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The Utility of Chromogenic Factor X Assay in Monitoring Warfarin Therapy in a Patient with Triple-Positive Antiphospholipid Syndrome on Dialysis: A Case Report

Keith T. Veltri[1,2*] and David Braverman[1]

[1]Touro College of Pharmacy, New York, NY

[2]Montefiore Medical Center, Bronx, NY

***Corresponding Author:** Keith T. Veltri and David Braverman, Touro College of Pharmacy, New York, NY.

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Abstract:

Antiphospholipid syndrome (APLS) is an autoimmune prothrombotic disorder characterized by recurrent venous or arterial thromboses in the presence of persistent antiphospholipid antibodies. In a subset of APLS patients, standard anticoagulation monitoring using the International Normalized Ratio (INR) is unreliable due to antibody-mediated interference with prothrombin time (PT) assays. This interference can complicate warfarin management and increase the risk of both thrombotic and hemorrhagic complications. We present the case of a 54-year-old female with triple-positive APLS and end-stage renal disease on maintenance warfarin therapy (8mg daily) titrated to a therapeutic INR. Despite adherence and clinical stability, she experienced persistently fluctuating INR values, both subtherapeutic and supratherapeutic, due to prolonged baseline prothrombin time caused by antiphospholipid antibody interference, which rendered INR measurements inaccurate and unreliable. Following hematology consultation, a chromogenic factor X (CFX) assay was adopted as an alternative method for monitoring anticoagulation. CFX results consistently reflected appropriate anticoagulation levels and correlated with the patient's stable clinical course, despite wide variability in INR values throughout a prolonged hospitalization. Serial CFX assays demonstrated factor X activity within the therapeutic range (20–40%) when periodically measured, while INR values fluctuated between subtherapeutic and supratherapeutic levels. Warfarin dosing adjustments guided by CFX assay results enabled safe and effective anticoagulation, with no thrombotic events or major bleeding episodes during the hospitalization. This case highlights the limitations of INR-based monitoring in patients with triple-positive APLS and supports the use of CFX assays as a reliable surrogate marker for warfarin anticoagulation. Chromogenic factor X activity assays offer a valuable adjunct or alternative to traditional INR monitoring in patients with unreliable PT results. Despite challenges such as increased cost, longer turnaround times, and lack of widespread standardization, incorporation of CFX testing into clinical practice may improve therapeutic precision and reduce adverse outcomes. Integration of CFX assays into anticoagulation protocols could help optimize warfarin management and minimize the risk of thrombosis and bleeding in this high-risk population.

Keywords: Antiphospholipid syndrome; autoimmune prothrombotic disorder; antiphospholipid antibodies

Introduction:

Antiphospholipid syndrome (APLS) is a systemic autoimmune thrombophilia defined by the presence of one or more clinical events (most commonly vascular thrombosis or pregnancy morbidity) in conjunction with persistently elevated antiphospholipid antibodies (aPLs), which include lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2 glycoprotein I (aβ2GPI) antibodies. A diagnosis is made based on the revised Sapporo criteria (also known as the Sydney criteria), requiring one clinical and one laboratory criterion confirmed at least 12 weeks apart [1,2].

The underlying pathophysiology of APLS is multifactorial, involving aPL-mediated endothelial dysfunction, platelet activation, inhibition of natural anticoagulants, and complement activation. These prothrombotic processes are mediated primarily by the β2GPI-dependent pathway, which leads to activation of tissue factor on monocytes and endothelial cells, promoting thrombin generation and fibrin formation [1,3]. Triple-positive APLS—referring to simultaneous positivity for LA, aCL, and aβ2GPI—is associated with a significantly higher thrombotic burden, recurrence risk, and resistance to conventional anticoagulation [4,5].

