Testing and monitoring direct oral anticoagulants

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Direct oral anticoagulants (DOACs) have significantly improved the care of patients requiring anticoagulation. With similar or better efficacy and safety outcomes and easier use in the outpatient setting compared with the standard-of-care vitamin K antagonists and low molecular weight heparin, DOACs are now endorsed as first-line treatment of indications including prevention of stroke and systemic embolism in nonvalvular atrial fibrillation and treatment of venous thromboembolism. DOACs are easy-to-use oral agents that offer simple dosing and short half-lives, with no need to test levels because of the wide therapeutic window and limited drug-drug interactions. After almost a decade of DOAC use, the question of testing DOAC levels in certain clinical situations has become the focus of debate. Although guidance for using routine coagulation tests is available, these tests are inadequate for optimal care. DOAC-specific tests have been developed but have limited availability in Europe and less availability in the United States. None are licensed. DOAC testing may be useful in the setting of critical clinical situations such as life-threatening bleeding or need for emergent surgery, especially with the availability of DOAC reversal agents. Patients with characteristics that fall outside the normal range may benefit from the guidance that DOAC testing could offer. Obstacles to adopting DOAC testing have been raised, such as test reliability and staffing costs; however, these problems are rapidly being resolved. Further investigation of the role of DOAC testing is needed to explore its full potential and role in clinical practice. (Blood. 2018;132(19):2009-2015)

Introduction

Direct oral anticoagulants (DOACs) have been available for almost a decade. Dabigatran, a direct thrombin inhibitor, was approved in 2008 in the United States, rapidly followed by the direct factor Xa inhibitors (Xais) rivaroxaban, apixaban, and edoxaban. All are approved to prevent stroke and systemic embolism associated with atrial fibrillation (AF) and to treat venous thromboembolism (VTE) and, except for edoxaban, VTE prophylaxis after joint replacement surgery. Betrixaban, an Xai, was recently approved in the United States for extended-duration VTE prophylaxis in medically ill patients.

DOACs have positively affected patients requiring anticoagulation. Historical options for outpatient anticoagulation, vitamin K antagonists (VKAs) and low molecular weight heparin, carry significant burden, requiring lifestyle modifications for many patients. Although DOACs have many advantages compared with VKAs, driving factors for use include similar or improved efficacy, decreased major bleeding, and ease of administration. DOAC use has now surpassed that of VKAs in the United Kingdom and other European countries, and in the United States, >43% of the dispensed oral anticoagulant prescriptions were for DOACs in 2016. The number of patients treated with oral anticoagulants has also increased. Recent data suggest that >2.9 million US patients take one of the Xais. Although bleeding complications with DOACs are lower, the increased number of patients treated with anticoagulants suggests that a higher absolute number of patients are at risk. Anticoagulant drugs have been responsible for more visits to emergency rooms than any class of medication.

As DOAC use has increased, attention has turned to measuring DOAC levels. Indications for measuring DOAC levels can be considered in 2 categories. One category, critical clinical situations, such as major bleeding or need for emergent or elective surgery, would use a 1-time measurement to determine if a DOAC, ideally along with its concentration, is present. It has been suggested that measurement of DOAC concentration before planned surgery is the preferable strategy to avoid bleeding complications rather than trying to predict drug-level decline based on renal function and drug half-life. With DOAC antidotes approved, the case to measure concentration has also been made. Idarucizumab, the reversal agent for dabigatran, has been approved worldwide. Andexanet alfa has been approved by the US Food and Drug Administration and is under review in other countries.

The other category of DOAC testing is to determine the optimal dose for an individual patient, or to monitor. It is recognized that the fixed-dose strategy of DOACs may be suboptimal for some patient populations. Patients who might benefit from testing drug levels include those with weight extremes, renal insufficiency, gastrointestinal absorption concerns, or need for concomitant medications with strong effects on metabolic pathways. These indications for testing DOAC concentration and currently available strategies to assess DOAC anticoagulation will be reviewed.
Critical clinical situations

Patients taking DOACs may develop bleeding from trauma or medical disease or may require emergent surgery. Renal function may unexpectedly decrease, resulting in excessive levels. Patients may present for surgery with recent ingestion of DOACs. These realities of daily practice were recognized soon after DOACs became available. Multiple studies have assessed the effect of DOACs on available clinical laboratory coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT).14,15

