Direct Oral Anticoagulant Monitoring in the ICU: Clinical Utility and Limitations of Anti-Xa Levels in Unstable Physiology

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Abstract- ***Direct oral anticoagulants work well in stable patients because they have predictable effects and usually do not need routine tests. In the ICU, the situation is very different. Critical illness changes how the body absorbs and clears medication, and treatments like vasopressors, dialysis, and ECMO can affect drug levels. This makes it hard to know how much anticoagulant effect a patient actually has. Because the usual blood tests do not reflect DOAC activity, many hospitals use anti Xa assays to check whether the drug is still active. These tests can be helpful during emergencies, such as active bleeding, urgent surgery, suspected overdose, or severe kidney failure. They give clinicians a sense of whether DOAC effects are present. However, anti Xa levels are not perfect in the ICU. Organ failure, fluid shifts, inflammation, and various supportive therapies can make the results unreliable. A level may not always match the patient's true risk of bleeding or clotting, so the test should be used only as a guide and always interpreted alongside the clinical picture. This article explains when anti Xa testing can be useful in the ICU, what its limitations are, and how it can support better decision making in critically ill patients.***

Keywords: ***DOACs, AntiXa, ICU, Criticalillness, Unstablephysiology, Renaldysfunction, Bleedingrisk, Thrombosis, Extracorporeal, Absorption, Anticoagulation***

I. INTRODUCTION

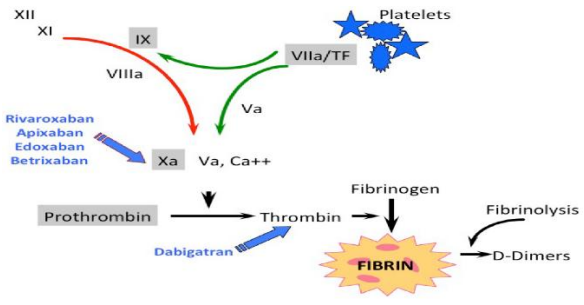

Figure 1: Mechanism of action of direct oral anticoagulants (DOACs) within the coagulation cascade.

1.1 Background on direct oral anticoagulants (DOACs)

The use of vitamin K antagonists (VKAs) for anticoagulation therapy is challenged by numerous drug and dietary interactions, narrow therapeutic ranges, and routine laboratory monitoring with frequent dose adjustments based on the international normalized ratio (INR). During the mid-2010s, direct oral anticoagulants (DOACs) became the first-line therapy for several commonly encountered thrombotic indications, including the prevention and treatment of venous thromboembolism (VTE) and stroke prevention in patients with nonvalvular atrial fibrillation (AF). To date, several DOACs have entered clinical use. Direct Factor Xa Inhibitors (DXaI) include rivaroxaban, apixaban, and edoxaban, while dabigatran is the oral direct thrombin inhibitor (DTI). Primary advantages of DOACs, compared to VKAs, include fixed dosing, rapid onsets of action, and fewer reported drug interactions when they entered into routine clinical practice.

Although DOACs are generally thought to provide at least similar efficacy and safety profiles to VKAs, there remain unaddressed concerns pertaining to pharmacokinetics and patient risk factors that lead to unprecedented or unexplained bleeding and thrombotic events. Between 2017 and 2019, anticoagulation agents, including DOACs, have surpassed antiplatelets, antibiotics, opioids, and diabetic agents as the number one medication class leading to emergency department (ED) visits for adverse drug events in the United States, accounting for over 20% of total ED visits.

In this article, we aim to review clinical scenarios that highlight potential benefit and utility of DOAC drug-level monitoring (DLM) which would support efforts to increase and improve anticoagulation stewardship

among health care systems. We also summarize the current strategies and limitations pertaining to testing, concluding with strategies to standardize.

1.2 The challenge: lack of routine monitoring and uncertainty in critically ill patients

Normally there is no indication for anticoagulation monitoring for the DOACs, and drug levels should not be followed or used for dose adjustments. However, the assessment of drug exposure and the anticoagulant effect may be needed in special clinical situations such as for patients who present with renal or hepatic insufficiency, potential drug-drug interactions, suspected overdosing, a need for urgent surgery or emergency situations, such as serious bleeding or thrombotic events. Factor Xa inhibitors can be assayed with anti-factor Xa-based chromogenic assays using specific calibrators; alternatively, a simple anti-FXa assay similar to that used for heparins can be utilized. In the latter case, observed values of therapeutic intensity differ considerably from those of the heparins, so a careful estimation and validation have to be carried out. In its investigator's brochure, each manufacturer has published observed levels of the respective drug activity for various indications.