Oral anticoagulation with vitamin K antagonists (VKAs), most commonly warfarin, remains the cornerstone of long-term management for thrombotic APLS, with a recommended INR target of 2.0–3.0 for venous events, and in some cases up to 3.0–4.0 for arterial events or recurrent thromboses [6]. However, a critical limitation in this paradigm arises from the reliance on the prothrombin time (PT) and INR to monitor warfarin activity. In approximately 5–10% of APLS patients, the presence of LA interferes with the PT assay by binding phospholipids required for coagulation cascade activation in vitro, leading to an artifactual prolongation of PT and falsely elevated INR values [7,8]. This phenomenon creates substantial challenges in clinical management, increasing the risk of inappropriate warfarin dose reductions and subsequent thromboembolic complications.

Chromogenic factor X (CFX) assay offers an alternative for monitoring anticoagulation intensity in such settings. Unlike PT/INR-based measurements, the CFX assay is a two-stage chromogenic method that directly quantifies functional activity of factor X via a colorimetric reaction, independent of phospholipid content and thus unaffected by LA or other aPLs [9,10]. Since warfarin decreases hepatic production of factor X, the CFX assay provides a more reliable surrogate for anticoagulant intensity, with target therapeutic warfarin levels corresponding to a CFX activity of 20–40% [11].

Despite promising validation studies, CFX assays remain underutilized in routine practice due to logistical and economic constraints, including test availability, lack of standardization across laboratories, longer turnaround times, and absence of consensus guidelines regarding their integration into anticoagulation protocols [12]. Nevertheless, in patients with known or suspected INR unreliability, particularly those with triple-positive APLS or persistently prolonged baseline PT—the benefits of incorporating CFX monitoring may outweigh the limitations.

This report presents a case of a triple-positive APLS patient with erratic INR readings and prolonged PT, in whom serial CFX assays were critical to maintaining therapeutic anticoagulation throughout a prolonged hospitalization. We discuss the clinical rationale, interpretative framework,

and broader implications of using CFX testing in complex APLS cases.

Case Presentation:

A 54-year-old African American female with a complex medical history—including end-stage renal disease (ESRD) on intermittent hemodialysis, seizure disorder, prior ischemic stroke secondary to septic emboli, and triple-positive antiphospholipid syndrome (APLS) on long-term warfarin therapy—was admitted to the hospital in May 2023. The patient was transferred from her nursing home facility after missing a scheduled dialysis session and was noted to be acutely agitated on presentation, prompting further evaluation and inpatient management.

Past Medical History

The patient had been diagnosed with APLS in early 2023 following a cerebrovascular accident (CVA) attributed to septic emboli from infective endocarditis, complicated by right internal jugular vein thrombosis. Subsequent laboratory workup confirmed triple positivity for lupus anticoagulant, IgG anticardiolipin antibodies, and IgG anti-β2 glycoprotein I antibodies, fulfilling the Sydney criteria for APLS. Her warfarin dose had been adjusted multiple times since diagnosis due to erratic INR values. Other comorbidities included depression with psychotic features, aphasia post stroke, and ESRD managed via tunneled dialysis catheter, with dialysis sessions scheduled on Tuesdays, Thursdays, and Saturdays.

Home Medications

Upon admission, her medication regimen included:

- warfarin 8mg PO daily; dose titrated based on INR trends
- atorvastatin 80mg PO QHS
- furosemide 80mg PO BID
- metoprolol tartrate 100mg PO BID
- gabapentin 300mg PO nightly
- sevelamer carbonate 1600mg PO TID with meals
- docusate, senna, polyethylene glycol, and famotidine for bowel and gastric support
- Nephro-Vite for renal supplementation
- cefazolin 2g IV daily, completed a 6-week course ending in May 2023, for treatment of endocarditis

Admission Findings

On initial physical examination:

- Vital signs were stable with no signs of acute infection
- Neurological exam was notable for decreased sensation over the mid and lower face bilaterally and aphasia, consistent with previous stroke sequelae
- Skin was dry and flaky
- ENT exam revealed edentulism (no teeth)

Baseline laboratory studies revealed:

- INR 2.3
- Prolonged PT of 21.6 seconds

Throughout hospitalization:

INR fluctuated erratically, accompanied by a persistently prolonged baseline PT, raising concerns about the reliability of INR as a surrogate marker for warfarin effect. As a result, frequent adjustments to her anticoagulant dosing were required. Given her history of triple-positive antiphospholipid syndrome (APLS) and consistently abnormal baseline coagulation parameters, the hematology team was consulted for further guidance.