Guidance for using routine coagulation tests focuses on a binary yes or no answer for the presence of anticoagulant effect, such as a normal vs elevated TT for dabigatran14 or a normal vs elevated PT for rivaroxaban; however, there can be errors with this approach.16 A normal aPTT may be obtained despite a dabigatran concentration that could result in bleeding or lack of hemostasis during surgery (ie, a concentration that is clinically relevant).17 Although there is a linear correlation between the aPTT and dabigatran at expected concentrations, at elevated concentrations, the aPTT plateaus and does not correlate with increasing dabigatran levels; result can also vary with reagents.15,16 Similarly, the PT is not sensitive to apixaban, and when used for rivaroxaban or edoxaban, it has variation based on the reagents used.13,18,19 Patients with clinically relevant rivaroxaban levels can have a normal PT.20 Much of the variability is due to different sensitivities of the assay systems. There is no international normalized ratio to normalize the reagents for DOAC testing. Although the TT and anti-Xa calibrated for heparins are sensitive and can exclude drug effects if results are normal, positive results cannot be used to gauge degree of anticoagulation.21,22

At our center, we have used routine clinical coagulation tests to manage patients presenting with unexpected events while taking DOACs. We have used the TT and aPTT for patients taking dabigatran presenting with acute renal failure,23 requiring emergent surgery for acute aortic dissection 4 hours after taking dabigatran,24 or requiring heart transplantation.25 At one associated community hospital, the aPTT was the only option for a patient taking dabigatran and bleeding.26 As discussed, the PT and aPTT assays may yield false-negative results despite the presence of DOAC concentrations that could impair hemostasis, making it difficult and potentially dangerous to rely on these tests to care for patients.15,21,27,28

The availability of antidotes highlights the need for DOAC testing. In the clinical trials of the reversal agents, the idarucizumab REVERSE-AD trial12 and the andexanet alfa trial ANNEXA-4 trial13 treatment was not based on laboratory values at the time of presentation. The strategy used to determine the 5-g dose of idarucizumab was based on the dose needed to reverse up to the 99th percentile of the total-body load of dabigatran-treated patients in the RELY trial.12 This dose of idarucizumab can be in excess of what a patient might need, but in the setting of life-threatening bleeding without knowledge of drug concentration, it can be appreciated as being appropriate. The dosing strategy for andexanet alfa is different and requires knowledge of the type of Xai and time from last ingestion, basing the dose on the anticipated blood concentrations achieved by the different DOACs.13 Patients receive a bolus followed by a 2-hour continuous infusion because of the short half-life of andexanet alfa. In both trials, samples were drawn before administration of the reversal agent, and DOAC concentration was analyzed in central laboratories. Some patients had no or low levels of anticoagulant present. Forty-two patients (8.3%) treated with idarucizumab in the completed REVERSE-AD trial had normal diluted TT (dTT) or ecarin clotting time (ECT) results, indicating no need for reversal; however, 130 had normal aPTT results.12 If the aPTT had been used to determine if idarucizumab should be administered, 88 patients with drug activity would not have been treated.12 At 12 hours after receiving idarucizumab, 23% had an increase in dabigatran concentration >20 ng/mL (the level determined to be the threshold value for impairing hemostasis), but results were not available to treating clinicians.12 Ten of these patients had recurrent or continued bleeding; however, only 3 were treated with a second dose of idarucizumab.12 The availability of DOAC levels may have aided clinicians in providing appropriate care. In the interim report of the ANNEXA-4 trial, 18 of 67 patients were excluded from the efficacy analysis because DOAC activity level at entry was deemed to be too low.12 Final analysis of the ANNEXA-4 study should yield more information.