1.3 Purpose and Scope of the Review

The purpose of this review is to give clinicians a practical understanding of how anti-Xa assays can be used when caring for critically ill patients who are taking direct oral anticoagulants. It looks at how unstable physiology in the ICU, such as sudden changes in kidney or liver function, fluid shifts, and altered metabolism, can affect DOAC activity and create uncertainty in treatment.

This review explains when anti-Xa testing may offer meaningful guidance, when it may have limited value, and how results should be interpreted within the context of critical illness. The goal is to provide a balanced, clinically useful overview that helps ICU teams make safer and more informed decisions about anticoagulation in complex situations.

1.4 Key questions to address

This review focuses on the most practical questions clinicians face when considering anti-Xa testing for patients on direct oral anticoagulants in the ICU. It explores the specific situations in which an anti-Xa level can genuinely guide care, such as suspected overdose, urgent surgical needs, unexpected bleeding, or when organ failure raises concern for drug accumulation. It also explains the major limitations of anti-Xa testing in critical illness, including the lack of standardized assays, variable correlation with true drug concentrations, and the influence of unstable physiology on test reliability. These limitations can make results difficult to interpret, especially when rapid clinical decisions are required.

Finally, the review discusses how results should be interpreted in real-world practice. Instead of relying on a single value, clinicians are encouraged to view anti-Xa levels as one piece of information that must be weighed alongside vital signs, organ function, bleeding risk, and the patient's overall trajectory. The aim is to ensure clinicians know when to trust the test, when to be cautious, and when it should not be used to guide care.

II. PHARMACOLOGY AND LABORATORY FUNDAMENTALS

2.1 Mechanism and Kinetics of DOACs

Imatinib, a targeted cancer therapy, has made significant strides toward curing chronic myeloid leukemia (CML) and other cancers caused by BCR-Abl fusion proteins. CML results from an abnormal genetic combination between BCR and Abl genes that creates a hyperactive tyrosine kinase enzyme that promotes uncontrollable cell division, leading to CML. Imatinib works by targeting an overactive BCR-Abl tyrosine kinase fusion protein. Imatinib's mechanism of action relies on its ability to compete for binding sites within BCR-Abl's active site and disrupt its activity. Tyrosine kinases (TKs) are integral in cell signalling pathways, regulating cell growth and division processes. Tyrosine kinases are critical in CML as their constant activation is linked with cancer progression. BCR-Abl fusion protein leads to continuous activation of these pathways, contributing to cancer's spread. The BCR-Abl fusion protein has a pocket-like region called the tyrosine kinase domain, which is responsible for the kinase's activity. Imatinib's structure is designed to fit precisely into this pocket, resembling the natural substrate that the kinase acts upon. This binding interaction prevents the transfer of phosphate groups from ATP (adenosine

triphosphate) to target proteins via their tyrosine residues - an essential step in signal transduction. Imatinib works by binding to the active site of BCR-Abl tyrosine kinase and inhibiting its ability to phosphorylate downstream signalling molecules, interrupting an aberrant signalling cascade that drives uncontrolled cell growth in CML and thus disabling proliferative cancer cells from spreading further and evading cell death. BCR-Abl also disrupts the Janus kinase-signal transducer and activator of the transcription (JAK-STAT) pathway that regulates cell proliferation and immune response. BCR-Abl increases JAK activity leading to constitutive STAT activation. Consistent STAT signalling boosts the transcription of genes essential to cell survival, proliferation, and avoidance of apoptosis. Furthermore, BCR-Abl oncoprotein influences the focal adhesion kinase (FAK) pathway, which controls adhesion migration invasion processes in cells. BCR-Abl activation facilitates focal adhesion formation, contributing to leukemia cells' migration and invasion abilities. Furthermore, activating BCR-Abl increases focal adhesion formation while simultaneously modulating the Wnt/β-catenin signalling pathway-an essential regulator of stem cell self-renewal and fate determination - by inhibiting its phosphorylation and degradation processes, stabilizing b-catenin by stabilizing it through inhibition of its phosphorylation and degradation processes which results in increased nuclear translocation and transcriptional activity thereby maintaining leukemic stem cell maintenance and expansion.

