MEASUREMENT OF DOACS LEVELS

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BACKGROUND

DOACs improve the care for patients requiring anticoagulation and are first-line therapy for atrial fibrillation and VTE. Unlike warfarin, DOACs have predictable PK, short half-lives, and a wide therapeutic index, allowing fixed dosing without routine monitoring. Measuring DOAC levels may be important in cases of acute bleeding, emergency surgery, and drug interactions. We performed a literature review of ASH and ISTH, and a retrospective analysis of patient cohorts stratified by drug type, indication, renal function, BMI, and co-medications. We also evaluated a point-of-care (PoC) coagulometer for rapid clotting time assessment compared with manual whole blood clotting time. DOACs acting directly, selectively, and reversibly inhibit factors IIa or Xa, usually do not require monitoring due to predictable PK and fixed dosing, testing may be necessary in certain cases.

LIMITATIONS FOR DOAC MONITORING

Local verification of in vitro neutralizing agents to assure (1) adequate DOAC neutralization by using sensitive techniques and (2) no deleterious effect on the test method is required before clinical use. Although guidance for routine coagulation tests is available, these tests are inadequate for optimal care. DOAC-specific tests have been developed but are currently limited in availability in Europe and even less so in the U. S.

The onset of action, 1/2 life, etc. of DOACs are shown in Table 1.

Assay	Direct Thrombin Inhibitor	Direct Xa Inhibitor [§]
APTT	Prolonged ↑↑	Prolonged ↑[v]
PT/INR	Prolonged ↑	Prolonged ↑↑[#]
TCT	Prolonged ↑↑↑	No effect

METHODS

Testing Approaches

Routine coagulation tests (PT, INR, aPTT, TT) are not reliable for quantifying DOAC concentrations but may provide qualitative insight when considering timing of last dose and clearance factors (renal/ hepatic function, drug interactions).

DOAC-specific assays: Can accurately quantify concentrations but are not always widely available, particularly in urgent settings, and lack established therapeutic ranges.

Liquid chromatography-mass spectrometry (LC-MS/MS): Gold standard for DOAC measurement but limited by cost and turnaround time.

Consensus methods: Clotting or chromogenic assays with specific calibrators and controls.

Point-of-Care and Novel Tests

- Urine dipstick (DOASENSE): Reliable qualitative test (<15 min turnaround), distinguishing between factor Xa inhibitors and dabigatran. High NPV for edoxaban/rivaroxaban (98-100%) and lower for apixaban (82%).
- TEG/ROTEM: Whole-blood viscoelastic tests that assess overall coagulation but have limited availability and insufficient sensitivity for trough DOAC levels.
- TGAs: Promising but with conflicting data; mainly used in research.

Emerging technologies:

- Go-DOAC (Haematex, Australia): Based on dRVVT; correlates with dabigatran/rivaroxaban but less sensitive to apixaban.
- MRX PT DOAC (Nordic Biomarker, Sweden): Uses DOAC-sensitive vs DOAC-insensitive PT ratios.
- MicroDOAC (iLine Microsystems, Spain): POC semi-quantitative analyzer; distinguishes between Xa and thrombin inhibitors.
- When Monitoring is useful
- critical clinical events: Major bleeding, acute renal failure, trauma, emergent surgery (e.g., dabigatran-treated patient requiring surgery soon after dosing).
- The features of DOAC's are shown in Table 2.

Feature	DOACs	Warfarin
Onset of Action	Rapid	Delayed (2–3 days)
Monitoring Requirement	Rarely needed	Frequent INR checks are required
Dietary Restrictions	Minimal	Extensive
Half-life	Short (5–17 hours)	Long (~36–42 hours)
Antidote Availability	Available for some agents	Vitamin K
Interpatient Variability	Low	High

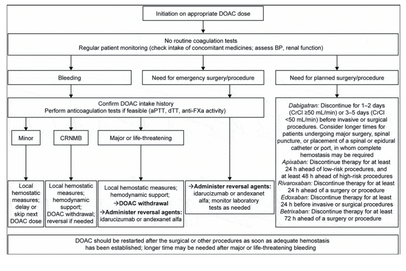

Figure 1: Initiation on appropriate DOAC dose

RESULTS

- DOACs affect screening assays (PT, APTT, TT), and results depend on reagent composition.
- These tests are inadequate for patient management.
- DOAC-specific tests exist but are limited and not licensed.
- In 2018, the ICSH issued laboratory guidance on DOAC measurement.
- A PoC coagulometer, based on reagent-free native whole blood clotting time (similar to manual WBCT), has been developed to assess DOAC-induced coagulopathy and other conditions but is not yet FDA-approved.
- Associations with DOAC Levels
- Above-peak DOAC levels: linked to older age (71 vs. 61 yrs, p 0.001), reduced renal clearance (<50 mL/min), atrial fibrillation indication, P-gp inhibitor use, and higher rates of antiplatelet co-therapy.
- Significant U.S. gaps remain in assay availability, standardization, and turnaround.

Dabigatran

Dabigatran etexilate = prodrug of dabigatran, easily absorbed.
MOA: directly, specifically, and reversibly inhibits free and clot-bound thrombin.

Rivaroxaban and apixaban: reduce thrombin-induced platelet aggregation (indirect via thrombin inhibition).
Dabigatran, rivaroxaban, and apixaban: enhance fibrinolysis (thrombomodulin-dependent).
Caution required in interpreting coagulation test results for DOAC-treated patients.

CONCLUSION

Routine DOAC monitoring is generally unnecessary for most patients, but targeted testing can enhance safety in high-risk or emergent situations. Routine PT and aPTT coagulation tests are not particularly useful in assessing the effect of DOACs because of their high variability in sensitivity. Thrombin time is susceptible to dabigatran, and when normal, it suggests a clinically insignificant amount of dabigatran in plasma. Specific DOAC-calibrated non-FDA-approved assays are available; however, few hospitals can provide a rapid turnaround time (TAT) of 30 minutes or less. Rapid point-of-care assays offer a promising solution, enabling faster and more informed clinical decisions. User-friendly rapid assays are necessary to meet the clinical needs of patients taking DOACs.