DOAC tests should have simple sample procurement and processing and rapid turnaround times to be useful in emergent situations. A 2-tiered testing approach might be considered for patients with life-threatening bleeding. Plasma-based DOAC concentration assays have a turnaround time of roughly 35 minutes in optimal situations.29 New point-of-care assays are being developed with turnaround times of 10 minutes. A rapid test to detect DOAC activity above a certain threshold could be performed and acted on, with administration of a fraction of the antidote dose if positive or no antidote if negative. Threshold values for administering reversal agents have been suggested by the International Society on Thrombosis and Haemostasis.28 A positive rapid test result would allow 2.5 g of idarucizumab or the initial bolus of andexanet alfa to be administered. Once the DOAC concentration is known, the dose can be tailored, particularly the 2-hour infusion of andexanet alfa. This approach offers large cost savings if the result of the first test reveals no clinically relevant anticoagulant activity, and more effective treatment if the concentration is higher than expected, and avoids unnecessary patient exposure to antidotes. A rapid assay could also be effective for patients presenting with thromboembolic stroke when thrombolysis is considered or when emergent invasive procedures are required. Although a rapid test that also provides concentration would be ideal; a pilot study demonstrated that rivaroxaban levels with a plasma-based anti-Xa assay using rivaroxaban calibrators is feasible and allowed thrombolysis to be used to treat thromboembolic stroke in one-third of patients who would otherwise have been ineligible.30

Although time is critical when patients present with life-threatening problems, laboratory tests are already part of routine care. Complete blood count, type, and screen and creatinine are routinely sent during initial patient assessments. Adding DOAC-specific testing should be easy to incorporate, especially with rapid turnaround tests. Small published case series and pilot studies support both the need for DOAC-specific testing and the ability to incorporate DOAC testing into the emergency room workflow. In a report of 7 administrations of idarucizumab in a busy US inner city emergency room, 2 of 7 administrations were given despite a
normal aPTT. It is unknown whether these patients had clinically relevant dabigatran levels not detected by the aPTT or whether they received unnecessary idarucizumab. Either a rapid result assay or an assay able to provide dabigatran concentration with the same turnaround time as the aPTT could have been used to determine whether to administer idarucizumab. In 4 patients, the aPTT was elevated and idarucizumab was administered, demonstrating that testing before administration of a reversal agent was performed. In one center, feasibility and reliable turnaround times for rivaroxaban concentration using a calibrated anti-Xa assay were also demonstrated during routine working hours (median, 34 minutes; range, 30-56 minutes) and after hours (median, 35 minutes; range, 29-75 minutes), confirming that levels can be obtained in emergency settings and used to guide treatment decisions.

A report of 11 patients treated with idarucizumab in European centers demonstrates the advantages of DOAC testing. A commercially available dTT with dabigatran calibrators was used in 6 cases to determine dabigatran concentration. Of 3 patients with acute thromboembolic stroke, 2 were determined to have elevated levels; they were given idarucizumab, allowing the use of tissue plasminogen activator. Two patients with fractures had elevated coagulation tests (TT, aPTT) at presentation; dabigatran concentration was not initially measured. The teams waited 24 and 72 hours, respectively, for dabigatran levels to decline and coagulation tests to normalize, but this took longer than expected. Both ultimately were found to have elevated dabigatran levels and were treated with idarucizumab, 1 and 3 days after presentation, respectively, because surgery could no longer be delayed. These patients could have been treated at presentation if levels had been checked and found to be high, saving prolonged hospitalization, added morbidity, and cost. In all cases, dabigatran levels measured after idarucizumab dropped significantly, allowing safe use of tissue plasminogen activator or invasive procedures. Our institution has had difficulty determining whether patients with borderline indications for reversal should be treated with andexanet alfa now that it is commercially available. We believe that DOAC tests yielding a positive or negative result would be of significant benefit.

DOAC testing is feasible to guide decision making in critically ill patients, as demonstrated by the limited data from these small real-world experiences, which also highlight the complexity of these patients; they require ongoing management after initial presentation. Treatment of the bleeding patient or one who requires emergent surgery does not stop with administration of the antidote. DOAC test results could guide care posttreatment with antidotes, especially for those with continued bleeding or in those with impaired renal function with slower clearance of DOACs. In our experience managing a patient requiring 2 doses of idarucizumab, knowledge of dabigatran concentration could have resulted in earlier administration of the second dose of idarucizumab, possibly halting bleeding sooner. In 2 similar cases in Europe, dabigatran test results were used to guide decisions regarding administration of a second dose of idarucizumab.