2.2 How Anti-Xa Assays Work

Anti-Xa assays were first developed for heparin monitoring but have since been adapted to estimate DOAC activity in the blood. The test measures the capacity of circulating anticoagulants to inhibit activated factor Xa in vitro. When calibrated with drug-specific standards, the assay can provide an approximate DOAC concentration rather than only activity. This capability is valuable for confirming recent ingestion, detecting accumulation, or guiding management in emergencies.

2.3 Variability Across Laboratories

Despite their usefulness, anti-Xa assays vary significantly. Differences in reagents, calibrators, and analytical platforms result in widely differing sensitivities across laboratories. Drug-specific calibrators provide better accuracy, while generic or non–drug-specific calibrators are prone to greater error, especially at lower concentrations where interpretation is most challenging. Assay performance may also be affected by the presence of other anticoagulants or the altered coagulation environment seen in critical illness. ICU-focused studies highlight these limitations, demonstrating inconsistent agreement between point-of-care and standard laboratory tests, and showing that anti-Xa levels often diverge from traditional markers such as the activated partial thromboplastin time. Emerging tools such as thrombin generation assays may offer more comprehensive assessment, but they remain investigational and are not routinely available. Overall, understanding the strengths and limitations of anti-Xa assays is essential before applying them in the ICU, where physiologic instability can further complicate interpretation.

III. HOW CRITICAL ILLNESS DISRUPTS DOAC PHARMACOKINETICS

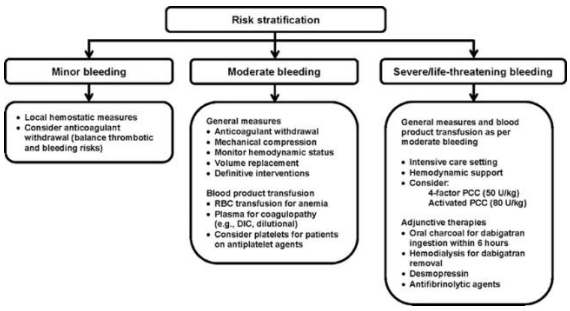

Fig: Management of DOAC-associated bleeding

3.1 Altered Pharmacokinetics in Critical Illness

Critical illness profoundly disrupts the normal pharmacokinetic profile of anticoagulants, including DOACs. Changes in kidney and liver function are common in the ICU and can either reduce clearance or accelerate elimination depending on the stage of illness. Fluid shifts, capillary leak, and aggressive resuscitation alter the drug's volume of distribution, while hypoalbuminemia can increase the free fraction of highly protein-bound agents. These fluctuations make it difficult to predict drug exposure and can lead to unexpected bleeding or thrombotic events. Studies in ICU populations consistently show that anticoagulant levels become less predictable when

organ dysfunction, metabolic instability, and acute inflammatory states coexist, highlighting the need for careful interpretation of any laboratory measurement. In the case series by Singh et al., all 5 cases of dabigatran-associated acute bleeding had an acute decline in the renal functions, and all of them were on a stable dose of DOAC before the critical events. Unfortunately, so far, there are no safety and efficacy data on DOACs in acute kidney injury patients. Switching DOACs to alternative anticoagulants is suggested for patients with acute kidney injury.

3.2 Effects of Common ICU Interventions

Several interventions used routinely in critical care further complicate anticoagulation management. Continuous renal replacement therapy may remove drugs to varying degrees depending on filter type, flow rate, and membrane characteristics. Extracorporeal membrane oxygenation introduces additional variables, including drug sequestration in the circuit and altered volume of distribution. Research involving patients receiving heparin or low molecular weight heparin underlines the degree to which extracorporeal therapies distort the relationship between administered dose, anti-Xa values, and clinical effect. Even when dosing regimens appear adequate, studies show that anti-Xa levels may be unexpectedly low or high, creating uncertainty in decision-making. Similar concerns apply to DOACs, though less thoroughly studied. Other interventions such as massive transfusion, plasma exchange, and rapid crystalloid infusion can dilute circulating anticoagulants or shift baseline coagulation parameters, complicating interpretation of anti-Xa assays.

