Utilization of anti–factor Xa levels to guide reversal of oral factor Xa inhibitors in the emergency department

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Purpose. Oral factor Xa inhibitors (FXaIs) are increasingly utilized for outpatient anticoagulation therapy; however, laboratory monitoring is not routinely used to assess the safety and efficacy of these agents. We aimed to evaluate the role of chromogenic anti–factor Xa (anti-Xa) assays in the emergency department (ED) in the setting of patients with an acute bleed or requiring emergent procedures.

Methods. A retrospective review of anti-Xa levels obtained in the ED between June 1, 2019, and April 30, 2020, was completed. Data were collected to describe the clinical setting of anti-Xa level collection, oral FXaIs used before admission, administration of reversal agents, and patient disposition to further characterize the role of anti-Xa levels in the management of rivaroxaban and apixaban reversal.

Results. Thirty anti-Xa levels were included in the final analysis. The median time from sample collection to anti-Xa assay result was 45.9 minutes (interquartile range, 35.3-54.7 minutes). Eleven patients (37%) received anticoagulation reversal after their anti-Xa levels were determined. Anticoagulation reversal agents included either activated prothrombin complex concentrates (aPCCs) or prothrombin complex concentrates (PCCs). Anti-Xa levels were collected in 2 patients who had received PCCs before arrival at our ED. Of the patients with anti-Xa levels below 30 ng/mL, none received aPCCs or PCCs after their anti-Xa levels were determined. Anti-Xa assays were used to rule out the presence of FXaIs in 3 patients.

Conclusion. This study illustrates the novel role of anti-Xa levels in managing patients with an emergent need for reversal in the ED. The assay may be used to rule out the presence of oral FXaIs and avoid unnecessary administrations of anticoagulation reversal agents.

Keywords: anticoagulation reversal, anti-Xa assay, emergency medicine, factor Xa inhibitor

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Oral factor Xa inhibitors (FXaIs) are approved in the United States for the treatment of venous thromboembolism (VTE), secondary VTE prevention, primary medical VTE prevention, prevention of thromboembolic stroke in atrial fibrillation (AF), prevention of VTE after hip or knee replacement surgery, and secondary prevention of VTE in coronary artery disease and peripheral artery disease.[1] The most commonly prescribed FXaIs in the United States are apixaban and rivaroxaban.[2] Although routine laboratory monitoring is not indicated to guide dosage adjustments, utilization of laboratory measures to determine drug presence and activity has been suggested in patients requiring emergent reversal of anticoagulation due to a life-threatening bleed or the need for an emergent procedure.[3,4] Widely available anticoagulation laboratory tests including those measuring partial thromboplastin time (PTT) and prothrombin time (PT) have not shown reliable sensitivity or specificity to

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assess anti–factor Xa (anti-Xa) activity in vivo.[5,6] Chromogenic anti-Xa assays calibrated to rivaroxaban and apixaban are preferred for measurement of the anticoagulation effect of FXaIs.[5] These assays may be especially useful when the timing of the last anticoagulant dose is unknown.

Use of anti-Xa levels has previously been described in the outpatient setting to assess adherence to therapy, determine anticoagulation status in patients at risk of having subtherapeutic doses, and evaluate levels in anticipation of outpatient surgical procedures.[7] There is limited evidence addressing the use of anti-Xa assays in the emergency department (ED). Furthermore, the impact of anti-Xa levels on clinical decision-making for oral FXaI reversal has yet to be evaluated.[7] Our institution recently developed and implemented apixaban and rivaroxaban anti-Xa assays that are limited to clinical use in measurement of anti-Xa activity in patients undergoing emergent and urgent procedures or with life-threatening bleeds associated with apixaban or rivaroxaban use. The objective of this study was to describe the use of these anti-Xa assays to guide anticoagulation reversal in the ED.

