation of PT/INR, and actual apixaban level as measured by anti-factor Xa in those with elevated body weight.

2. Methods

2.1. Part 1: apixaban anti-factor Xa validation

This was a prospective cohort study. Institutional approval was provided. Thirty-seven adults receiving apixaban were identified through the OU Physicians clinic electronic health record and enrolled in the study. Fourteen healthy controls were identified from staff related to the cardiovascular section and clinic. Inclusion criteria for apixaban patients were: older than 18 years of age, taking apixaban, and able to provide informed consent. Exclusion criteria for apixaban patients were: pregnant, or younger than 18 years of age. Controls were not receiving anticoagulation medication. Data collected were age, sex and race of patient, dose and time of oral intake of apixaban, indication and length of apixaban treatment, comorbidities, and current medications.

Patients who were taking apixaban had a total of three blood samples drawn and collected into to 3.2% sodium citrate tubes. Subjects had their initial blood draw at approximately 8 am, followed by ingestion of their usual apixaban medicine. Subjects were then asked to remain for a blood draw at 2 and 4 h post ingestion to complete sample collection. Plasma was obtained by standard clinical method of centrifugation, divided into 4 aliquots and stored at −70C for batch measurements at the completion of the study. For the 14 controls, 1 blue top tube (4.5 mL) was taken from each of the 14 healthy subjects not receiving anticoagulants.

Apixaban levels were determined using an anti-factor Xa activity assay (STA-Liquid Anti-Xa) using STA-Apixaban Calibrator and STA-Apixaban Controls on the STA-R Evolution analyzer (Diagnostica Stago, Asnieres, France) at the completion of sample collection of all patients. The PT/INR was determined using Neoplastine (ISI = 1.27) (Diagnostica Stago). The PTT assay was performed with STAPTT-Automated (Diagnostica Stago, Asnieres, France).

Apix MS, using manufacturer provided apixaban standard, was performed on plasma following dilution with a basic solution containing stable labeled internal standards, incubation for 2 h, extraction via turbulent flow liquid chromatography and subsequent analytical chromatographic separation. An ABSciex API5000 triple quadruple mass spectrometer (ABSciex, Toronto, Canada), operating in positive electrospray ionization mode was used for detection. Quantification of analyte and internal standards was performed in selected reaction monitoring mode (SRM). The back-calculated amount of the apixaban in each sample was determined from calibration curves generated by spiking known amounts of purified apixaban into drug-free defibrinated plasma from 5.0 to 1000 ng/mL.

2.2. Part 2: measurement of anti-factor Xa in patients with body weight > 120 kg

A further twenty adults receiving apixaban 5 mg bid, who weighed at least 120 kg, were able to sign the consent form and agreeable to participate in the study, were enrolled. Information regarding age, sex of patient, dose and time of oral intake of apixaban, indication and length of apixaban treatment, and other current medications were collected on all patients.

Two blue top tubes (4 mL each) were collected using sterile technique at the time intervals: just prior to ingestion, and at 2 and 4 h post ingestion of medication.

Anti-factor Xa levels were measured on thawed samples with STA®-Liquid Anti-Xa and STA®-Apixaban Calibrator and STA®-Apixaban Controls at the completion of sample collection of all patients as per part 1 of the study. PT/PTT were measured using standard clinical protocols as per part 1 of the study.

These 20 were added to the 26 participants from part 1 who took 5 mg doses of apixiban for a total sample of 46 participants to study associations of Anti-factor Xa levels with body weight and body mass index.

3. Statistical analysis

The primary outcome measures were anti-factor Xa levels at each draw time, rate of change in anti-factor Xa between draw times and area under the curve (AUC). Rates of change (change in anti-factor Xa levels over time between draws) were used to remove any effects of variation in time between draws between patients, AUC was calculated as the area between the curve and the x-axis. Group descriptive statistics are expressed as mean ± SD for continuous measures or grouped frequencies (percentages) for categorical measures. Pearson correlations were calculated to measure association between continuous variables (e.g., anti-factor Xa levels as measured using Anti-Xa vs. levels measured using Apixaban Calibrator). *t*-Tests were used to compare groups for continuous measures (e.g., age, apixaban activity, AUC); Pearson chi-squared tests for categorical measures (e.g., gender). The primary covariate of interest was body weight (kg) as a continuous measure, as well as dichotomized at 120gk and 150 kg. In addition, all analyses were repeated using body mass index (BMI: kg/m^2) as the primary covariate. Other covariates were age, gender, race, and PT/PTT/INR. Statistical analyses were performed using the program packages gmodels (version 2.18.1) and lme4 (version 1.1-19) in R (version 3.5.1). A level of $p \leq 0.05$ was considered statistically significant.