3.3 Coagulopathy, Bleeding Risk, and Drug Interactions in Unstable Patients

Critical illness often produces a complex and dynamic coagulation environment. Sepsis, trauma, shock, and systemic inflammation can trigger both prothrombotic and bleeding tendencies, creating a physiology that behaves differently from stable outpatient settings. These conditions alter platelet function, clotting factor levels, and endogenous anticoagulant pathways. Sepsis is commonly encountered among hospitalized patients and is associated with coagulation abnormalities. Patients with sepsis are at high risk of multiorgan dysfunction and poor outcomes as sepsis is associated with microvascular thrombosis or bleeding due to depletion of coagulation factors and platelets. Sepsis increases the risk of AF and VTE. Observational data have shown that the use of warfarin in patients with AF during critical illness is associated with an increased risk of bleeding. Drug interactions are also more frequent in the ICU, where patients commonly receive antibiotics, antifungals, vasopressors, analgesics, sedatives, and parenteral nutrition. These therapies may affect absorption, metabolism, or clearance of anticoagulants in ways that standard laboratory values cannot fully capture. Evidence from ICU studies involving heparin and LMWH shows a frequent disconnect between measured anti-Xa levels, clinical bleeding, and thrombotic outcomes. Some patients experience bleeding despite anti-Xa levels within expected ranges, while others show low levels without thrombotic events. These findings emphasize that anti-Xa activity reflects only one component of a broader and highly variable coagulation picture.

3.4 Unpredictability of DOAC Concentrations in Unstable Physiology

Because DOACs were designed for predictable pharmacokinetics in stable patients, the unstable physiology of the ICU introduces a level of variability that challenges their safe use. Reduced gut perfusion may impair absorption. Fever, shock, and acute phase reactions affect drug distribution and metabolism. Organ dysfunction alters clearance, and extracorporeal therapies may remove or sequester circulating drug. Studies involving anticoagulation monitoring in ICU settings consistently demonstrate that fixed dosing rarely aligns with measured activity, regardless of the anticoagulant used. In some cohorts, patients achieved adequate clinical prophylaxis even when anti-Xa levels were low, whereas in others, conventional dosing resulted in unexpectedly high drug activity. This disconnect underscores the need to interpret DOAC measurements cautiously and in context, rather than relying on anti-Xa values alone to guide care. There is a lack of data to guide clinicians whether to use thrombolysis in patients who develop pulmonary embolism (PE) while taking a DOAC and require thrombolysis due to haemodynamic compromise. It may be reasonable to consider thrombolysis in cases of arrest or peri-arrest due to PE in the setting of concomitant DOAC use. Endovascular intervention

could be an option in patients with intermediate to high risk.

IV. CLINICAL UTILITY OF ANTI-XA MONITORING IN THE ICU

Although far from perfect, anti-Xa measurement can provide helpful information in several scenarios.

4.1 Active or Life-Threatening Bleeding

Anti-Xa measurement can help clarify whether residual anticoagulant activity is contributing to severe bleeding episodes. In critically ill patients receiving DOACs or LMWH, determining whether the drug remains pharmacologically active is essential when considering reversal agents or blood product administration. Direct antidotes for all DOACs have been recently produced and successfully tested for efficacy and safety in phase I/II trials, and phase III trials are ongoing. Idarucizumab is a humanized monoclonal antibody Fab-fragment, which binds specifically to dabigatran and reverses the anticoagulant effect immediately. Andexanet alfa is a recombinant FXa decoy, binds directly FXa inhibitors and immediately reverses the anticoagulant effect. Arapazine (PER977) is a third small synthetic molecule, which binds both FXa- and FIIa-inhibitors, thus acting as a “universal” antidote. Currently only the preparation against dabigatran is available for clinical use on a named patient use program (idarucizumab, PraxBind®). Both andexanet alfa and arapazine are not yet registered for clinical use. Findings from ECMO cohorts demonstrate that coagulation markers, including anti-Xa values, correlate with bleeding complications and can therefore support decisions on whether aggressive reversal is warranted (Moussa et al., 2021). Although anti-Xa interpretation must consider overall coagulation disturbances, its ability to quantify remaining activity provides meaningful guidance during life-threatening hemorrhage.

4.2 Preparation for Urgent or Emergency Procedures

ICU procedures often require immediate intervention, and waiting for complete anticoagulant clearance may be unsafe. Anti-Xa levels offer a rapid means of estimating whether significant anticoagulant effect persists before high-risk interventions such as central line placement, thoracostomy, or emergent laparotomy. Earlier work on viscoelastic testing in unstable populations shows that laboratory-based and point-of-care coagulation markers can influence procedural timing and bleeding risk assessment (Mallett et al., 2013; Rajsic et al., 2021). Anti-Xa data contribute to this decision-making process by identifying patients who may require delay, reversal, or additional optimization.