Diagnostic Reevaluation and CFX Monitoring

Hematology recommended the use of a Chromogenic Factor X (CFX) assay to determine the true anticoagulation status. This assay, being independent of phospholipid-based interactions, is not affected by lupus anticoagulant and is considered a more accurate measure of warfarin anticoagulation in patients with unreliable INR.

- The initial CFX activity was 36% (reference range: 20–40%), indicating therapeutic anticoagulation despite the supratherapeutic INR.

Ongoing Monitoring and Clinical Course

Throughout the patient's prolonged hospitalization, warfarin dosing required meticulous and frequent adjustments. These modifications were guided by an integrated approach that combined clinical evaluation, trending of International Normalized Ratio (INR) values, and, critically, serial measurements of chromogenic Factor X (CFX) activity. Despite intermittent fluctuations in INR—both subtherapeutic and supratherapeutic—the CFX assay consistently demonstrated activity levels within the therapeutic range of 20–40%, which correlates with an effective anticoagulant state (Table 1). This consistent CFX activity provided reassurance of adequate anticoagulation even when the INR appeared unreliable.

The use of CFX assays was pivotal in safely maintaining anticoagulation without precipitating thrombotic or hemorrhagic events during the patient's hospital course. This was particularly significant given the patient's complex clinical context, which included end-stage renal disease (ESRD) requiring hemodialysis three times a week, fluctuating serum albumin levels, and polypharmacy—all of which are known to complicate warfarin metabolism and pharmacodynamics. Variable nutritional and inflammatory states further contributed to unpredictable anticoagulant responses, undermining reliance on INR alone for monitoring. Additionally, heparin administered during dialysis to prevent circuit clotting can increase bleeding risk when combined with warfarin, and although warfarin is not dialyzable, dialysis-induced fluid shifts and changes in plasma protein levels can indirectly affect its pharmacodynamics and contribute to INR variability.

Overall, the integration of CFX testing into routine management allowed for more precise warfarin dosing, reducing the risk of both under- and over-anticoagulation in this high-risk population. This case underscores the importance of alternative monitoring strategies in patients with antiphospholipid syndrome (APLS) and unreliable INR readings, especially in the setting of comorbidities that affect coagulation and warfarin metabolism.

Discussion:

The management of thrombotic APLS is fraught with complexity, particularly in patients with triple-positive serologies, which confer a significantly elevated risk of recurrent thrombotic events, even with standard anticoagulation [4,6]. The case presented illustrates one of the fundamental clinical challenges in this population: INR instability due to lupus anticoagulant interference, leading to unreliable assessment of warfarin effect.

The lupus anticoagulant exerts its effect by targeting phospholipid-dependent coagulation reactions, particularly the initiation of thrombin generation via the extrinsic and intrinsic pathways. In vitro, this leads to prolongation of PT and activated partial thromboplastin time (aPTT), despite the patient being hypercoagulable in vivo [13,14]. This paradox not only confounds diagnosis but also compromises warfarin monitoring, particularly in patients with high-intensity or long-term anticoagulation requirements.

Several studies have highlighted the dangers of misinterpreting INR values in this context. Cohen et al. (2021) found that patients with LA-associated PT prolongation frequently exhibited discordant INR and anticoagulant levels, with a risk of subtherapeutic warfarin dosing in over 40% of cases [5]. Crowl et al. (2014) and Baumann Kreuziger et al. (2014) further demonstrated that warfarin dose reductions based on falsely elevated INR values may predispose patients to preventable thrombotic complications [7,8].