4. Results part 1

There were 37 patients (17 male, 20 female) and 14 controls, (5 male, 9 female) enrolled in the study. Table 1 summarizes their demographic and clinical characteristics. One patient (black, female, 60 years old, 123 kg) was excluded from the analysis as a highly influential outlier with extreme values (> mean + 3SD) in multiple measures (all apixiban levels, Pt/PTT/INR) for which there was no obvious cause. Including this patient created many strong correlations that were not seen otherwise. Eight patients were receiving apixaban for treatment of venous thromboembolism; the remainder carried a diagnosis of atrial fibrillation.

Fig. 1 summarizes the strength of the associations between measures of coagulation tested and HPLC-MS/MS (Apix MS). There was a strong correlation between apixaban activity and plasma Apix MS ($r = 0.95$, $p < 0.0001$) over a wide range of concentrations of apixaban from 5 ng/ml to 347 ng/ml. The lower limit of the assay is established by the lowest value of the calibrators, here to 25 ng/mL. In addition, only one

Table 1
Demographic and clinical data for apixaban studies.

	Part I	Part 2	
		Weight ≤ 120 kg	Weight > 120 kg
N	36*	23	23
Gender [female]	19 (53%)	11 (48%)	8 (35%)
Age [years]	64 ± 16 [23–83]	65 ± 12.9 [35–83]	61 ± 11.1 [29–82]
Race [Caucasian]	32 (89%)	22 (96%)	18 (78%)
Weight [kg]	96.6 ± 29.2 [48.6–162.0]	92.9 ± 18.6 [62.3–119.3]	147.7 ± 17.2 [122.0–190.1]
BMI [kg/m^2]	32.8 ± 9.5 [19.0–55.9]	31.0 ± 6.6 [20.9–49.1]	49.0 ± 8.2† [34.5–69.2]
Apixaban dose			
2.5 mg bid	10 (28%)		
5 mg bid	26 (72%)	23 (100%)	23 (100%)
Indication			
Atrial fibrillation	27 (75%)	19 (83%)	15 (65%)
Venous thromboembolism	8 (22%)	3 (13%)	5 (22%)
Peripheral arterial disease	1 (3%)	1 (4%)	3 (13%)

Values given as N (%) or mean ± SD [range]; BMI = body mass index.
* Outlier removed.
† $p < 0.05$ difference between < 120 kg vs > 120 kg.

patient had anti-factor Xa activity > 400 ng/ml. The majority of anti-factor Xa activity measurements were within the expected peak and trough for patients receiving treatment doses.

We found a statistically significant correlation between INR compared to plasma measurements of apixaban anti-factor Xa activity ($r = 0.68$, $p < 0.0001$). There was poor correlation between PTT and plasma apixaban concentration ($r = 0.35$).

5. Results part 2

There were 46 patients included in the analysis of the effects of body weight on apixiban anti-factor Xa levels. Table 1 summarizes the demographic and clinical data of these patients. The mean weight was 143.6 kg, BMI 47.48 kg/m2 with 21 patients with BMI > 40. Eight patients in this cohort had a diagnosis of venous thromboembolism and the remainder had atrial fibrillation.

The rate of increase in apixaban levels from baseline to 2 h following taking apixaban is significantly associated with body weight; the rate of increase in apixaban levels decreases with increasing body weight (Fig. 2). As shown in Fig. 3A, many patients with body weight over 120 kg show little to no change in apixaban levels over the 4 h following medications. In patients > 120 kg, there was a statistically significant lower anti-factor Xa levels at 2 h compared to those weighing < 120 kg ($p = 0.0053$, Fig. 3C); levels were notably higher at 4 h but the difference between groups was not significant ($p = 0.13$). This difference between patients < 120 kg and those > 120 kg was also demonstrated in the rate of change in anti-factor Xa over the baseline to 2 h time interval and 2 h to 4 h (Fig. 3D), as well as for area under the curve for apixaban anti-factor Xa levels (Fig. 3B). These all suggest that the levels of apixaban achieved in patients < 120 kg is higher than in patients > 120 kg. These analyses were repeated using BMI in place of body weight with similar trends, however, the associations were stronger (as determined using Akaike's Information Criterion: AIC [7] when using body weight).