4.3 Suspected Drug Accumulation or Overdose

The fact that most of the DOACs are substrates of P-glycoprotein induces a potential risk of drug-drug interactions. Relevant interactions are known for antiarrhythmics (Dronedarone, Amiodarone, Digoxin, Chinidin, Propafenon, Verapamil), antihypertensives (Carvedilol, Felodipin, Nifedipin, Timolol, Propranolol, Labetalol, Diltiazem, Aliskiren), antiplatelet drugs (Clopidogrel, Ticagrelor, Dipyridamol), statins (Atorvastatin, Lovastatin), oncologics, antibiotics (Erythromycin, Clarithromycin, Rifampicin, Fluconazol, Ketoconazol), and HIV protease inhibitors (Ritonavir). Because critically ill patients often experience acute changes in renal or hepatic function, drug accumulation remains a major concern. Anti-Xa monitoring helps detect unexpectedly elevated drug activity in patients with new-onset renal failure, hepatic derangements, or inadvertent double dosing. Several investigations highlight that anticoagulant activity does not always correspond with standard dosing strategies in the ICU, particularly when low anti-Xa levels coexist with adequate thromboprophylaxis or when levels rise unpredictably in multiorgan failure (Benes et al., 2022). Monitoring can therefore guide whether therapy should be held, reduced, or reversed.

4.4 Suspected Sub-Therapeutic Absorption

Gastrointestinal dysfunction is common in the ICU, and many DOACs depend on stable absorption for predictable effects. Patients receiving drugs through nasogastric tubes, or those experiencing vomiting or impaired gut perfusion, may not achieve therapeutic levels. In such cases, an undetectable or unexpectedly low anti-Xa result may indicate inadequate anticoagulation. Observations in pediatric and neonatal anticoagulation emphasize that drug effect cannot always be assumed in populations with variable absorption or altered physiology, reinforcing the value

of laboratory confirmation when treatment reliability is uncertain (Monagle & Newall, 2018).

4.5 Decision-Making After Bleeding Events

Anti-Xa measurement can inform when anticoagulation may be safely restarted after major bleeding or surgery. By identifying whether drug activity has resolved, clinicians can better balance the competing risks of recurrent bleeding and thrombosis. In the individual DOAC VTE treatment trials [3–10], GI bleeding event rates were too low to draw definite conclusions (dabigatran and rivaroxaban numerically higher rates of GI bleeding, apixaban and edoxaban numerically lower rate of GI bleeding) compared to conventional anticoagulation therapy. A meta-analysis of data from 11 phase-3 DOAC NVAF or VTE treatment trials found no significant difference in major gastrointestinal bleeding between DOACs and warfarin (2.09 vs. 1.7 %; RR 0.94; 95 % CI 0.75–1.99; $p = 0.62$, I^2 71 %) [35]. Even so, careful consideration should be exercised in regards to DOAC use in patients with a history of gastrointestinal bleeding. Guidance documents on DOAC pharmacology explain that residual activity may persist longer than expected in organ dysfunction, aging, or drug–drug interactions (Levy et al., 2014; De Caterina et al., 2012). Objective measurement through anti-Xa testing therefore supports individualized timing of therapy resumption, especially in patients with ongoing hemodynamic instability or multi-system failure.

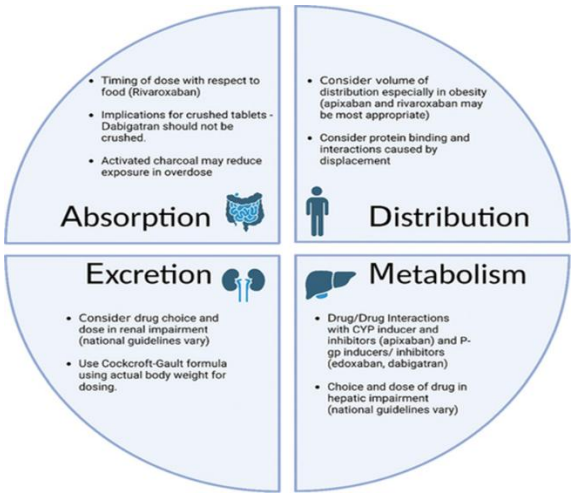

Figure: Pharmacokinetic considerations in DOAC prescribing (Figure created with biorender.com).

