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

Smrithi Sukumar BS¹ | Melissa Cabero BS² | Sharon Tiu BA² | Margaret C. Fang MD, MPH³ | Scott C. Kogan MD⁴ | Janice B. Schwartz MD³

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. 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. 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.

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/m² (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
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. One patient with a subdural hematoma of unknown
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. A recent review covers both the guidelines and recent investigations of DOACs in the settings of high BMI and decreased renal or hepatic function. 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. 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.

ACKNOWLEDGMENTS
Publication made possible in part by support from the UCSF Open Access Publishing Fund.

RELATIONSHIP DISCLOSURE
JBS reports grant funding from Bristol-Myers Squibb, Inc outside the submitted work. All other authors declare no conflicts of interest.

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.
REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, et al.; ESC Scientific Document Group. ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;2016(37):2893-2962.

2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125-e151.

3. Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. *Thromb Haemost*. 2018;118:437-450.

4. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI. Subcommittee on control of anticoagulation. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14:623-627.

5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

6. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-694.

7. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemost*. 2018;16:209-219.

8. Gosselin RC, Adcock DM, Douxfils J. An update on laboratory assessment for direct oral anticoagulants (DOACs). *Int J Lab Hematol*. 2019;41(suppl 1):33-39.

9. Chen A, Stecker E, Warden BA. Contemporary reviews. Direct oral anticoagulant use: a practical guide to common clinical challenges. *J Am Heart Assoc*. 2020;9(13):e017559. https://doi.org/10.1161/JAHA.120.017559

10. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv*. 2018;2(22):3257-3291.

11. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. *Am J Hematol*. 2019;94(6):697-709.

12. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(5):594-622.

How to cite this article: Sukumar S, Cabrero M, Tiu S, Fang MC, Kogan SC, Schwartz JB. Anti–factor Xa activity assays of direct-acting oral anticoagulants during clinical care: An observational study. *Res Pract Thromb Haemost*. 2021;5:e12528. https://doi.org/10.1002/rth2.12528