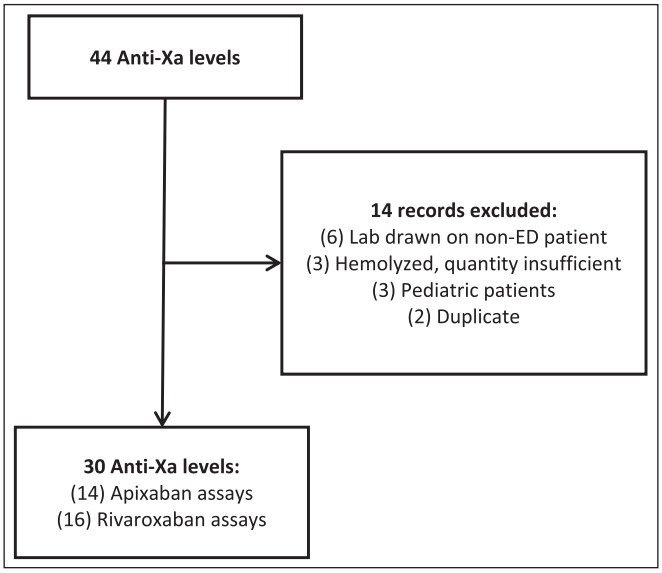
KEY POINTS

- Anti–factor Xa (anti-Xa) assays are a novel tool that may be used to inform clinicians about the in vivo presence of apixaban or rivaroxaban in patients who may require anticoagulation reversal.
- Anti-Xa assays are not widely available, and more work is required to ensure consistent turnaround times before their regular implementation in clinical practice.
- Patients failing to achieve hemostasis secondary to anticoagulant activity should still receive anticoagulation reversal agents regardless of anti-Xa assay results at the discretion of the clinician.

Methods

We assembled a case series of all rivaroxaban and apixaban anti-Xa levels obtained at our institution between June 1, 2019, and April 30, 2020. Our ED is a 46-bed unit at a Midwest adult and pediatric level I trauma center and stroke center with an average volume of 60,000 patients per year. The retrospective study protocol was approved by the institutional review board (protocol no. 202003303). Oral FXaI levels were retrieved using the reporting workbench functionality within our electronic medical record. Collected data included age, gender, height, weight, plasma creatinine level, PT/international normalized ratio (INR), preadmission oral FXaI dose and indication, clinical setting of anti-Xa assay ordering, administration of reversal agents, timing of reversal agent administration, admission location, and disposition at discharge. The clinical settings for use of anti-Xa assays included intracranial hemorrhage (ICH), life-threatening bleeds, and emergent procedures. ICH included both traumatic and nontraumatic subdural hemorrhage (SDH), intraparenchymal hemorrhage (IPH), and epidural hemorrhage, as characterized on computed tomography (CT). Emergent procedures were defined as cases that required emergent arrival to the operating room. Life-threatening bleeds were defined as bleeds associated with hemodynamic instability or administration of blood products. Patients were excluded if specimens for anti-Xa testing were collected outside of the ED, if duplicate samples were collected, or if the anti-Xa level could not be determined owing to preanalytical error (eg, hemolysis or insufficient blood volume), as shown in Figure 1. Selection of the reversal agent used was driven by institutional protocol and provider discretion. At the time of the study, aPCCs were utilized for reversal of rivaroxaban and apixaban before emergent procedures or for life-threatening bleeds. Our institutional protocol for aPCC administration for apixaban and rivaroxaban reversal utilizes factor 8 inhibitor bypass activity (FEIBA) as the aPCC of choice. Coagulation factor Xa (recombinant), inactivated-zhzo was added to the formulary during the study period but had criteria for restricted use limited to ICH.

Figure 1. Summary of included and excluded records. Anti-Xa levels indicates anti–factor Xa levels; ED, emergency department.