When the REVERSE-AD trial was planned, regulatory agencies agreed that randomized placebo-controlled trials were not possible because it would be unethical to withhold reversal agents from those who might benefit. Therefore, end points of REVERSE-AD are reversal of anticoagulant effect measured by change in coagulation tests and decrease in dabigatran concentration measured in a central laboratory. The ANNEXA-4 trial has 2 coprimary end points: change in anti-Xa activity (using DOAC-specific anti-Xa tests) and clinician assessment of heparinostatic efficacy. Both idarucizumab and andexanet alfa have demonstrated rapid reduction in drug concentrations, as well as normalization of coagulation tests. Limited and often conflicting data exist regarding the effects of what might be considered other standard-of-care treatments for reversing the anticoagulant effects of DOACs in in vitro and human volunteer studies. A prospective real-world cohort study relied on clinician assessment of the effectiveness of 4-factor prothrombin complex concentrates in patients with major bleeding taking rivaroxaban or apixaban. In 30% of patients, 4-factor prothrombin complex concentrates were deemed ineffective. This study corroborated that the PT and aPTT are not useful to determine the absence of drug; although 38% to 65% of patients had normal results depending on the test, the authors noted that the drug had to have been on board because ingestion of drug within 24 hours was an eligibility criterion.

Although 2 small retrospective analyses of DOAC testing at single centers found low use of testing (both did note significant increase in volume over the study duration), limitations include the time period when DOACs had just been approved, provider lack of knowledge of test availability, lack of availability of specific antidotes for most of the study periods, and other factors such as a 10-day turnaround time. In these studies, test results changed practice in the perioperative setting, affecting decisions regarding timing of surgery. Availability of rapid turnaround DOAC tests could aid clinicians faced with deciding whether to proceed to surgery or use costly reversal agents. Tests could help interpret studies using nonspecific reversal strategies in treating or preventing DOAC-related bleeding. Reversing anticoagulation is only part of the care of the bleeding patient. Assessing outcomes of reversal agents should focus on reversal of anticoagulant activity as the first step. Changing the outcome of a patient who presents with anticoagulant-related bleeding is a different end point that is difficult to study but is an important next step.

DOAC monitoring

Although testing DOAC concentration in emergency situations could affect patient care, the benefits in guiding routine therapy are less certain. For a majority of patients, the current fixed doses of DOACs, with minimal modifications for renal function and, with some DOACs, age and weight, have similar or even better efficacy and safety than VKAs. However, bleeding and thrombotic complications do occur. Emerging data suggest that for certain patients, outcomes might be improved by evaluating and measuring DOAC concentration.

Analyses of trough DOAC concentrations in the pivotal phase 3 AF trials demonstrate significant interpatient variability, despite careful selection of patients. Outcomes with fixed dosing were favorable for preventing thrombotic events with lower serious bleeding compared with standard of care; however, in clinical practice, there is an even higher range of variability. One
retrospective health claims database analysis found that the rates of bleeding were higher than in the pivotal phase 3 trials, thought to be due to older age and more advanced kidney disease. Secondary analyses and modeling studies suggest that a so-called sweet spot exists for DOAC concentration that maximizes the benefit of decreased thrombotic events with a DOAC while minimizing the risk of major bleeding. One simulation analysis of dabigatran in a phase 3 AF trial suggests that ≈40% of patients were receiving a suboptimal dose. Data derived from patients in the community setting on the appropriate fixed dose showed that those with low DOAC trough concentrations had an increased incidence of thrombotic events. This was most prominent in patients with the highest cardiovascular risk, as assessed by the CHA2DS2-VASc score, at 7.9% compared with 0% in patients with similar scores but higher trough levels. Although age seems to play a role in the thrombosis and bleeding associated with dabigatran, labeling advises dose adjustments for renal function only. Pooled analysis of fragile patients, defined as age >75 years, calculated creatinine clearance <50 mL/min, or low body weight <50 kg, in the rivaroxaban VTE studies demonstrated numerically higher rates of VTE recurrence (2.7% vs 1.9%) and major bleeding (1.3% vs 0.9%) than in nonfragile patients. The creatinine clearance threshold of 50 mL/min is generous; with a lower cutoff, the difference might be larger. Case reports of treatment failure because of excessive weight, concomitant drugs affecting DOAC metabolism, or impaired gastrointestinal absorption suggest that these patients might also benefit from monitoring. Patients with drug-drug interactions, such as patients with cancer undergoing treatment, may also derive benefit from assessing DOAC levels, because the clinical impact and degree of change in DOAC concentration are unknown.