V. LIMITATIONS AND PITFALLS OF ANTI-XA MONITORING IN UNSTABLE PHYSIOLOGY

5.1 Variability Related to Drug Class and Pharmacologic Profile

Anti-Xa assays were initially designed for heparin monitoring, but their performance becomes more complex when applied to direct oral anticoagulants (DOACs). Unfractionated heparin remains the most widely used agent in the prevention and acute treatment of thrombosis. Pharmacological complexities of this intriguing agent mandate frequent monitoring of its anticoagulant properties to maintain safe and effective hematological outcomes. Although activated partial thromboplastin time has been the standard test to monitor unfractionated heparin therapy for many decades, the anti-Xa assay has emerged as a substitute or adjunct in many institutions. Although DOACs such as apixaban, rivaroxaban, and edoxaban exert their effects primarily through Factor Xa inhibition, assay responsiveness varies substantially across drugs. Some assays are not calibrated for specific DOACs, leading to underestimation or overestimation of true anticoagulant effect (Levy et al., 2014). Furthermore, differences in bioavailability, half-life, and protein binding influence the measured activity, making it difficult to interpret results in isolation. Position statements from major cardiovascular societies emphasize that anti-Xa assays should not be viewed as a universal surrogate for DOAC pharmacodynamics because the degree of inhibition observed does not always correspond with clinical anticoagulation intensity (De Caterina et al., 2012). This creates inherent diagnostic uncertainty in critically ill individuals receiving modern anticoagulant therapies.

5.2 Influence of Multisystem Organ Dysfunction

In the ICU, hepatic impairment, acute kidney injury, and circulatory shock affect the accuracy and reliability of anti-Xa values. Liver disease, in particular, presents a unique challenge because patients may exhibit a “rebalanced hemostatic state” in which both pro- and anticoagulant pathways are altered simultaneously (O’Leary et al., 2019). As a result, an elevated or reduced anti-Xa level may not reflect the true bleeding or thrombotic risk. Patients with cirrhosis may show unexpectedly low anti-Xa

activity despite significant anticoagulant exposure due to reduced antithrombin levels, a necessary cofactor for heparin responsiveness. Conversely, decreased clearance of DOACs in hepatic dysfunction may prolong activity even when anti-Xa values fall in the lower therapeutic range. These physiologic disturbances complicate interpretation and underscore the need to integrate anti-Xa results with broader clinical and laboratory assessment.

5.3 Challenges in Neonates, Children, and Adolescents

Pediatric populations demonstrate uniquely variable pharmacokinetics that significantly limit the interpretability of anti-Xa monitoring. Neonates and infants have lower antithrombin concentrations, immature hepatic metabolism, and altered protein binding, all of which modify how anticoagulants exert their effects (Hepponstall et al., 2017). Studies note that therapeutic ranges derived from adults often do not apply to younger patients, resulting in wide variability in measured levels and inconsistent correlation with clinical outcomes (Goldenberg et al., 2015). In critically ill children—particularly those receiving parenteral nutrition, vasoactive therapy, or undergoing ECMO support—the discrepancy between laboratory anti-Xa results and true anticoagulant effect becomes even more pronounced. These limitations make anti-Xa only one part of a larger decision-making framework rather than a definitive guide.

5.4 Limited Predictive Value in Acute Thrombotic or Embolic Conditions

In acute pulmonary embolism and other high-risk thrombotic conditions, anti-Xa levels may not reliably indicate whether anticoagulant therapy is effective. The pathophysiology of pulmonary embolism is dynamic, influenced by clot burden, right-ventricular strain, shock physiology, and patient-specific inflammatory responses. Clinical management guidelines highlight that therapeutic outcomes in pulmonary embolism are shaped more by hemodynamic stability, clot progression, and systemic factors rather than small variations in anti-Xa activity (Panahi et al., 2021). As such, relying solely on anti-Xa values to adjust therapy may misrepresent the true therapeutic needs of unstable patients.

5.5 Difficulty Distinguishing Therapeutic Failure from Laboratory Artifact

In unstable physiology, laboratory anomalies, hemodilution, high fibrinogen states, and factor deficiencies can distort anti-Xa values. Critically ill patients often receive large volumes of fluids, blood products, or extracorporeal support, all of which may cause spurious readings. This challenge is especially evident during rapid anticoagulant reversal or resuscitation, where anti-Xa changes lag behind clinical changes. Advanced viscoelastic tools such as rotational thromboelastometry (ROTEM) can detect the presence of anticoagulant effect much faster than standard laboratory assays and may be more useful in emergency reversal settings (Pavoni et al., 2022). These technologies reveal that anti-Xa results can be misleading when clotting dynamics shift rapidly, emphasizing the importance of complementary testing.