Blood samples for anti-Xa testing were collected in 3.2% sodium citrate, centrifuged at 3,500 rpm for 12 minutes, and assayed immediately on Siemens instrumentation (BCS-XP before December 3, 2019, and CS-5100 thereafter; Siemens AG, Munich, Germany). The clinical laboratory's preexisting anti-Xa reagent (Siemens Innovance Heparin) was calibrated for apixaban and rivaroxaban using commercially available materials (Hyphen Biomed, Neuville-sur-Oise, France). A target turnaround time (TAT) of 60 minutes was established by a multidisciplinary anticoagulation committee taking into consideration the logistics of sample transport, the workflow within the clinical laboratory, and the clinical indications for testing, among other factors. The performance of these laboratory-developed assays for apixaban and rivaroxaban was validated by documenting precision, accuracy, sensitivity, reportable range, and specificity. The within-run and between-run imprecision for both oral FXaIs was less than 5% coefficient of variation (CV) and 15% CV, respectively. Recovery studies yielded measured anti-Xa concentrations within 30% of the expected values assigned by mass spectrometry. Method comparison studies with a reference laboratory revealed good agreement (apixaban: slope, 0.78; intercept, 24.8; rivaroxaban: slope, 1.04; intercept, 6.4) and correlation ($R^2 \geq 0.95$ for both drugs). The functional sensitivity for apixaban and rivaroxaban was 11.8 ng/mL and 7.5 ng/mL, respectively. The reportable range was 20 to 550 ng/mL for apixaban and 20 to 450 ng/mL for rivaroxaban. These assays were not significantly affected by hemolysis (up to 0.6 g/dL hemoglobin), icterus (up to 30 mg/dL bilirubin), lipemia (up to approximately 600 mg/dL triglycerides), warfarin (INR up to 6.3), or dabigatran (up to 500 ng/mL dabigatran). Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) falsely elevate anti-Xa–based apixaban and rivaroxaban measurements. Statistical analysis consisted of analysis of descriptive statistics (eg, median and interquartile range [IQR]) and was completed using Excel (Microsoft, Redmond, WA).

Results

Thirty anti-Xa levels from unique patients were included in the study (Figure 1). Demographic data for the patients are presented in Table 1. Twenty-seven patients (90%) were taking an oral FXaI before arrival. Twenty patients (66.6%) were prescribed an oral FXaI for AF, while 6 patients (20%) were prescribed the medication for VTE. Four patients had no indication for oral FXaI noted either due to not taking an oral FXaI before admission (3 patients) or lack of documentation of the indication in the medical record (1 patient). Sixteen patients (53%) had rivaroxaban anti-Xa levels measured, and 14 patients (47%) had apixaban anti-Xa levels measured. These all corresponded correctly with the reported medication patients were prescribed before arrival. Rivaroxaban anti-Xa levels were determined for the 3 patients who were not taking an oral FXaI before admission. The majority of patients (57%) had an anti-Xa level obtained in the setting of ICH, with the next most common clinical settings including a life-threatening bleed (20%) and an emergent procedure (17%). One patient had a rivaroxaban anti-Xa level obtained for monitoring purposes only after it was determined that the patient

Table 1. Patient Characteristics

Characteristic	Patients (*n* = 30)
Age, median (IQR), years	78 (69.3-82.8)
Gender (male), No. (%)	15 (50)
Weight, median (IQR), kg	91.5 (70.9-100.9)
Renal function (creatinine clearance), No. (%)	
<30 mL/min	4 (13)
30-60 mL/min	7 (23)
>60 mL/min	18 (60)
Hemodialysis dependent	1 (3)
Preadmission oral FXaI, No. (%)	
Apixaban	14 (46.7)
Rivaroxaban	13 (43.3)
None	3 (10)
Oral FXaI indication, No. (%)	
AF	20 (66.7)
VTE	6 (20)
Not applicable[a]	3 (10)
Unknown[b]	1 (3.3)
Clinical scenario, No. (%)	
Intracranial hemorrhage	18 (60)
Life-threatening bleed	6 (20)
Emergent procedure	5 (16.7)
Monitoring	1 (3.3)

Abbreviations: AF, atrial fibrillation; FXaI, factor Xa inhibitor; IQR, interquartile range; VTE, venous thromboembolism.
[a]Patients were not on an oral factor Xa inhibitor before admission.
[b]Unknown indication based on available information in the medical record.

had received tissue plasminogen activator before transfer to our facility while on rivaroxaban in the outpatient setting.

