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Measuring Direct Oral Anticoagulant (DOAC) Levels: Applications, Limitations, and Future Directions

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ABSTRACT

Introduction: There are important challenges with the measurement and interpretation of direct oral anticoagulant (DOAC) anticoagulant effect including a lack of therapeutic ranges, inaccuracy of routinely available coagulation assays, lack of established thresholds for clinically significant effect, and uncertainty about how to apply the results to patient care.

Objective: In this narrative review, we provide a practical approach to DOAC measurement in clinical practice.

Methods: By summarizing the literature and using illustrative cases, we highlight key principles of commonly available tests, outline potential indications for measuring DOAC drug levels, and provide guidance on interpreting results to inform management decisions.

Conclusion: While DOACs do not require routine monitoring of anticoagulant effect, assessment of plasma DOAC concentration may be helpful in select emergency and non-emergency clinical scenarios.

1 | Introduction

Direct oral anticoagulants (DOACs), including apixaban, rivaroxaban, edoxaban, and dabigatran, are commonly used to prevent and treat venous thromboembolism (VTE) and to reduce the risk of stroke and systemic embolism in patients with atrial fibrillation. These agents offer comparable efficacy and improved safety to warfarin [1] (or low molecular weight heparin) while providing several advantages, including predictable pharmacokinetics, short half-lives, a wide therapeutic window, and fixed dosing that precludes the need for regular coagulation monitoring [2].

Despite these benefits, there are clinical scenarios for which assessing the anticoagulant effect of DOACs could inform management decisions, especially when anticoagulated patients experience emergencies such as major bleeding, urgent invasive medical procedures, or acute ischemic stroke requiring thrombolysis. Therapies such as prothrombin complex concentrate (PCC) or specific DOAC reversal agents (e.g., idarucizumab or andexanet alfa) can be given to support hemostasis in DOAC-treated patients, but their judicious use is essential due to an increased risk of thromboembolism (~4%–8% for PCC [3–5], ~4%–5% for idarucizumab [6], ~10% for andexanet alfa [7]). In an emergency, quantitative DOAC levels can help clinicians identify which patients are most likely to benefit from these treatments, while avoiding their overuse in patients with absent or clinically insignificant DOAC levels.

However, several challenges complicate the interpretation of coagulation testing in DOAC-treated patients, including: (i) the absence of established therapeutic ranges for quantitative DOAC assays, (ii) uncertainty about thresholds for a clinically significant drug effect, (iii) inaccuracies of routine coagulation assays, and (iv) lack of high-quality evidence on how test results should guide individual patient care. In this article, we outline a practical approach to integrating DOAC drug level measurement into clinical practice. We discuss key principles of commonly available tests, outline potential indications for measuring DOAC drug levels, and provide guidance on interpreting results to inform management decisions.

1.1 | Case 1

A 58-year-old woman is taking edoxaban 60 mg daily for a history of recurrent unprovoked deep vein thrombosis (DVT). She has a seizure disorder managed with phenytoin and has a body weight of 32 kg. Due to reduced mobility, warfarin monitoring is infeasible, and she is unable to self-inject low molecular weight heparin. Concerns arise about the efficacy and safety of anticoagulation due to her low weight and a potential drug–drug interaction between edoxaban and phenytoin, which is a known inducer of p-glycoprotein (p-gp) and cytochrome P450 3A4 (CYP3A4) enzymes. A peak edoxaban anti-Xa level is measured at 139 ng/mL (expected range 91–221 ng/mL based on Phase II/III clinical trials). Should her anticoagulant prescription be modified?

1.2 | Case 2

A 76-year-old man with atrial fibrillation, prior ischemic stroke, hypertension, and Type 2 diabetes mellitus (CHA_2DS_2VASc score of 6) is taking apixaban 5 mg BID for stroke prevention. He presents to the emergency department (ED) with lower gastrointestinal bleeding resulting in hemodynamic instability. The timing of his last apixaban dose is unknown. Laboratory tests in the ED reveal an international normalized ratio (INR) of 1.0 (reference range 0.8–1.1) and activated partial thromboplastin time (aPTT) of 27 s (reference range 24–34 s). His creatinine clearance is 52 mL/min. His apixaban level is 45 ng/mL, as measured by a drug-specific anti-Xa assay. Should an anticoagulant reversal drug be given?