We found poor correlation of apixaban anti-factor Xa levels and INR in patients over 120 kg ($r = 0.46$).

There were no associations of apixaban levels with age, gender or race.

6. Discussion

Apixaban anti-factor Xa activity provided a reliable assessment of apixaban plasma levels for patients receiving anticoagulant treatment at a variety of doses for different indications. The association of anti-factor Xa activity and apixaban MS was strongly linear through a wide range of concentrations, including through the expected therapeutic range, so clinically it would be expected to perform as an activity assay method. Lower levels of apixaban were detectable to a lower limit concentration of 5 ng/ml. It is unlikely that it would be important to measure levels lower than this limit of detection. In addition, since there were few anti-factor Xa activity measurements above 300 ng/mL (two in this study including the excluded patient), it would be important to reproduce this positive association at higher concentrations

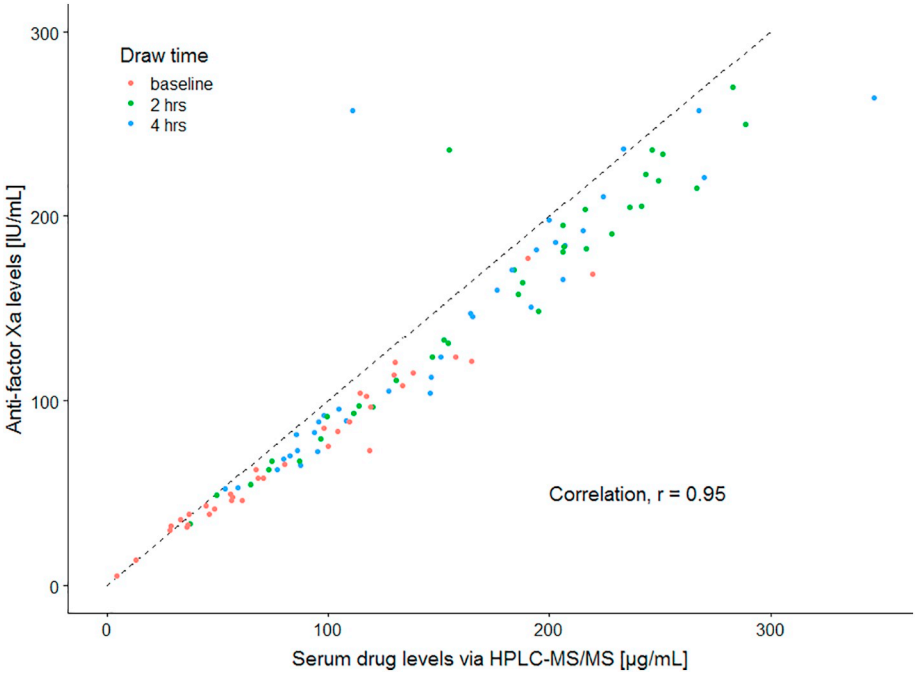

Fig. 1. Scatterplot of STA-Liquid Anti-Xa compared to serum Apixaban Mass Spectrometry.

