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BRIEF REPORT

Anti–factor Xa activity assays of direct-acting oral anticoagulants during clinical care: An observational study

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Abstract

Background: Direct-acting oral anticoagulants (DOACs) are increasingly used to prevent and treat thromboembolism. Although measurement of DOAC concentrations is not currently recommended as part of routine patient care, measurement of DOAC concentrations with anti–factor Xa activity assays have recently become clinically available.

Objectives: Our goal was to determine the clinical conditions under which DOAC concentration measurements are requested.

Materials and Methods: Retrospective electronic medical record analysis of indications for DOAC concentration measurements by anti–factor Xa activity assay at a single academic medical center from July 2015 through April 2020.

Results and Conclusions: Ninety-one DOAC concentration measurements were made in 69 patients: 28 received apixaban and 41 received rivaroxaban. The most frequent indication for concentration measurement was drug exposure assessment (38/69; 55%) in patients with potentially altered pharmacokinetics (altered absorption or clearance), recurrent thromboembolic events, or possible medication nonadherence. Fourteen of 69 patients had repeated measurements during preoperative evaluation before emergent surgery; one-third of those with detectable levels upon presentation had repeated measurements until concentrations were undetectable. Levels were undetectable in 4 of 4 patients scheduled for elective surgery. Eleven of 69 patients had DOAC measurements in the setting of major bleeding; 5 of these 11 received a specific DOAC reversal agent. While most of the observed indications appear in clinical guidelines, altered absorption does not. Overall, clinicians are requesting DOAC concentration measurements to evaluate drug exposure in patients with conditions that might alter the absorption or clearance of the DOAC, to evaluate surgical bleeding risk, and in the setting of major bleeding.

KEYWORDS
anti–factor Xa activity assay, apixaban, direct oral anticoagulant, retrospective electronic medical record, rivaroxaban

Essentials

- Direct oral anticoagulant (DOAC) assays are available and being used clinically.
- Medical records at one center were reviewed to determine indications for DOAC assays.
- Most assays were ordered to assess drug exposure during chronic therapy.
- One-third of DOAC measurements to assess drug exposure were out of expected ranges.

1 | INTRODUCTION

Direct-acting oral anticoagulants (DOACs) have surpassed warfarin as the most commonly prescribed oral anticoagulants in the United States. Advantages of DOACs include fixed dosing, few drug and food interactions, wide therapeutic index, and the lack of a need for laboratory test monitoring.[1,2] Yet measurement of DOAC concentrations may be useful in selected situations, including confirming minimal anticoagulant effect before invasive/surgical procedures, when drug distribution or clearance may be altered due to marked obesity, in patients with chronic kidney disease, or during concomitant administration of medications with drug-drug interactions.[2-4] DOAC concentration measurements with anti–factor Xa activity assays are now available in hospital and national laboratories (Quest, Mayo, Labcorp), but it is not clear when clinicians request such information. The goal of this retrospective single-center study was to assess the clinical indications for obtaining measurements of apixaban and rivaroxaban, the two mostly commonly prescribed DOACs in our health care system. We anticipated the use of concentration data in the setting of major bleeding as well as preoperative risk assessment, but were surprised to find that greater than half of the assays ordered were used by providers to assess the appropriateness of drug concentrations or drug exposure.

2 | METHODS

We searched the Epic (Verona, WI, USA) based electronic medical records for all DOAC anti–factor Xa activity assays ordered between July 2015 through April 2020 at the University of California, San Francisco Medical Center, a tertiary-care teaching hospital. We reviewed the medical record of each patient with a DOAC concentration measurement to collect demographic and medical information surrounding the time of measurement including DOAC dose, dose time, concomitant diagnoses, and medications. Two independent reviewers reviewed the records, including medical notes and laboratory requisition slips, to identify any mention of DOAC assays, concentration monitoring, adherence issues, dosage considerations, and considerations related to administration of anticoagulation or reversal agents to ascertain the stated or implied indications for each assay, with a third reviewer invited to review in case of disagreements. The indications were then grouped into major categories by consensus for further analyses. Assay results were reported as concentration (ng/mL), below the lower limit of detection (<25 ng/mL for rivaroxaban and <29 ng/mL for apixaban), or above the upper limit of the assay (>500 ng/mL). Results were further categorized as within, above, or below the 5% to 95% range for the indication, dose, and time after dosing.[3]

Data are presented as mean ±standard deviation, and as raw numbers and percentages. The study was approved by the University of California, San Francisco Institutional Review Board.

3 | RESULTS AND DISCUSSION

3.1 | Results

Ninety-one DOAC measurements were made in 69 patients, of whom 20 received apixaban and 49 received rivaroxaban (Table 1).