The median time from sample collection to receipt in the laboratory was 6.7 minutes (IQR, 5.6-8.5 minutes), and the median time from receipt to anti-Xa result was 39.0 minutes (IQR, 28.1-46.7 minutes). Overall, the median time from sample collection to anti-Xa result was 45.9 minutes (IQR, 35.3-54.7 minutes). Our target TAT of 60 minutes from sample collection to anti-Xa result was achieved for 80% of patients. Of note, approximately 50% of the anti-Xa tests performed were add-on orders for an already collected blood specimen; in these instances, the time of add-on order placement was used to calculate the receipt-to-result TAT.

Most patients included in this study (53%) did not receive oral FXaI reversal after anti-Xa assays were performed, with only 11 patients (37%) undergoing anticoagulation reversal after their anti-Xa levels were determined. All 11 of these patients received aPCCs. Only 4 of the 30 patients had anti-Xa levels obtained after administration of PCCs or aPCCs. Of these 4 patients, 3 were given PCCs before transfer from outside facilities and 1 was given aPCCs at our institution as the initial anti-Xa test resulted in a laboratory error and clinicians elected to administer aPCCs in the absence of a level because of the clinical circumstance. Of the 3 patients who received anticoagulation reversal before transfer to our institution, only 1 received a further dose for anticoagulation reversal after the anti-Xa level was obtained because of clinical deterioration. The other 2 patients had drug-calibrated anti-Xa levels of 182 ng/mL (46 minutes after administration of a PCC) and 120 ng/mL (260 minutes after administration of a PCC). Neither of these patients was administered another dose of an aPCC or coagulation factor Xa (recombinant), inactivated-zhzo upon arrival at our ED based on clinician discretion. Of note, repeat CT scans of both patients showed stable hematoma size upon arrival to our ED. Of the patients with anti-Xa levels below 30 ng/mL, none received aPCCs or PCCs after their anti-Xa levels were determined. Information on each case is shown in Table 2.

Discussion

Our study describes the utilization of anti-Xa levels in the ED setting. Anti-Xa assays have a limited role in defining therapeutic anticoagulation ranges for FXaIs; however, the results of our study suggest that they may serve as a tool to guide the need for anticoagulation reversal as well as to rule out the presence of oral FXaIs.[5] With the theoretical risk of thrombosis with PCCs and aPCCs and considerable cost associated with reversal agents for oral FXaI-OUP: change hyphen to en dash associated life-threatening bleeds, it is warranted to rule out the presence of oral FXaI activity in patients who do not have the ability to provide an accurate medical history.[8] When interpreting anti-Xa levels, it is crucial to evaluate whether patients received medications such as UFH or LMWH, as these lead to elevated levels in anti-Xa assays.

Previous small studies have described the role of anti-Xa levels in clinical practice. One study published by Martin et al[7] in 2016 reported a total of 48 direct oral anticoagulant (DOAC) levels obtained for 28 patients. Three of these patients had dabigatran levels obtained for emergent circumstances; however, no patients taking apixaban or rivaroxaban had anti-Xa levels obtained to guide the use of emergent anticoagulation reversal before procedures or due to life-threatening bleeds. A second study published by Gu et al[9] in 2019 reviewed 150 DOAC levels in inpatients and outpatients. Seventy-eight of these samples were collected from patients before an invasive procedure; however, only 34 of these levels were obtained in the inpatient setting, 6 of which were obtained in the ED. The generalizability to our study is limited as both studies included inpatient and outpatient samples as well as a combination of oral FXaIs and dabigatran. A strength of the current study is its focused sample of patients within the ED and specific description of the use of apixaban- and rivaroxaban-calibrated anti-Xa levels in the setting of emergent procedures or life-threatening bleeds. Our analysis is larger than the 2 previously completed analyses, with less heterogeneity, as rivaroxaban- or apixaban-calibrated anti-Xa assays were performed for all patients. Our study also specifically describes use of aPCCs and PCCs alongside anti-Xa assays in the ED, further demonstrating the high-acuity nature of this patient population.