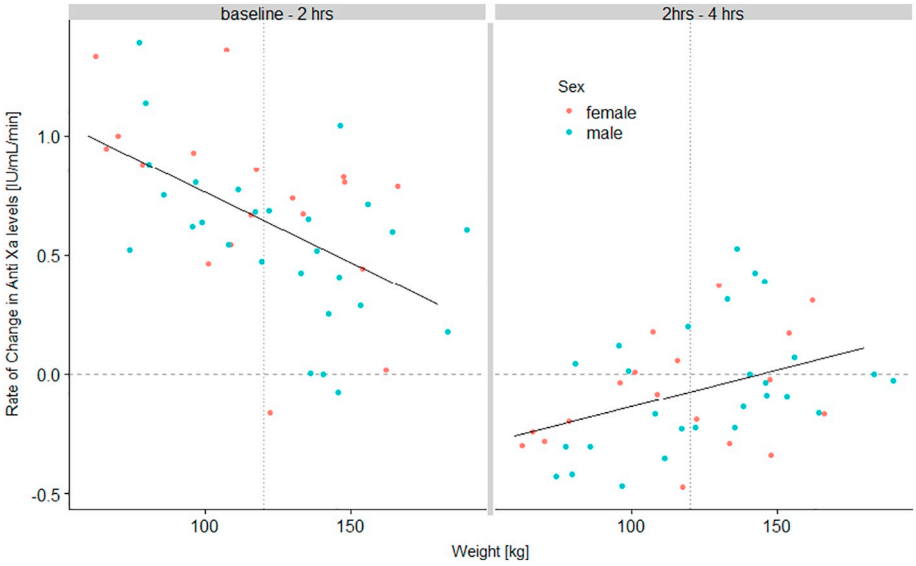

Fig. 2. Rate of change in anti-factor Xa levels by weight. Solid lines denote regression lines of rate of change in Anti-factor Xa levels on body weight. The regressions is significant for both baseline–2 h ($p = 0.0002$) and 2 h–4 h ($p = 0.0065$). The vertical dotted line denotes weight = 120 kg.

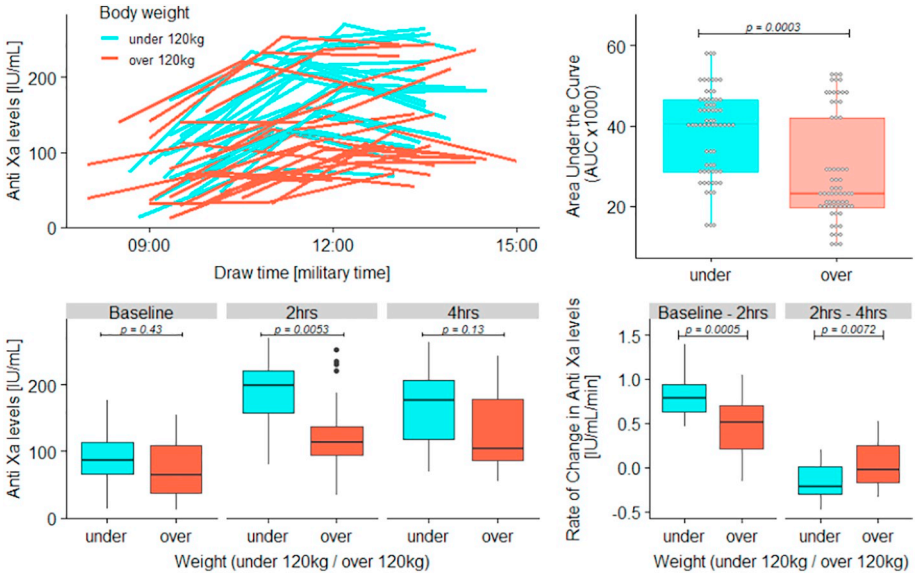

Fig. 3. Anti-factor Xa levels over time by weight (under/over 120 kg).

using a larger number of samples.

Currently, there is no established therapeutic range for apixaban, however, it is known that the peak plasma concentration is observed 1 to 3 h after administration and the half-life is 8–15 h in non-elderly patients [8]. Although monitoring is not required for routine use of apixaban, there are a number of clinical scenarios where assessment of anticoagulant effect might be helpful, including in those with impaired renal function, elderly patients, extremes of body weight, patients with acute bleeding episodes, exclusion of over dosage, and monitoring compliance of therapy in cases of unexpected thromboembolic events. Most importantly, identification of the lowest level of detection where bleeding risk would be minimal would be clinically useful, especially in patients undergoing urgent procedures. To date, there is a paucity of studies assessing apixaban specific anti-factor Xa measurement in patients receiving apixaban for clinical use despite the widespread use of this medication. Because this assay is not FDA approved, some have shown that heparin-calibrated anti-Xa activity may correlate with apixaban specific measurement and could be used clinically [9,10]. However, this approach has not been prospectively validated clinically.