The most frequent indication for DOAC concentration measurement was exposure assessment (38/69 patients; 55%). This included provider concerns regarding altered gastrointestinal absorption due to prior surgery or body mass index (BMI) > 40 kg/m^2 (of those with BMI >40, BMI ranged from 44 to 61.2), recurrent thromboembolic events, potential drug-drug interactions, impact of metastatic malignancy, adherence, and possible overdose. Three of the 38 had levels above the expected 5% to 95% range for their diagnosis and dose, with all three having a creatinine clearance and estimated glomerular filtration rate >60. In the patient with the potential overdose and one other patient, concentrations exceeded the upper limit of detection (>500 ng/mL). The patient with an apparent overdose was monitored in the hospital, and the other had a hematology consultation for dosage adjustments. Nine of the 38 patients evaluated for drug exposure had levels below the lower limit of detection during a dosing interval, and three had levels above the expected 5% to 95% range for their diagnosis and dose (in two, this exceeded the upper limit of detection [>500 ng/mL]). Hence, 32% of patients who had DOAC measurements to assess exposure had values that were outside expected clinical ranges (see Figure 1). Dosage changes were made in three patients evaluated for drug exposure. Twenty patients were evaluated while inpatients on the internal medicine services, and 18 were evaluated while outpatients. Of the 18 outpatients with assays for drug exposure in the outpatient setting, the ordering physicians were hematologists in 9, or half, followed by internal medicine (n = 4), rheumatology (n = 2), family medicine (n = 1), medical oncology (n = 1), and neurosurgery (n = 1).

Evaluation before surgery ordered by the surgical teams was the second most common indication (18/69 patients; 26%). DOAC

TABLE 1 Patient demographics and characteristics

Patients	Total	Rivaroxaban	Apixaban
Number	69	49	20
Age, y	62.2 ± 17.4[a]	59.2 ± 18.1	69.6 ± 13.3
Weight, kg	89.0 ± 31.0	90.7 ± 33.7	84.8 ± 31.5
Body mass index (kg/m^2)	30.7 ± 10.4	31.2 ± 10.1	29.3 ± 11.1
Sex, n (%)			
Male	39 (57)	29 (59)	10 (50)
Female	29 (42)	19 (39)	10 (50)
MTF	1 (1)	1 (2)	
Race, n (%)			
White	34 (49)	24 (49)	10 (50)
Black/African American	14 (20)	11 (22)	3 (15)
Asian	9[b] (13)	6 (12)	3[b] (15)
Native Hawaiian or Other Pacific Islander	3[b] (4)	0 (0)	3[b] (15)
American Indian or Alaska Native	2 (3)	2 (4)	0 (0)
Other	8 (12)	6 (12)	2 (10)
Ethnicity (Hispanic, non-Hispanic, Unknown)	9 (13), 57 (83), 3 (4)	7 (14), 41 (84), 1 (2)	2 (10), 16 (80), 2 (10)
DOAC indication and dose, n (%)			
NVAF Dose, mg/d	26 (38)	16 (33) 20 (n = 11), 15 (n = 4), unknown in overdose (n = 1)	10 (50%) 10 (n = 5), 5 (n = 4), unknown (n = 1)
Pulmonary emboli/DVT Dose, mg/d	32 (46)	24 (49) 20 (n = 16), 30 (n = 4), 15 (n = 2), 10 (n = 2)	9 (45) 10 (n = 8), unknown in overdose (n = 1)
NVAF +DVT Dose, mg/d	2 (3)	0 (0)	1 (5) 5 (n = 1)
Other indication[c] Dose, mg/d	9[c] (13)	9[c] (18), 20 (n = 4), 30 (n = 1), 15 (n = 1), 10 (n = 1), 5 (n = 1), unknown in overdose (n = 1)	0 (0)
Creatinine, mg/dL	1.1 ± 1.2	1.1 ± 1.3	1.1 ± 1.1
Creatinine clearance, mL/min[d] (range)	109 ± 62 (8-330)	113 ± 57 (8-289)	98 ± 74 (14-330)
Number with multiple measurements, n (%)	15 (22)	9 (18)	6 (30)
Measurements/patient (range)	1 ± 1 (1-5)	1 ± 1 (1-5)	1 ± 1 (1-4)

Abbreviations: DOAC, direct-acting oral anticoagulant; DVT, deep vein thrombosis; MTF, male-to-female transgender; NVAF, nonvalvular atrial fibrillation.

[a]Data are mean ± SD.

[b]One patient identified as >1 race.

[c]Other = non-DVT venous thrombosis in 2 (including splenic vein, superior mesenteric vein, and basilic vein), antiphospholipid syndrome in 2, left ventricular thrombus in 1, postventricular tachycardia ablation in 1, superficial femoral arterial thrombus in 1, peripheral artery disease in 2.