Several thresholds have been recommended for anti-Xa levels (eg, 30 or 75 ng/mL) below which emergency procedures can be performed with relative safety, but there are limitations with these cutoffs that should be considered in clinical practice.[3,10] Six patients in our study had anti-Xa levels of less than 30 ng/mL, none of whom received PCCs or aPCCs for anticoagulation reversal after the level was obtained. In 3 of these patients, it was possible to rule out the presence of apixaban and rivaroxaban in the absence of clear patient medication use history. One patient had an apixaban anti-Xa level of 23 ng/mL, which was obtained after the patient received an aPCC. It is important to keep in mind that the anti-Xa result should be paired with clinical assessment to dictate patient management. For example, clinicians may elect to administer anticoagulation reversal in patients who fail to achieve hemostasis, regardless of the anti-Xa level. Additionally, patients may have expansion of a bleed despite the defined anti-Xa thresholds utilized to guide anticoagulation reversal treatment. Notably, the presence of an oral FXaI was ruled out in 3 patients in this study with anti-Xa assay results of below 20 ng/mL. The assay can be utilized in this setting to exclude the presence of oral FXaIs for which coagulation tests for detection are otherwise unreliable.

In the ANNEXA-4 trial, an anti-Xa level of 75 ng/mL or greater was utilized for inclusion in the efficacy analysis.[11] Our institution adopted this specific

Table 2. Anti-Xa Levels, Clinical Setting, and Administration of Reversal Agents

Patient	Preadmission Oral FXaI	Clinical Setting	Anti-Xa Assay Result, ng/mL	Reversal Agent Received	Disposition at Discharge
1	API	ICH	93	aPCC (1,932 units)	SNF
2	API	ICH	108	No	Home
3	RIV	Right forearm swelling with hematoma; initial concern for compartment syndrome with need for surgical intervention	59	No	Home
4	RIV	Sepsis secondary to sacral abscess requiring surgical intervention	37	No	Deceased
5	API	Incarcerated hernia requiring surgical intervention	86	aPCC (1,932 units)	Home
6	RIV	ICH; anti-Xa level obtained 46 minutes after PCC administration at outside hospital	182	PCC[b] (2,215 units)	SNF
7	API	ICH	384	aPCC (2,712 units)	SNF
8	API	GIB	156	aPCC (2,495 units)	Home
9	RIV	Monitoring only; received tPA before arrival while also on reported rivaroxaban; last dose of rivaroxaban was reported to be approximately 26 hours before the anti-Xa level was obtained	<20	No	Home
10	API	ICH; anti-Xa level obtained 260 minutes after PCC administration at outside hospital	120	PCC[b] (2,495 units)	Deceased
11	API	Anti-Xa level obtained at initial patient presentation; concern for ICH, but CT scan of head was negative for ICH	107	No	Home
12	None[a]	Patient not on anticoagulation, anti-Xa level obtained because the patient was not able to provide information; known history of PE	<20	No	SNF
13	RIV	ICH	114	aPCC (2,089 units)	Deceased
14	RIV	GIB	77	No	SNF
15	RIV	GIB	80	No	Home
16	None[a]	Patient not on anticoagulation, anti-Xa level obtained because the patient was not able to provide information; known history of PE	<20	No	SNF
17	RIV	Large bowel obstruction; anti-Xa level collected in the event that the patient would require emergent reversal for surgical intervention	330	aPCC (3,333 units)	Home
18	API	Perforated colitis and developing abscess; anti-Xa level determined in the event that the patient would require emergent reversal for surgical intervention	>550	No	Deceased
19	API	ICH	256	No	Home
20	API	ICH	60	aPCC (2,235 units)	SNF
21	API	Acute cholecystitis requiring surgical intervention	42	aPCC (2,222 units)	Home

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Table 2. Anti-Xa Levels, Clinical Setting, and Administration of Reversal Agents