VI. ALTERNATIVE AND COMPLEMENTARY MONITORING STRATEGIES

6.1 Clinical Assessment and Patient-Specific Monitoring

While anti-Xa levels provide helpful information, clinicians in the ICU often rely on a broader set of observations to guide anticoagulation management. Changes in neurological function, hemodynamic stability, catheter patency, and signs of microvascular bleeding can provide early clues that laboratory values alone may miss. Jayaram (2022) emphasizes that effective monitoring requires pairing laboratory data with bedside findings, particularly in patients with neurologic injuries or those receiving multiple interacting therapies. This integrated approach ensures that shifts in clinical status are recognized quickly, even when laboratory markers appear stable. With the now existing wider range of opportunities in anticoagulation, choosing the best-tailored drug is important. In particular, secondary diagnoses and co-medication are especially to be considered. In the GARFIELD-AF Registry, the largest and longest-running registry of patients with newly diagnosed AF and at least one additional stroke risk factor, the use of anticoagulants was more frequent in patients with moderate to severe chronic kidney disease. Furthermore, one-year outcomes in 17,159 patients with AF reveal differences between patients with

moderate to severe chronic kidney disease (n = 1760) and those with no or mild chronic kidney disease (CKD)

6.2 Point-of-Care Coagulation Technologies

Point-of-care testing has become increasingly valuable in critical settings because it provides rapid insights into dynamic coagulation changes. Rajsic et al. (2021) describe how bedside tests help clinicians make faster decisions during acute instability by offering immediate visibility into clot formation, clot strength, and fibrinolytic activity. These tools often outperform standard laboratory assays in situations where delays in sample processing or transport could lead to misinterpretation. In high-acuity environments, the ability to obtain results within minutes supports more responsive and individualized anticoagulation adjustments.

6.3 Viscoelastic Testing

Viscoelastic methods such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) offer a real-time picture of how a patient's clotting system behaves as a whole. In conditions like liver failure, where standard tests may not reflect true bleeding risk, these tools provide a clearer understanding of the balance between clotting and anticoagulation (Mallett et al., 2013). Their ability to identify drug effects, hyperfibrinolysis, or coagulation factor disturbances makes them particularly useful when anti-Xa results seem inconsistent with clinical presentation. As anticoagulation therapy becomes more complex in the ICU, viscoelastic testing serves as an important complement to conventional assays.

6.4 Use of Clinical Pharmacokinetics Across Special Populations

Some patient groups, including children, neonates, and individuals with significant organ dysfunction, require a different approach to monitoring. In pediatric patients, developmental differences in liver metabolism, renal clearance, and antithrombin concentration can significantly alter anticoagulant response (Monagle & Newall, 2018). Heparin and low-molecular-weight heparin often behave unpredictably in these populations, making clinical observation and individualized dosing strategies essential. When anti-Xa levels fail to reflect true drug exposure, understanding expected pharmacokinetic patterns can help guide safer therapy adjustments.

6.5 Monitoring During ECMO Support

Extracorporeal membrane oxygenation introduces unique anticoagulation challenges because the circuit itself activates coagulation pathways. Moussa et al. (2021) showed that anti-Xa levels and aPTT do not always correlate well in patients undergoing ECMO, and neither reliably predicts thrombotic or bleeding events on their own. This discrepancy highlights why ECMO programs often use a combination of laboratory tests, clinical indicators, and sometimes viscoelastic tools to maintain safe levels of anticoagulation. A multimodal monitoring strategy is especially important when rapid physiological shifts occur.

6.6 Stability of Fixed-Dose LMWH Strategies

An alternative to intensive laboratory monitoring is the use of fixed-dose low-molecular-weight heparin. Benes et al. (2022) demonstrated that standard prophylactic doses of enoxaparin remained effective in mixed ICU populations even when measured anti-Xa levels were low. Their findings suggest that some patients may not require frequent monitoring if they fall within typical physiologic ranges and have no major risk factors for instability. This approach reduces the burden of repeated blood sampling and may help limit unnecessary dose adjustments in otherwise stable patients.

6.7 Integrating DOAC-Specific Considerations

Direct oral anticoagulants introduce additional complexity because standard laboratory tests often fail to reflect their true activity. Levy et al. (2014) and De Caterina et al. (2012) both highlight that DOAC levels vary significantly depending on renal function, absorption, drug interactions, and timing of the last dose. Because anti-Xa assays may not be calibrated for each drug, clinicians must rely on a combination of clinical evaluation, drug history, and—when available—specialized DOAC-specific assays. This integrated approach is especially helpful in critically ill patients where clearance is highly variable and physiologic instability can alter drug behavior within hours.

