

Direct Oral Anticoagulation Monitoring

A review of supporting literature and guidance for providers

1. Background

- a. Drug manufacturers do not recommend routine coagulation monitoring for patients on direct oral anticoagulants (DOACs) other than during an acute overdose.¹⁻⁴
- b. In 2013 a publication by HT Cate suggested DOAC monitoring up to 5-10 times per year maybe be warranted in patients >75 years old, while unmonitored therapy should only be recommended for relatively young and healthy patients.⁵
- c. EHRA (European Heart Rhythm Association) guidelines recommend non-coagulation monitoring every 1-6 months for DOAC patients but do not recommend any monitoring of coagulation assays.⁶
- d. The ACCP (American College of Chest Physicians) guidelines gently recommend chromogenic anti-factor Xa assays for DOACs with appropriate calibrations, although the required test validations may not be universally available.⁷
- e. The AHA (American Heart Association) guidelines recommend a few specific indications for utilizing commercial assays to measure DOAC serum levels, but also states that reference ranges derived from literature are variable and do not correlate with safety, efficacy, and clinical outcomes.⁸
- f. Most recent ASH (American Society of Hematology) guidelines discussing anticoagulation has not made a recommendation for coagulation assay monitoring for DOACs.⁹

2. Potential Monitoring Indications:

- Acute thrombosis
- Emergency situations (i.e., trauma)
- Major bleeding
- Assessment of medication adherence
- Overdose/attempted suicide
- Potential drug-drug interactions (e.g., cytochrome P450 (CYP) and p-glycoprotein (P-gp) inducers)
- Renal/liver failure
- Urgent invasive procedures
- Urgent surgery

3. Coagulation Laboratory Monitoring

- a. Activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) are widely available, but have poor sensitivity and specificity with lack of optimal dose-response relationships for monitoring DOACs.^{10,11}
 - i. Only used as qualitative tests to confirm if there is an anticoagulant effect with DOACs

- b. Maximum effect on the coagulation test will be at the maximum drug plasma concentration
 - i. Dabigatran – 2 hours post-dose
 - ii. Rivaroxaban – 2-4 hours post-dose
 - iii. Apixaban – 1-4 hours post-dose
 - Edoxaban – 1-2 hours post-dose
- c. Due to the complexities and lack of availability involved with coagulation monitoring of DOACs, monitoring through non-coagulation lab methods may provide more practical approach to routine follow-up care of patients on DOAC therapy.¹²

4. Non-coagulation Laboratory Monitoring

- a. Supporting Literature^{7,13-17}
 - i. Multiple studies have evaluated non-coagulation monitoring ranging from every 1 – 4 months.
 - ii. EHRA recommends regular follow-up visits at every 3 months during the initiation of DOACs
 - iii. Other studies have suggested follow-up for reassessment of therapy at least every 6 months and shorter (every 3-6 months) for high-risk patients
 - iv. Appropriate monitoring frequency will depend on individual patient-related factors
- b. Routine measurement of:
 - i. Serum creatinine (SCr)
 - 1. Renal impairment is a well-established risk factor for bleeding.¹⁸
 - 2. Ischemic stroke or VTE is higher with renal dysfunction (CrCl<60mL/min).¹⁹
 - 3. Dosing of DOACs are based on CrCl or eGFR (age, body weight, gender, SCr)
 - 4. Evaluating SCr during therapy is necessary as DOACs are partially eliminated through the kidneys, but recommended frequencies differ based on available literature:
 - AHA guidelines recommend monitoring SCr at baseline and at least annually⁸
 - ASH guidelines recommendations are based on CrCl⁹
 - i. CrCl <50mL/min – monitoring SCr about every 3 months
 - ii. CrCl >50mL/min – monitoring SCr every 6-12 months
 - ii. Complete blood count (CBC)
 - 1. Assess potential risks of anemia and/or bleeding
 - 2. Evaluate at baseline and at least every 6 months thereafter
 - iii. Liver function (LFT)
 - 1. Increased drug exposure has been demonstrated in patients with hepatic impairment (except dabigatran)^{20,21}
 - 2. DOACs are contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B-C)
 - 3. Evaluate at baseline and then reassess at least annually⁸

- c. Non-laboratory monitoring:
 - i. Medication adherence
 - 1. DOACs half-lives range ~9-14 hours → missing one dose may increase risk of thromboembolic events
 - 2. Risk of bleeding lower for twice-daily regimen than once-daily regimen²²
 - ii. Adverse reactions
 - 1. Dabigatran – GI side effects (avoid patients with GERD or history of PUD)
 - 2. Bleeding (GI, extracranial, etc.)
 - Assess bleeding risks using the HAS-BLED Score
 - iii. Comorbid disease states
 - 1. Blood pressure: hypertension is a common comorbidity in nonvalvular Afib and a risk factor for intracranial hemorrhage²³
 - 2. Elderly: higher risk for renal and hepatic impairment
 - 3. Obesity: BMI >40kg/m² or >120kg
 - 4. Underweight: BMI <18.5kg/m² → increased exposure to DOACs, increasing bleeding risk²⁴
 - 5. Others: fall risk, prior stroke, diabetes, history of GI bleeds
 - iv. Drug-drug interactions
 - 1. ASA, NSAIDs – if necessary, then closer follow-up and monitoring to minimize bleeding risk
 - 2. P-gp inhibitors/inducers (ex. verapamil, quinidine, amiodarone, rifampin, carbamazepine, St. John's wort)
 - 3. CYP3A4 inhibitors/inducers (ex. dronedarone, protease inhibitors, carbamazepine, phenytoin)
 - 4. Loop diuretics, thiazides, ACEis, ARBs, IV contrast dye, NSAIDs – increase risk of renal dysfunction

DOAC Monitoring Algorithm*

Initiation	<ul style="list-style-type: none">•Drug appropriateness and dosing•Concurrent medications and comorbidities•Baseline CBC, renal/liver function (SCr and LFTs)•Evaluate insurance coverage•Education (adherence, s/sx of bleeding/clotting)
4 Weeks (Tolerability Check)	<ul style="list-style-type: none">•Medication adherence•Medication adverse reactions•Bleeding complications
3 Months	<ul style="list-style-type: none">•Medication adherence and dosing adjustments•SCr (CrCl <50mL/min)•Bleeding/thrombotic complications•Concurrent medications and comorbidities
6-12 Months	<ul style="list-style-type: none">•Medication adherence and dosing adjustments•SCr (CrCl >50mL/min), CBC, and LFTs (annually)•Bleeding/thrombotic complications•Concurrent medications and comorbidities
Ongoing	<ul style="list-style-type: none">•Medication adherence and dosing adjustments•Bleeding/thrombotic complications•Concurrent medications and comorbidities•CBC every 6-12 months•SCr at least every 6-12 months (3 months if CrCl<50mL/min)•LFTs annually

*Monitor parameters may be modified based on clinical judgment

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