1.3 | What Are the Potential Benefits and Challenges of "Monitoring" DOAC Drug Effect in Stable Anticoagulated Patients?

Unlike vitamin K antagonists (VKAs), DOACs are prescribed at fixed doses, and routine coagulation monitoring is not recommended for stable patients on these medications. However, despite their improved safety profile compared to VKAs, randomized trials show that 1%–2% of patients taking DOACs experience thromboembolism [8] annually and 1%–3% have major bleeding complications [9] with higher rates among those treated in routine clinical practice. As efficacy and safety are dose-dependent, these adverse events may arise, at least in part, due to relatively higher or lower drug levels in individual patients. This raises the question of whether the safety of DOACs, like that of VKAs, could be enhanced with coagulation testing to tailor drug selection and dosing.

Post hoc analyses of pivotal phase III trials of DOACs compared to VKA for stroke prevention in atrial fibrillation including ENGAGE AF-TIMI 48 [10] (edoxaban), RE-LY [11] (dabigatran), ROCKET-AF [12] (rivaroxaban) and ARISTOTLE [2] (apixaban) showed that higher drug levels, prolonged PT, or higher areas under the curve (AUC) among DOAC-treated patients correlate with an increased risk of major bleeding. In the ENGAGE-AF TIMI 48 [10] and RE-LY [11] trials, lower trough drug levels were correlated with an increased risk of ischemic stroke, and in the ROCKET-AF [12] trial, a prolonged PT was associated with a reduced risk of ischemic stroke.

While these findings suggest associations between the degree of DOAC exposure measured using coagulation tests and clinical outcomes, several practical considerations limit the use of drug levels to guide clinical decisions [13, 14]. First, therapeutic ranges for DOACs remain undefined. Instead, clinicians rely on expected peak and trough levels derived from phase II and III clinical trials of DOACs in atrial fibrillation and VTE treatment (Table 1) to guide drug level interpretation [21]. Second, substantial inter- and intra-patient variability in DOAC concentrations complicates interpretation for an individual patient. Peak and trough DOAC levels in atrial fibrillation patients vary by as much as 34%–37% within individuals, and 46%–63% between individuals [22], and in the ARISTOTLE trial, apixaban levels overlapped substantially among patients with and without major bleeding [2]. Third, the relationship between drug levels and clinical outcomes is confounded by factors such as age, renal function, and weight, which are already accounted for in DOAC dose reduction criteria. Fourth, limited DOAC tablet and capsule strengths restrict the feasibility of tailoring doses to achieve desired drug levels. Finally, no adequately powered randomized trials have demonstrated a net clinical benefit of adjusting DOAC dose based on coagulation laboratory parameters. Conversely, off-label DOAC dosing is associated with harm. In a prospective registry of 5738 patients with atrial fibrillation [23], off-label dose reductions were associated with an increased risk of cardiovascular hospitalization, and off-label dose increases were associated with higher all-cause mortality compared to on-label dosing.

1.4 | Why Are Drug-Specific Coagulation Tests Useful, Above and Beyond Routine Coagulation Tests?

1.4.1 | Limitations of Routine Coagulation Tests

While a prolonged PT and/or APTT in the context of known dabigatran or Factor Xa inhibitor ingestion may provide *qualitative* evidence of DOAC exposure, these tests cannot exclude the presence of clinically significant DOAC concentrations and furthermore cannot *quantify* DOAC drug levels [24]. For dabigatran, a prolonged APTT lacks sufficient sensitivity to detect low drug levels, but if present suggests that there is a clinically significant drug concentration present (high specificity). In contrast, thrombin time (TT) is highly sensitive to the presence of low concentrations of dabigatran and can be used to "rule out" presence of the drug, but lacks specificity and cannot be used for dabigatran quantitation [25, 26].

TABLE 1 | Expected DOAC steady-state peak and trough plasma concentrations.