In patients with weight over 120 kg, we found a statistically significant reduction in peak levels and overall exposure to apixaban measured by area under the curve (AUC). It is unclear if this will result in reduced efficacy or whether demonstration of reduced anti-factor Xa levels in obese patients warrants dosage adjustment. When analyzed by BMI, the trend was similar but the association was not as strong compared to body weight. Upreti and colleagues studied 54 healthy subjects, of which 19 weighed > 120 kg (mean 137 kg), and measured anti-factor Xa levels after a single 10 mg dose. Compared to the reference body weight group, apixaban Cmax and AUC were 31% and 23% lower. Apixaban half-life was approximately 3 h shorter in the high body weight group. As in our study, the anti-factor Xa activity showed a direct linear relationship with apixaban plasma concentrations consistent across body weight groups [6]. In a retrospective study of 38 patients (7 taking apixaban), peak anti-factor Xa levels were found to be lower than expected in 21% of patients with weight > 120 kg. The authors stated that the study was not intended to look at associated clinical outcomes [11].

Despite data supporting reduced anti-factor Xa levels in patients

with elevated body weight, the limited published studies do not support reduced efficacy or variable bleeding in these patients. In a retrospective review of the Veterans integrated network that identified 133 patients > 120 kg and 1033 patients < 120 kg treated with DOACs for VTE, no significant difference was detected in recurrent VTE, although the authors note this could be influenced by the low rate of events [12] In a sub-analysis of the ARISTOTLE study in which patients received apixaban for prevention of atrial fibrillation associated stroke, higher BMI was associated with a lower risk of all-cause mortality (HR 0.63 95% CI 0.54–0.74), compared to normal BMI. There has been labeled as the "obesity paradox." [13]. This finding was confirmed in a prospective Dutch registry that showed reduced cardiovascular adverse outcomes and mortality in the obese cohort receiving apixaban for treatment of venous thromboembolism or atrial fibrillation [14].

Due to the paucity of studies regarding efficacy and safety in obese patients, the ISTH suggested that DOACs not be used in patients with a weight of > 120 kg due to limited clinical data that showed reduced peak concentrations, decreased drug exposures and short half lives in this population [15]. Further, they suggested that if DOACs are used in patients over > 120 kg, a drug-specific peak and trough level (Anti-factor Xa DOAC specific), be measured. If the level falls within the expected range, continuation of the DOAC was deemed reasonable. The 2019 updated AHA/ACC/HRS guidelines state that measurement of DOAC anti-factor Xa levels could be considered in "evaluation of drug absorption in severely obese patients (body mass index > 35 or weight > 120 kg)." They authors note that "reference ranges derived from published literature are variable and are not well correlated with safety, efficacy, and clinical outcomes." [16] Our study validates that the apixaban specific STA-Liquid Anti-Xa calibrators and controls can be used for such a purpose.

While INR correlated with apixaban anti-factor Xa activity in both normal weight and obese patients, the association was not sufficiently strong to be used clinically to manage patients, normal weight or obese. PT/INR may be more sensitive at higher concentrations, but is still not highly reliable [5]. PTT is less sensitive than PT and should not be used as a clinical monitor of apixaban serum level or anti-factor Xa activity.

The findings of our study have several limitations. While the INR also correlated here with apixaban MS, it is validated for vitamin K antagonists, and may not be accurate with other anticoagulants. These results reporting the correlation with anti-factor Xa or apixaban MS are exploratory given the small number of patients tested. The timing of sampling may have also affected results.

In conclusion, we have determined that apixaban anti-factor Xa activity measured with STA-Liquid Anti-Xa apixaban calibrators and controls provides a reliable assessment of apixaban plasma levels in a group of active patients receiving anticoagulant therapy. In patients weighing > 120 kg, anti-factor Xa levels were found to be lower with less overall exposure to drug. These findings have uncertain clinical consequence, however, could explain treatment failure in selected obese patients, although to date, studies have not reported this. While at least two clinical trials are in progress evaluating the use of preventative apixaban in bariatric surgery [17], further research is required to investigate the clinical utility of apixaban anti-factor Xa activity measurement in selected populations while FDA approval of validated assays is in progress. Until then, it may be advisable to avoid prescription of apixaban in patients who weigh > 120 kg.

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