Chromogenic Factor X assay has emerged as a viable alternative for measuring anticoagulation intensity in such patients. The assay bypasses the phospholipid dependency of PT by directly quantifying factor X enzymatic activity using a synthetic chromogenic substrate, yielding reproducible results unaffected by aPLs [9]. The therapeutic range for warfarin corresponds to a CFX activity of 20–40%, which aligns well with an INR of 2.0–3.0 in patients without interfering antibodies [11]. Multiple clinical studies, including those by Sanfelippo et al. (2009) and McGlasson et al. (2008), support the use of CFX assays as both a confirmatory and primary monitoring modality in selected high-risk patients [10,11].

Importantly, CFX assays consistently demonstrated therapeutic anticoagulation (25–36%) throughout the measured period of hospital stay, allowing clinicians to maintain appropriate warfarin dosing without risking under- or over-anticoagulation. These findings affirm the hypothesis that CFX monitoring can circumvent misleading INR values and provide a more accurate reflection of coagulation status in complex APLS cases.

From a broader clinical perspective, the use of CFX assays has several potential implications:

1. Improved patient safety: By reducing reliance on flawed INR values, clinicians can prevent inappropriate warfarin dose adjustments that may lead to bleeding or thrombotic complications.
2. Precision medicine in autoimmune thrombophilia: CFX allows individualized anticoagulation management, particularly in patients with known assay interferences, comorbidities (e.g., ESRD), or those with indwelling catheters and infection risk.
3. Support for future guidelines: Despite current guideline ambiguity regarding CFX use, this and other emerging case reports and cohort studies could provide the evidence base for formal recommendations on integrating CFX assays into standard care for high-risk APLS patients [6,12].

Nonetheless, the implementation of CFX testing is not without limitations. As a send-out test in many institutions, it is associated with longer turnaround times and higher costs compared to point-of-care INR testing. Furthermore, there is currently no universal reference standard for correlating CFX activity with precise INR values across different reagents and populations, which may affect interpretation. These barriers emphasize the need for broader standardization, laboratory access, and education among clinicians regarding CFX testing [13].

Conclusion:

Antiphospholipid syndrome (APLS) presents significant challenges in anticoagulation management, particularly due to the presence of lupus anticoagulant and other antiphospholipid antibodies that interfere with standard coagulation assays such as the International Normalized Ratio (INR). This case highlights the clinical complexities of warfarin monitoring in a patient with triple-positive APLS and prolonged baseline prothrombin time, where conventional INR values proved unreliable and inconsistent throughout the hospital course.

The incorporation of the chromogenic factor X (CFX) assay proved invaluable in accurately assessing anticoagulation status. Unlike the INR, which depends on thromboplastin reagents that can interact with antiphospholipid antibodies leading to falsely elevated or unpredictable results, the CFX assay directly measures factor X activity independently of phospholipid interference. This assay provided a reliable and objective biomarker to guide warfarin dose adjustments, ensuring therapeutic anticoagulation while minimizing the risk of both thrombotic and hemorrhagic complications in a patient with high thrombotic risk.

Despite certain limitations, including increased cost, longer turnaround times, and the lack of widespread standardization, the use of CFX assays in APLS patients on warfarin represents a critical advancement in individualized patient care. By enabling clinicians to more precisely tailor anticoagulation therapy, the assay offers a practical solution to overcome the pitfalls of traditional coagulation monitoring in this complex patient population.

This case underscores the need for heightened clinical awareness of the limitations of INR in APLS and supports broader adoption of alternative monitoring strategies like CFX assays in similar clinical scenarios. Future research should focus on establishing standardized protocols for CFX assay use, evaluating its cost-effectiveness, and further defining its role in optimizing anticoagulation management across diverse patient populations affected by APLS and other coagulopathies.