Direct oral anticoagulant	Dose	Atrial fibrillation	Venous thromboembolism	Unspecified	
		Expected peak plasma concentration (ng/mL), median (5th–95th %ile)	Expected peak plasma concentration (ng/mL), median (5th–95th %ile)	Expected peak plasma concentration (ng/mL), median (5th-95th %ile)	Expected trough plasma concentration (ng/mL)
Apixaban	2.5 mg twice daily	123 (69–221)	67 (30–153)[a]	—	—
	5 mg twice daily	171 (91–321)	132 (59–302)	—	103 (41–230)
Rivaroxaban	10 mg once daily	—	—	125 (91–196)	26 (6–87)
	15 mg once daily	—	—	229 (178–313)	
	20 mg once daily	249 (184–343)	270 (189–419)	—	
Edoxaban	30 mg once daily	169 (10–400)	164 (99–225)	—	22 (10-40)[b]
	60 mg once daily	300 (60–569)	234 (149–317)	—	
Dabigatran	110 mg twice daily	—	—	126 (52–275)	90 (31–225)
	150 mg twice daily	—	—	175 (74–383)	

Note: Adapted from [15–20]. Peak plasma concentrations are expressed as median (5th–95th percentile range) with the exception of dabigatran 110 mg twice daily (AF) which is expressed as median (10th–90th percentile range).
[a]Dose adjusted population based on two of three dose reduction criteria in the ARISTOTLE study.
[b]Interquartile range.

APTT, PT, and TT must be interpreted cautiously in critically ill patients because liver impairment, disseminated intravascular coagulation (DIC), factor deficiencies or inhibitors, or pre-analytical error may confound the interpretation of a prolonged clotting time. Furthermore, the sensitivities and specificities of these tests for DOACs vary depending on the reagent, calibrator, and analyser in use.

Low molecular weight heparin (LMWH) or unfractionated heparin (UFH) anti-Xa assays may be a suitable alternative to drug-specific assays to detect low concentrations of Factor Xa inhibitors in laboratories with validated protocols specific to their combination of reagent, calibrator, and analyser [27, 28]. These assays have a lower limit of detection of 20–30 ng/mL for factor Xa inhibitors with a rapid turnaround time (less than 30 min) and could potentially help “rule out” the presence of a Factor Xa inhibitor in an emergency. Important caveats are that testing cannot distinguish between Factor Xa inhibitors and LMWH or UFH, and that LMWH anti-Xa thresholds corresponding to a clinically significant drug level (> 30–50 ng/mL) vary widely between coagulation instruments and reagents used for testing [27].

1.4.2 | Drug-Specific Assays for Factor Xa Inhibitor Quantitation

Drug-specific anti Xa assays utilising specific calibrators for edoxaban, rivaroxaban, and apixaban are preferred over LMWH anti-Xa assays, particularly, when there is a need to quantitate drug levels above 30–50 ng/mL [25]. These assays can be conducted routinely on coagulation analysers and demonstrate high sensitivity, specificity, and good correlation with tandem liquid chromatography-mass spectrometry (LC–MS/MS), which is regarded as the gold standard test for DOAC quantification.

These assays can cross-react with other drugs that exhibit anti-Xa activity, such as UFH or LMWH, which can result in reporting falsely elevated DOAC levels. This limitation emphasizes the importance of carefully interpreting test results in patients taking multiple anticoagulants, or in whom sample contamination with heparin is suspected. To obtain accurate measurements of drug levels, clinicians must identify the specific anticoagulant(s) the patient was taking at the time of testing.

Standardization remains an important issue regarding DOAC-specific anti-Xa assays, and validation of the method employed, taking into account the specific reagent and analyser being used, is critical for accurate results. LC–MS/MS is not used to measure DOACs in clinical practice due to lack of availability, labor intensiveness, complexity, and slow turn-around time [25].