VII. RESEARCH GAPS AND FUTURE DIRECTIONS

7.1 Limited Evidence in Critically Ill Populations

Despite increasing ICU use of direct oral anticoagulants (DOACs) and low-molecular-weight heparins, high-quality prospective studies on anti-Xa–guided therapy in critically ill patients remain scarce. Most data are derived from observational studies, case series, or extrapolated from stable outpatient populations. This leaves substantial uncertainty about optimal therapeutic targets, timing of monitoring, and the clinical significance of measured anti-Xa levels in unstable physiology (Gilbert et al., 2022; Kumano et al., 2021).

7.2 Need for Standardized Assays

A major barrier to wider adoption of anti-Xa monitoring is the lack of universally standardized assays. Variability in calibration, sensitivity, and drug-specific adjustments makes inter-laboratory comparisons challenging. Standardization is especially critical in ICU populations, where rapid physiologic shifts, organ dysfunction, and drug interactions can dramatically alter anticoagulant activity (Billoir et al., 2022; Moussa et al., 2021).

7.3 Point-of-Care and Rapid Turnaround Technologies

Current laboratory-based anti-Xa assays often suffer from delayed turnaround times, which limit their usefulness in urgent or emergent ICU scenarios. Point-of-care platforms and viscoelastic methods, such as rotational thromboelastometry (ROTEM) and thrombin generation assays, offer promising alternatives by providing immediate feedback on anticoagulant effect (Pavoni et al., 2022; Jayaram, 2022). Future research should focus on validating these rapid testing modalities in critically ill populations and correlating results with clinical outcomes.

7.4 Pharmacokinetic and Pharmacodynamic Modeling

ICU patients experience profound variability in drug absorption, distribution, metabolism, and clearance. Current dosing and monitoring guidelines often fail to account for this variability. Advanced pharmacokinetic and pharmacodynamic modeling, incorporating patient-specific factors such as renal function, albumin levels, and extracorporeal therapies, could improve prediction of anticoagulant effect and bleeding or thrombosis risk (Levy et al., 2014; De Caterina et al., 2012). Prospective studies are needed to validate these models and translate them into bedside decision support tools.

7.5 Pediatric and Special Population Considerations

Data remain particularly limited for neonates, children, and patients with hepatic dysfunction. These populations demonstrate unique pharmacologic profiles that may not align with adult-derived anti-Xa targets, increasing the risk of over- or under-anticoagulation (Monagle & Newall, 2018; O'Leary et al., 2019). Focused research is required to define safe and effective monitoring strategies in these high-risk groups, including development of age- and organ function-specific thresholds.

7.6 Integration of Multimodal Monitoring Approaches

Future directions should also explore the integration of multiple monitoring strategies, combining anti-Xa measurements, viscoelastic testing, point-of-care coagulation assays, and clinical assessment. This multimodal approach may provide a more accurate representation of coagulation status and allow individualized therapy adjustments in real-time (Rajsic et al., 2021; Mallett et al., 2013).

VIII. CONCLUSION

Direct oral anticoagulants have transformed anticoagulation management, offering predictable pharmacokinetics and ease of use compared to traditional therapies. However, in the intensive care setting, unstable physiology including organ dysfunction, altered protein binding, fluid shifts, and extracorporeal therapies can significantly affect drug levels and anticoagulant effect. Anti-Xa monitoring provides valuable information in select scenarios, such as emergency bleeding, urgent procedures, or suspected subtherapeutic exposure, but it is not a standalone solution.

Clinicians must interpret anti-Xa results within the broader clinical context, integrating patient assessment, pharmacologic knowledge, and, where available, complementary assays such as viscoelastic testing or point-of-care coagulation platforms.

Standardized, rapid, and drug-specific monitoring methods remain limited, highlighting the urgent need for prospective studies and the development of ICU-adapted protocols.

Ultimately, anti-Xa monitoring represents a potentially useful tool for enhancing safety and guiding therapy in critically ill patients, but its value depends on judicious application, clinical expertise, and an understanding of its limitations. A multimodal and individualized approach remains the cornerstone of anticoagulation management in the ICU, with future research poised to refine and optimize its use across diverse patient populations.

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