[d]Estimated with Cockcroft and Gault equation.[5]

concentrations were undetectable in the 4 patients scheduled for elective surgery. Fourteen patients had surgeries considered urgent, and DOAC concentrations were undetectable in 3. Of the remaining 11 patients needing urgent procedures, surgeries were performed without delay and without a reversal agent in 5, limited to low bleeding risk procedures in 3, and surgery was delayed in 3 until concentrations were minimal or undetectable.

Eleven of the 69 patients (16%) had DOAC concentration measurements ordered in the emergency room in the setting of major bleeds.[6] One patient with a subdural hematoma of unknown

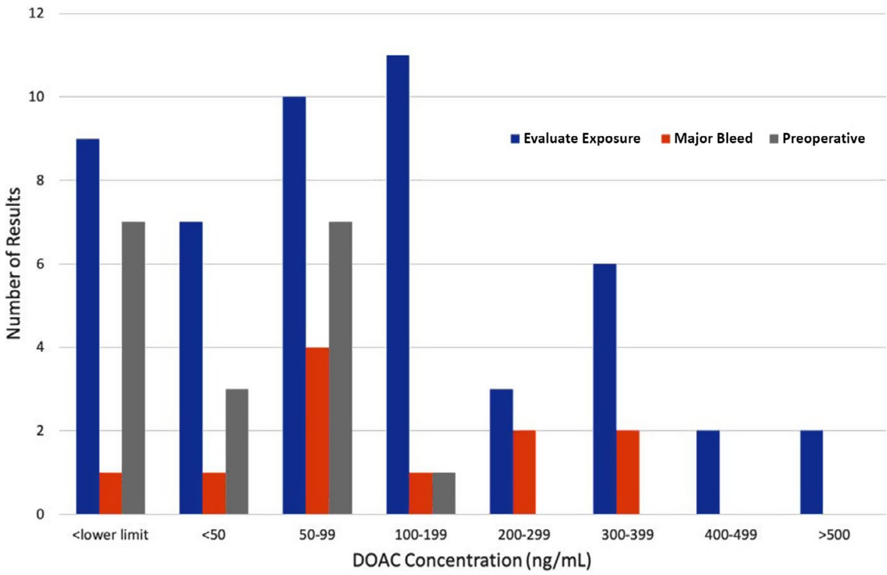

FIGURE 1 Direct-acting oral anticoagulant (DOAC) concentration results grouped by indication for measurement. For major bleeds and preoperative evaluations (four elective), only the first measurement is plotted

duration had an undetectable level, while the other 10 had levels within ranges reported in clinical trials. Five of the 11 patients with major bleeding received the specific reversal agent coagulation factor Xa (recombinant), inactivated-zhzo. Repeated assays after administration were not performed.

Finally, two patients had DOAC measurements to evaluate abnormal coagulation parameters; DOAC concentrations were undetectable in one and 46 ng/mL in the other.

3.2 | Discussion

Routine measurements of DOAC concentrations are not currently recommended but may be warranted in certain situations. At our medical center, we found the most common indication for measurement to be drug exposure evaluation, either due to potentially altered pharmacokinetics or in the setting of potential treatment failure. DOAC concentration measurements in the presence of high BMI, decreased renal function, and potential drug-drug interactions were consistent with guideline recommendations.[1,2,7,8] A recent review covers both the guidances and recent investigations of DOACs in the settings of high BMI and decreased renal or hepatic function.[9] DOAC concentration measurement in the setting of potentially altered gastrointestinal absorption, while logical, is not included in current treatment guidelines. In about one-third of patients who had measurements to assess exposure, concentrations were either undetectable or above ranges reported in clinical trials, suggesting the need to reevaluate the dosing regimen, adherence, and clinical conditions as we learn more about the potential role of measuring anti–factor Xa activity in real-world patients with complex thromboembolic clinical scenarios. Guidelines provide conflicting recommendations about the utility of measuring DOAC activity during acute hemorrhage or before procedures, acknowledging the lack of a strong evidence base.[10,11,12] DOAC measurements were performed in patients presenting with major bleeding, but treatment and decisions regarding use of reversal agents may have been made before return of assay results.

Our study had several limitations, including the single-center nature, small sample size, and the lack of accurate information on dosing time precluding detailed pharmacokinetic analyses. Additionally, our study was not designed to ascertain the denominator of all patients prescribed DOACs at our center. We also note that these assays are available at our site and reimbursable in the United States but may not be elsewhere.

4 | CONCLUSION

In conclusion, we found that clinicians in our health system obtain DOAC concentrations primarily to evaluate drug exposure in patients with potentially altered pharmacokinetics or with recurrent thromboembolic events. The information on DOAC concentrations appeared to contribute to clinical decision making.

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RELATIONSHIP DISCLOSURE

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AUTHOR CONTRIBUTIONS

SS: study design, data collection, data analysis, and manuscript writing. M C and ST: data collection and assay performance. MCF and SK: study design, data collection, data analysis, and manuscript writing. JBS: study concept, study design, data collection, data analysis, and manuscript writing.

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