1.4.3 | Drug-Specific Assays for Dabigatran Quantitation

Unlike the TT, the dilute thrombin time (dTT) can be used to quantify dabigatran drug levels [29, 30]. The patient sample is diluted with normal saline, buffer, or pooled plasma. Pooled plasma has the advantage of eliminating interference due to low prothrombin or fibrinogen. Ecarin-based assays that utilize dabigatran calibrators, including the ECT (ecarin clotting time) and ECA (ecarin chromogenic assays), and chromogenic anti-FIIa assays are also available to measure dabigatran levels. However, the ECT can be affected by low prothrombin or fibrinogen levels [30]. The use of prothrombin buffer safeguards the ECA assay from interference with prothrombin deficiency.

1.5 | How Do Clinicians Use DOAC Drug Levels to Influence Treatment Decisions?

Whether to measure a DOAC drug level depends on the goal(s) of testing, which can be characterized as follows: (i) to determine whether a minimum clinically significant concentration of DOAC is present in an emergency situation (i.e., to guide anticoagulant reversal decisions for major bleeding, prior to urgent surgery, or before systemic thrombolysis for acute ischemic stroke), or (ii) to determine whether DOAC levels are outside the typical "on-therapy" range (i.e., excessively high or low) in a stable patient (e.g., to rule out malabsorption after major gastrointestinal surgery, or to rule out bioaccumulation in a patient with chronic kidney disease) [26]. Examples of clinical scenarios where decision making may be influenced by knowledge of drug levels are shown in Table 2.

1.5.1 | Goal 1: Determine Whether a Clinically Significant DOAC Concentration Is Present in an Emergency

In emergencies such as urgent surgery, systemic thrombolysis for acute ischemic stroke, or treatment of serious bleeding, determining whether there is a "clinically significant" DOAC concentration may help guide clinical decisions. The International Society on Thrombosis and Hemostasis (ISTH) suggests that patients with DOAC drug levels below 30–50 ng/mL are unlikely to benefit from anticoagulant reversal strategies to treat major bleeding or correct hemostasis before urgent surgery [31]. However, these thresholds are based on expert opinion and have not been evaluated in clinical studies. Prior studies have shown that even very low DOAC drug levels < 10 ng/mL can impair in vitro thrombin generation, but the clinical significance of this finding is unknown [32, 33]. In the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study [34], patients on apixaban and rivaroxaban held their DOAC for 4–5 half-lives prior to scheduled high-bleed risk surgery, and a drug level was measured in a subset of patients immediately before the procedure. The 30-day risk of perioperative bleeding was ~3%, and most patients (97%–99%) had a DOAC drug level below 50 ng/mL [34]. Logistical challenges, including limited availability of drug-specific anti-Xa assays and delayed test turnaround times for emergencies (often exceeding 30 min), limit the practical utility of testing in many centers.

In practice, clinicians assess factors including time since the last dose and drug half-life (about 10 to 12 h for DOACs), estimated drug clearance (based on renal and hepatic function), and the presence of interacting medications to estimate the likelihood of clinically significant DOAC levels [35]. Time from the last dose is likely the most important factor but is often uncertain or unknown in an emergency. For example, in the ANNEXA-4 study [7] which evaluated andexanet alfa for major bleeding in patients on factor Xa inhibitors (taken within the previous 15 h), almost one-third of patients had factor Xa inhibitor drug levels below 75 ng/mL, underscoring the need for rapid, DOAC-specific testing methods to help clinicians identify which patients are most likely to benefit from anticoagulant reversal strategies.

1.5.2 | Goal 2: Determine Whether Drug Levels Are Outside the Expected On-Therapy Range (i.e., Excessively High or Low) in a Stable Patient

In stable patients, drug-specific quantitative testing can help identify levels outside the typical on-therapy range, particularly when bioaccumulation, malabsorption, or clinically relevant drug–drug interactions are suspected [25]. For example, patients undergoing bariatric surgery or other malabsorptive gastrointestinal procedures are at high risk for DOAC malabsorption [36]. Peak drug levels are below the expected on-therapy range in around one-third of such patients [37, 38], although the clinical significance of this finding remains unclear. In patients who are at high risk of thromboembolism and who have low drug levels (below on-therapy range), adjustments such as switching to a DOAC with more suitable absorption characteristics (i.e., based on site of absorption), or transitioning to a VKA may be necessary after shared decision making involving the patient or their caregiver [38]. Consensus guidance from the ISTH [39] recommends against the use of DOACs for treatment or prevention of VTE for at least 4 weeks after bariatric surgery and suggests measuring trough levels if a DOAC is prescribed thereafter.