A concerning finding is that clinicians are reducing DOAC doses even when patients do not meet criteria. A prospective registry study found that 9.4% of 5738 patients treated with a lower dose than their clinical characteristics dictated had a higher rate of bleeding risk than those in the phase 3 trials. Similarly, a retrospective health claims database analysis found that patients prescribed an inappropriate DOAC dose had worse outcomes for both bleeding and thrombosis. The inappropriate dose reduction allowed for increased thrombotic events without avoidance of bleeding.

The results from clinical trials and real-world studies suggest that individualized dosing might maximize the therapeutic effect and minimize the risk of DOACs for some patients. The availability of testing might make treating clinicians more likely to prescribe the recommended dose in high-risk patients if levels are reassuring. Although the idea of optimal DOAC levels improving net clinical benefit makes sense, how to achieve this in practice and demonstrate benefit is not yet clear. The concept of on-therapy levels, with wide ranges for peak and trough values, has been developed. Data for drug concentrations are available from pharmacokinetic/pharmacodynamic studies in healthy volunteers, as well as pooled data from the large phase 3 studies. More than 42,000 patients were treated with DOACs in 4 AF trials, with many assessing drug concentrations. For the non-average patient, finding levels at extreme ends of the range could prompt alterations in dose. As many have noted, how to titrate the dose-administered existent tablet strengths is also unknown, although new strength formulations are achievable. Different approaches to assessing degree of anticoagulation with DOACs, such as measuring changes in endogenous factor X activity rather than drug concentration, need to be explored more fully. AF was estimated to affect 33 million people worldwide in 2010 with that number expected to double. The fraction of patients who might benefit from DOAC monitoring should be large, offering opportunities to gain further understanding of how to use DOAC monitoring to maximize net clinical benefit.

Clinical laboratory DOAC assays

Although standard coagulation tests are not optimal for care of patients taking DOACs, the gold-standard liquid chromatography/tandem mass spectrometry (LC-MS/MS) is not practical for clinical laboratory use. Adaptations of coagulation tests have been developed for measuring DOAC levels (Table 1). Tests for dabigatran concentration employ a DTT with dabigatran calibrators, which can be used on existing laboratory platforms. Ecarin converts thrombin to meizothrombin, which is sensitive to direct thrombin inhibitors but not heparin or antiphospholipid antibodies, and can be used to measure direct thrombin inhibitor concentrations. The ECT is based on the time it takes to form a clot; the ecarin chromogenic assay relies on color generation. However, ecarin, a snake venom, is available in limited quantities. Measurement of factor Xa concentrations can be based on the chromogenic anti-Xa assay using specific calibration reagents to determine concentration. These chromogenic anti-Xa assays can be run on the standard coagulation analyzers currently used in many institutions. The DTT with dabigatran calibrators, the ECT and ecarin chromogenic assay, and the DOAC-specific anti-Xa assays have been demonstrated to have validity over a wide range of DOAC concentrations in plasma and have been validated with LC-MS/MS.

Arguments against implementing DOAC testing in clinical laboratories have included reliability, performance, and cost. Many studies have demonstrated that these DOAC-specific assays are reliable and reproducible when tested in different clinical laboratories. Proficiency testing results across laboratories in Italy demonstrate that these tests are not difficult to run or implement and have limited variability that is not different from that of international normalized ratio measurements. Findings from 30 participating laboratories in a study from France also demonstrate that commercially available DOAC-specific assays have good interlaboratory precision and accuracy.

Despite advances in laboratory technology, one rate-limiting step is the separation of plasma from whole blood. Although
Table 1. DOAC-specific tests

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<th>DOAC</th>
<th>Test</th>
<th>Mechanism</th>
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<td>Dabigatran</td>
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<td>Factor Xa inhibitors</td>
<td>Conventional*</td>
<td>Anti-Xa for LMWH/UFH¶</td>
<td>Chromogenic assay</td>
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<td>Normal range: Xai concentration not affecting coagulation</td>
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ECA, ecarin chromogenic assay; ECT, ecarin clotting time; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

*Conventional: Approved clinical laboratory tests not specific for DOACs. Results useful as a positive or negative indication of the presence of DOAC activity. For dabigatran, if the TT is normal, there is either no drug on board or the concentration is not high enough to impair coagulation; if the result is elevated, the dabigatran concentration is high enough to affect coagulation. Similarly, for the Xai, if the anti-Xa for LMWH/UFH is normal, the Xai concentration is 0 or not high enough to impair coagulation. If the anti-Xa LMWH/UFH is elevated, the Xai concentration is high enough to impair coagulation. However, elevated results cannot be interpreted as they would be for LMWH/UFH regarding degree of anticoagulation.