Patient	Preadmission Oral FXaI	Clinical Setting	Anti-Xa Assay Result, ng/mL	Reversal Agent Received	Disposition at Discharge
22	RIV	GIB	231	No	Home
23	RIV	Epidural hematoma with cord compression requiring surgical intervention	>450	aPCC (3,333 units)	SNF
24	API	ICH; initial anti-Xa level before aPCC administration resulted in lab error and additional level was determined 92 minutes after administration; aPCC was given before results as to not delay reversal	23	aPCC[b] (4,176 units)	SNF
25	RIV	ICH; received PCC at an outside hospital and the anti-Xa assay was performed 71 minutes after PCC administration; aPCC was given after the anti-Xa level was obtained based on clinical course	306	PCC[b] (1,500 units), aPCC (1,962 units)	SNF
26	API	ICH; left posterior cerebral artery stroke with hemorrhagic transformation; per report, had not taken apixaban for 2 days	<20	No	SNF
27	RIV	ICH	46	aPCC (2,943 units)	Home
28	RIV	ICH	49	No	SNF
29	API	ICH	133	No	SNF
30	None[a]	Trauma patient unable to provide history; previously on apixaban per report	<20	No	SNF

Abbreviations: aPCC, activated prothrombin complex concentrate; API, apixaban; CT, computed tomography; FXaI, factor Xa inhibitor; GIB, gastrointestinal bleed; ICH, intracranial hemorrhage; PCC, prothrombin complex concentrate; PE, pulmonary embolism; RIV, rivaroxaban; SNF, skilled nursing facility; tPA, tissue plasminogen activator; Xa, factor Xa.
[a]Rivaroxaban anti-Xa levels were obtained in all patients who were not taking an oral factor Xa inhibitor before admission.
[b]Reversal agent was administered before collection of a sample for an anti-Xa assay.

threshold in our protocol for use of coagulation factor Xa (recombinant), inactivated-zhzo when the timing of the last dose of apixaban or rivaroxaban was unknown. This is a further use for anti-Xa levels within our institution. During the study period, no patient requiring emergent reversal of apixaban or rivaroxaban received coagulation factor Xa (recombinant), inactivated-zhzo. Use of coagulation factor Xa (recombinant), inactivated-zhzo was subject to evaluation of each patient's global clinical status and compliance with our institutional protocol for use.

An additional practical consideration for use of anti-Xa levels in emergency medicine clinical decision-making is the TAT for results from the laboratory. Our study demonstrated rapid arrival of specimens to the laboratory from the time of sample collection (median, 6.7 minutes; IQR, 5.6-8.5 minutes) with more variable time to results after specimen receipt by the laboratory (median, 39.0 minutes; IQR, 28.1-46.7 minutes). This is longer than the typical receipt-to-result TAT for traditional anticoagulation tests (eg, PT: median, 15.7 minutes; IQR, 14.0-18.5 minutes) but is more in line with the time required for anti-Xa assays to monitor heparin anticoagulation (median, 30.4 minutes; IQR, 24.9-38.9 minutes). One variable that prevents faster TATs in determining anti-Xa rivaroxaban and apixaban levels is the low volume of testing relative to other anticoagulation tests (eg, PT testing or anti-Xa assays for heparin). Despite the TAT challenges, anti-Xa levels were still useful in guiding emergent management of patients taking an oral FXaI. Certainly, the use of these tests must be paired with clinical decision-making regarding the timeliness of test results and administration of anticoagulation reversal agents.

Our study has several limitations. First, this was an observational study, so it is possible that documentation was missing or inaccurate. However, we selected data variables that were likely to be documented accurately for the majority of patients in the population. Second, because this was a retrospective study, the timing of the last DOAC administration was not captured as it was not readily available from chart review. Additionally, while the goal of ordering anti-Xa levels in the ED is to

guide anticoagulation reversal therapy, there could have been clinical decisions that were made to determine whether the patient required anticoagulation reversal regardless of the anti-Xa level. Finally, our study was a single-center study with internally calibrated anti-Xa levels, which limits the external validity of our findings for other institutions.

Conclusion

Our findings describe the utilization of anti-Xa levels for oral FXaI reversal guidance in the ED. Anti-Xa levels have the potential to provide additional insight on the anticoagulation status of patients with an acute life-threatening bleed or the need for an emergent procedure in the ED and further inform the use of reversal agents in this patient population. Specifically, anti-Xa levels can be used in the context of a particular patient to elucidate whether the patient is currently taking apixaban or rivaroxaban and requires emergent reversal. Use of these levels may further drive stewardship of costly reversal agents in the ED setting.

Disclosures

The authors have declared no potential conflicts of interest.

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