Similarly, patients with advanced renal failure, extremes in body weight, or pharmacokinetic drug interactions may also benefit from DOAC level monitoring. The degree of renal clearance varies among DOACs, with dabigatran having the highest renal dependency (80%), followed by edoxaban (50%), rivaroxaban (36%), and apixaban (27%) [40]. Although apixaban and rivaroxaban are approved for use in advanced renal failure, dosing recommendations vary, and evidence from randomized trials is limited [41–43]. While drug level measurement could theoretically resolve uncertainty around drug selection and dosing in at-risk patients, high-quality clinical studies are needed before this strategy is employed in routine practice.

1.6 | What Novel Assays Are Being Developed to Detect DOAC Drug Effect?

Urine dipstick technology (DOASENSE) has emerged as a reliable qualitative test for the presence of DOACs and has a short turnaround time of less than 15 min [44]. The test can also distinguish between factor Xa inhibitors and dabigatran. A recent systematic review showed that DOASENSE has a high negative predictive value (NPV) for the presence of edoxaban and rivaroxaban (98%–100%) but comparatively lower NPV to detect apixaban (82%), which is the most widely prescribed DOAC [45]. This may be because apixaban is less renally cleared than the other DOACs. Testing requires a urine sample, which may be practically difficult to obtain in an emergency setting, and results do not reflect in-the-moment plasma drug levels.

Thromboelastography and rotational thromboelastometry (TEG/ROTEM) are viscoelastic point-of-care tests that use whole blood samples to provide a more complete assessment of

TABLE 2 | Clinical scenarios where quantitative DOAC drug level measurement may inform decision-making.

Scenario	Timing of measurement	Potential impact on clinical decision making
Is a "clinically significant" DOAC concentration present?		
Urgent invasive procedure or surgery with high bleeding risk	Random drug level drawn immediately before the procedure.	• Guide use of anticoagulant reversal agent or non-specific hemostatic therapy (e.g., prothrombin complex concentrate) • Determine timing of surgery/procedure • Guide use of neuraxial anesthesia
Serious bleeding	Random drug level drawn at presentation with serious bleeding.	• Guide use of anticoagulant reversal agent or non-specific hemostatic therapy (e.g., prothrombin complex concentrate)
Acute ischemic stroke	Random drug level drawn at presentation with acute stroke.	• Guide use of intravenous thrombolysis and/or alternatives (mechanical thrombectomy)
Is the DOAC concentration "excessively high" (above on-therapy range)?		
Severe chronic kidney disease and/or end-stage renal disease	Drug level drawn at trough, just before the next dose is due, and after at least four to five doses to ensure drug level is checked at steady state.	• Guide decisions regarding alternatives including switching to a VKA • Plan duration of DOAC interruption for elective surgery/procedure

(Continues)

Scenario	Timing of measurement	Potential impact on clinical decision making
Pharmacokinetic drug–drug interactions	Drug level drawn at trough (just before the next dose is due) and after at least five doses to ensure drug level is checked at steady state.	• Consider alternative DOAC or change to VKA
Is the DOAC concentration "excessively low" (below on-therapy range)?		
Malabsorptive gastrointestinal surgery	Drug level drawn at peak (1–4 h after drug ingestion), and/or at trough (just before the next dose is due). Drug level should be measured after at least five doses to ensure steady state is achieved.	• Consider alternative DOAC depending on site of absorption or switch to VKA.
Pharmacokinetic drug–drug interactions	Drug level drawn at peak (1–4 h after drug ingestion) and after at least five doses to ensure drug level is checked at steady state.	• Consider alternative DOAC or change to VKA
Suspected breakthrough thrombosis while on treatment	Random drug level drawn at the time of diagnosis of the thromboembolic event.	• Assess and optimize risk factors for non-adherence if applicable (e.g., switch from twice daily drug to once daily), or switch anticoagulant (e.g., to a VKA with regular INR monitoring).

Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

coagulation but may have limited availability in clinical practice. They are not sufficiently sensitive for detecting trough DOAC levels and therefore are not routinely used for this indication [46, 47]. Thrombin generation assays (TGAs) are another global coagulation platform showing promise, but data conflict on which parameters of the TGA have the greatest utility for this purpose [48]. Primarily used in research, the association between TGAs and clinical outcomes are not well established.

Other tests in development include Go-DOAC (Haematex, Hornsby, Australia), which is based on the dilute Russell's Viper Venom Time (dRVVT) and correlates with dabigatran and rivaroxaban concentrations but also has lower sensitivity to apixaban, MRX PT DOAC (Nordic Biomarker, Umeå, Sweden) which measures the functional effect of DOACs using a ratio between a DOAC-sensitive PT and DOAC-insensitive PT [49] and MicroDOAC (iLine Microsystems, Donostia, Spain), a point-of-care analyser that provides semi-quantitative analysis of DOAC concentration and can distinguish between Factor Xa and direct thrombin inhibitors.

2 | Case Resolution

2.1 | Case 1

This patient's low body weight of 32 kg and co-administration of edoxaban and phenytoin may alter DOAC pharmacokinetics. Low body weight (< 50 kg) is associated with higher DOAC drug exposure [50], whereas treatment with phenytoin, which is a strong inducer of P-gp and CYP3A4 could theoretically lower DOAC exposure and contribute to an increased risk of thromboembolism. While reduced dose edoxaban is indicated for individuals with low body weight, in this case, the standard dose was prescribed due to the potential for reduced exposure in the setting of phenytoin use. A recent systematic review of 15 studies suggested that co-administration of an anticonvulsant with edoxaban may be safer than with other factor Xa inhibitors due to lesser metabolism of edoxaban by CYP3A4 compared to other DOACs, but the data are not definitive [51]. In this case, the patient's peak edoxaban drug level was in the on-therapy range (139 ng/mL; expected range 91–221 ng/mL). After shared decision making acknowledging the uncertainty of how to interpret this drug level and the risks and benefits of alternative therapies (warfarin), she elected to continue taking edoxaban 60 mg daily with close follow-up.

2.2 | Case 2

This 76-year-old man taking apixaban 5 mg BID for atrial fibrillation (CHA_2DS_2VASc score of 6) presents to the ED with severe GI bleeding causing hemodynamic instability. In this case, a random drug level was drawn with acceptable turnaround time for emergency assessment of clinically significant DOAC concentration to guide the use of anticoagulant reversal or nonspecific hemostatic therapy. These therapies were not administered based on an apixaban level of 45 ng/mL (below the ISTH threshold [31]) and preserved kidney function. Instead, he was successfully resuscitated with intravenous fluids and transfusion of packed red blood cells. Urgent endoscopy identified a colonic arteriovenous malformation (AVM) which was definitively treated. He restarted apixaban 5 mg BID 5 days after resolution of the bleed without recurrent bleeding.

3 | Conclusion

The extent of DOAC exposure, as assessed by coagulation testing, has been linked to clinical outcomes including thromboembolism and bleeding. Quantitative drug level measurement may be useful in specific emergency scenarios (e.g., to guide anticoagulant reversal decisions) and can potentially help clinicians optimize drug selection and dosing in patients at risk of DOAC bioaccumulation or malabsorption. However, several practical challenges must be addressed before DOAC levels can be routinely integrated into clinical decision-making. These include the absence of well-defined therapeutic ranges for quantitative assays, uncertainty regarding thresholds for clinically significant drug effects, and a lack of high-quality evidence supporting the use of drug levels to guide individual patient management. Further studies with clinical endpoints are warranted to clarify the role of DOAC testing in routine practice.

Author Contributions

S.M., C.W.T., and D.M.S. conceived of the manuscript, wrote the first draft, and edited the manuscript.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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