†Specific: Designed to quantitate DOAC concentration. LC-MS/MS directly quantitates drug concentration. Other types of assays require construction of a standard curve using known concentration of DOACs added to the assay to create a calibration curve. Results obtained from the patient sample are then compared with the curve to determine drug concentration and are reported as nanograms per milliliter. Threshold concentration values for administering reversal agents have been determined, and ranges of DOAC therapeutic windows have been identified. Reference curves must be run for each QC of the machine. The development of packaged sets of standards to construct reference curves has increased the appeal of these assays in the clinical laboratory because of decreased labor and decreased turnaround time. Commercial assays for these tests have been developed and are available but not yet approved by regulatory agencies.

§LC-MS/MS: LC-MS/MS is a sophisticated method for detecting plasma concentrations of all DOACs by analyzing the actual drug molecules in the sample. It is considered the gold-standard method but requires large expensive equipment and well-trained staff and has limited throughput, so it is not well suited for routine clinical laboratories.

†§dTT: Plasma-based assay. The TT measures the time it takes for thrombin to cleave fibrinogen and form a clot. The standard test is measured in seconds, with the normal range usually 15 to 20 seconds. Because direct thrombin inhibitors significantly interfere with thrombin activity, patient plasma is diluted 1:3 with normal plasma to dilute drug concentration but maintain normal levels of coagulation factors and fibrinogen. A small amount of bovine thrombin is added to initiate coagulation. The presence of dabigatran inhibits the thrombin activity proportional to drug concentration. The result of the test in seconds is compared with a reference curve constructed from known concentrations of dabigatran.

¶Ecarin-based assay: Plasma-based assay that uses the snake venom ecacin to cleave thrombin to meizothrombin, which is insensitive to heparins. For the ECT, a clot-based assay is run similar to the TT, with the patient sample results compared with the calibration curve to determine dabigatran concentration. In the ECA, meizothrombin activity is determined by cleavage of a chromogenic substrate. The cleavage is inhibited by dabigatran in a concentration-dependent manner; results are compared with known calibrators to determine dabigatran concentration.

Calibrated anti-Xa: Anti-Xa assays use a chromogenic substrate that is cleaved by factor Xa. Color production is proportional to Xa activity; exogenous Xa is added so that the patient’s Xa level is not rate limiting. The presence of DOACs that inhibit factor Xa (apixaban, edoxaban, rivaroxaban, betrixaban) will inhibit color generation. This assay is also used for heparins and fondaparinux. Drug concentration is inversely proportional to color generation and can be determined by comparing with the reference curve generated from calibration standards specific for each DOAC. When used for LMWH/UFH, the reference specific reference curves are expressed in units per milliliter, and when used for factor Xa DOACs, the results from the reference curve are expressed as nanograms per milliliter.

Conclusion

DOACs have improved the management of patients requiring anticoagulation. Although the current dosing strategies and the lack of need for testing work well for the majority of patients, the increasing use of DOAC in clinical practice has identified situations and patient populations where testing might provide benefit. Data supporting DOAC testing are limited to small case series and clinical observation, but the case for testing when patients present with critical bleeding or require emergent surgery is strong; results can guide decision making about the use of expensive reversal agents and the safety of proceeding with invasive procedures. The development of rapid turnaround DOAC assays for use in urgent clinical situations should be supported. The utility of DOAC testing in niche patient populations needs to be further explored in an effort to better understand and optimize the benefits and reduce the risks for patients outside the definition of average. Concerns about reliability, infrequent use, regulatory requirements, and cost are countered by the rapid improvement in assay technology, the demonstrated accuracy of testing, and the potential cost savings achieved when tests results are used to guide patient care in defined clinical circumstances. DOAC testing should be further evaluated in a variety of clinical settings to improve knowledge and understanding of its utility and role in delivering safe and effective care for patients requiring anticoagulation.
Authorship
Contribution: J.M.C. wrote the paper.

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REFERENCES
11. Sabor L, Raphaël M, Dogné JM, Mullier F, Douxfils J. Heparin-calibrated chromogenic anti-Xa assays are not suitable to assess the presence of significant direct factor Xa inhibitors levels. Thromb Res. 2017;156:36-38.