In conclusion, the successful management of this patient illustrates the clinical utility of the chromogenic factor X assay as a tool for monitoring warfarin therapy in APLS patients with unreliable INR measurements. Adoption of this approach can enhance therapeutic precision, reduce adverse events, and ultimately improve patient outcomes in this high-risk group.

Table 1: Interpretation: Selected Anticoagulation Monitoring Over Time

Date	INR	Warfarin Dose (mg)	Chromogenic Factor X (CFX) Activity (%)
3-Aug-23	2.3	8	
4-Aug-23	2.4	8	
5-Aug-23	1.6	8.5	
6-Aug-23	1.8	8.5	
7 Aug 2023[a]	1.7	8.5	—
8-Aug-23	3	8	
9-Aug-23	3.2	8	
10-Aug-23	2	8	
11-Aug-23	2.2	8	
12 Aug 2023[b]	2.3	8	36%
13-Aug-23	2.4	8	
14-Aug-23	2.5	8	
15-Aug-23	2.9	8	
9-Sep-23	3.4	0	
10-Sep-23	5.2	0	
11-Sep-23	5.5	0	40%
12 Sept 2023[c]	4.2	0	
13-Sep-23	3.1	6	
14-Sep-23	2.7	6	
14-Sep-23	2.5	6	
5-Oct-23	2.2	6	
6-Oct-23	2	6	
7-Oct-23	1.9	6	
8-Oct-23	1.6	7	
9-Oct-23	1.9	7	
10-Oct-23	2.6	6	
14-Oct-23	2.6	6	
15 Oct 2023[d]	2.5	6	29%
18 Oct 2023[e]	2.3	6	

- The table presents longitudinal data of selected INR values, corresponding warfarin dosing, and chromogenic Factor X (CFX) activity percentages during the patient's hospitalization from August to October 2023. CFX activity values, available for select dates, are within or near the therapeutic range (20-40%), suggesting adequate anticoagulation despite INR variability. This data underscores the challenges of relying solely on INR monitoring in patients with antiphospholipid syndrome on dialysis, as INR fluctuations may not accurately reflect anticoagulation status due to antibody interference with clotting assays.
- The use of the CFX assay provided more consistent evidence of therapeutic anticoagulation, albeit once monthly, guiding safer and more precise warfarin dosing adjustments over time.

- [a] August 3-7, 2023**:** Hematology recommended utilizing CFX assays to better assess the patient's anticoagulation status, particularly given the variability and limitations of INR measurements. To ensure correlation, INR levels were obtained concurrently with CFX assays during warfarin therapy. Given the patient's subtherapeutic anticoagulation status, IV heparin was started to attain anticoagulant coverage.
- [b] **August 12, 2023**: CFX activity was measured at 36% while the patient was receiving 8mg of warfarin daily, with a concurrent INR of 2.3. These results supported continuation of the current dosing regimen, and subsequent INR fluctuations were interpreted with caution in light of stable CFX activity.

Laboratory findings indicated underlying chronic kidney disease and signs of malnutrition, both of which may have contributed to increased warfarin sensitivity. In response, warfarin was temporarily withheld (0 mg) and subsequently restarted at a reduced dose of 6 mg daily (down from 8 mg) to allow for more controlled dosing. Although the CFX assay indicated therapeutic anticoagulation, the medical team prioritized INR monitoring as a more immediate and responsive measure of coagulation status. Efforts were directed toward achieving and maintaining INR stability. A repeat CFX assay later confirmed therapeutic factor X activity at 40%, further supporting the adequacy of anticoagulation.

- [c] **September 9–13, 2023**: The patient's INR unpredictably elevated to 5.5 without signs of bleeding in the absence of identifiable causes such as vitamin K intake variability or known drug interactions.
- [d] **October 7-15, 2023**: While receiving 6 mg of warfarin daily, the patient developed neurological symptoms suggestive of a possible cerebrovascular event. On presentation, the INR was subtherapeutic at 1.9, raising concern for inadequate

- anticoagulation. A brain CT ruled out acute infarction, with findings more consistent with chronic cerebrovascular changes. Given the clinical uncertainty and subtherapeutic INR, the patient was transitioned to a heparin infusion to ensure prompt and reliable anticoagulation. Bridging therapy was initiated, and the warfarin dose increased to 7 mg daily. This regimen was maintained until therapeutic INR levels were achieved, as confirmed by repeat CFX measurements. Notably, the CFX level remained therapeutic at 29%, suggesting preserved factor X inhibition despite earlier subtherapeutic INR values.

- [e] **October 18, 2023:** Patient stable for discharge. Hematology recommends continuing following anticoagulation monitoring and complete blood count (CBC) as an outpatient with the primary care provider (PCP) or in an outpatient clinic.

References:

1. Arreola-Diaz R, Majluf-Cruz A, Sanchez-Torres LE, Hernandez-Juarez J. The Pathophysiology of The Antiphospholipid Syndrome: A Perspective From The Blood Coagulation System. Clin Appl Thromb Hemost. 2022;28:10760296221088576. doi:10.1177/10760296221088576
2. Anglés-Cano E, Guillin MC. Antiphospholipid Antibodies and the Coagulation Cascade. Rheumatic Disease Clinics of North America. 2001;27(3):573-586.
3. Capecchi M, Abbattista MR, Ciavarella A, Uhr M, Novembrino C, Martinelli I. Anticoagulant Therapy in Patients with Antiphospholipid Syndrome. J Clin Med. 2022;11(23):6984.
4. Crowl A, Schullo-Feulner A, Moon JY. Warfarin Monitoring in Antiphospholipid Syndrome and Lupus Anticoagulant. Ann Pharmacother. 2014;48(11):1479-1483.
5. Cohen H, Efthymiou M, Devreese KML. Monitoring of anticoagulation in thrombotic antiphospholipid syndrome. J Thromb Haemost. 2021;19:892–908.
6. Baumann Kreuziger LM, Datta YH, Johnson AD, Zantek ND, Shanley R, Reding MT. Monitoring anticoagulation in patients with an unreliable prothrombin time/international normalized ratio. Blood Coagul Fibrinolysis. 2014;25(3):232-236.
7. Sanfelippo MJ, Zinsmaster W, Scherr DL, Shaw GR. Use of chromogenic assay of factor X to accept or reject INR results in warfarin-treated patients. Clin Med Res. 2009;7(3):103-105.
8. McGlasson DL, Romick BG, Rubal BJ. Comparison of a chromogenic factor X assay with international normalized ratio for monitoring oral anticoagulation therapy. Blood Coagul Fibrinolysis. 2008;19(6):513-517. doi:10.1097/MBC.0b013e328304e066
9. Gehrie E, Laposata M. Test of the month: The chromogenic antifactor Xa assay. Am J Hematol. 2011;87(2):194-196.
10. Vera-Aguilera J, Yousef H, Beltran-Melgarejo D, et al. Clinical Scenarios for Discordant Anti-Xa. Adv Hematol. 2016;2016:1-6.
11. D'Ippolito S, Barbaro G, Paciullo C, Tersigni C, Scambia G, Di Simone N. Antiphospholipid Syndrome in Pregnancy: New and Old Pathogenetic Mechanisms. Int J Mol Sci. 2023;24(4):3195.
12. Galli M, Finazzi G, Barbui T. Lupus anticoagulants are strong risk factors for thrombosis in patients with systemic lupus erythematosus. J Thromb Haemost. 2003;1(8):1740–1743.
13. Devreese KMJ. Standardization of antiphospholipid antibody assays. Semin Thromb Hemost. 2012;38(4):348–359.