El Hasbani G, Abdelrahman M, Baker M, Janowiecki C. When Apixaban and Rivaroxaban Interfere With Anti-Xa Assays: A Cohort Study. *Brown Hospital Medicine*. 2023;2(4). doi:10.56305/001c.85155

Original Research

When Apixaban and Rivaroxaban Interfere With Anti-Xa Assays: A Cohort Study

Georges El Hasbani[1], Mahmoud Abdelrahman[1], Mark Baker[2], Christopher Janowiecki[1]

[1] Medicine, St. Vincent's Medical Center,
[2] Pharmacy Services, St. Vincent's Medical Center

Journal of Brown Hospital Medicine
Vol. 2, Issue 4, 2023

Article Information

Keywords: Anticoagulation, coagulation assays, Side effects, apixaban, antiXa

https://doi.org/10.56305/001c.85155

Submitted: May 27, 2023 EDT

Accepted: August 13, 2023 EDT

Abstract

Background: The use of direct factor Xa inhibitors, such as apixaban and rivaroxaban, has improved medication adherence. However, in certain situations during hospital admission, patients on these medications may need to be transitioned to unfractionated heparin (UFH) infusions. This transition can skew results of anticoagulation monitoring, such as the anti-Xa assay, due to residual factor-Xa inhibitor activity. **Methods:** We conducted this retrospective chart among admitted patients to St. Vincent's Medical Center in Bridgeport, CT between December 2020 till June 2022. Patients who were maintained on Apixaban or Rivaroxaban, factor-Xa inhibitors, and were transitioned to unfractionated intravenous drip were included. A baseline plasma anti-Xa level was noted. Assessment for thrombotic or bleeding events during hospitalization was performed. **Results:** A total of 48 patients were included in this study. The majority of patients were bridged to UFH for NSTEMI (31%) or pre-procedure (23%). The mean baseline anti-Xa for all patients was 0.92 U/mL. Twelve patients (25%) and one patient (2%) of patients had bleeding and thrombotic events, respectively. Although the mean baseline anti-Xa level was higher for patients who had an adverse event compared to no event, the difference was non-statistically significant. Fifty seven percent of patients who had an adverse event had a supratherapeutic plasma anti-Xa baseline level. A gastrointestinal bleed was the most common type of bleeding event. **Conclusions:** To prevent thrombotic or bleeding events, we suggest adopting a standard practice of obtaining a baseline anti-Xa level in patients with recent exposure to factor Xa inhibitors in order to guide the timing of UFH initiation, the dosing of heparin, and determine the need for alternative assays, such as the activated partial thromboplastin clotting time.

BACKGROUND

The transition of care during hospital admission often necessitates adjustments to patients' home medications, including oral hypoglycemics and anticoagulants.[1] Direct factor Xa inhibitors have gained widespread use due to their efficacy, predictable pharmacokinetics, and ease of maintenance.[2] However, during hospitalization, these agents may need to be switched to different forms of anticoagulation, such as unfractionated heparin (UFH) or low molecular weight heparin (LMWH). This switch may be required in cases of acute coronary syndrome, acute kidney injury, inability to tolerate oral medications, treatment failure, or surgical procedures.[3,4]

The transition from direct factor Xa inhibitors to UFH requires careful monitoring to ensure appropriate anticoagulation. Commonly used laboratory assays for monitoring UFH include the activated partial thromboplastin time (aPTT) and anti-Xa assays, with the latter becoming increasingly popular. Anti-Xa assays offer several advantages, including a more direct measure of heparin activity, a standardized reference range across all laboratories, and a higher proportion of tests within the therapeutic range compared to aPTT.[5] However, direct factor Xa inhibitors can impact anti-Xa levels and potentially distort the accuracy of monitoring these levels, particularly during the initial stages of UFH initiation.[6,7]

Rivaroxaban and apixaban are direct inhibitors of human factor Xa, and their levels can be measured using liquid chromatography-mass spectrometry or commercially available anti-Xa chromogenic assays.[8-12] Factor Xa levels are interpreted based on factors such as the type and dose of anticoagulant, as well as the time elapsed since the last administration. In certain clinical events, such as breakthrough thrombosis or bleeding, it may be necessary to assess relevant factor Xa concentrations and consider the use of additional assays, such as the activated partial thromboplastin time.[13-15]

This study aims to evaluate the safety of employing the standard anti-Xa assay protocol in patients who are receiving apixaban or rivaroxaban as maintenance therapy and subsequently switched to UFH during their hospital stay. The primary objective is to determine the incidence of adverse events, including minor bleeding, major bleeding, and thrombosis.

METHODS

This is a retrospective chart review study that assesses possible bleeding or thrombotic events in patients who were started on UFH infusion during hospitalization following exposure to apixaban or rivaroxaban.

The study included patient records meeting the following criteria: any gender, any racial/ethnic background, age ≥18 and <90 years old, patients who were transitioned from apixaban or rivaroxaban to intravenous UFH at St. Vincent's Medical Center (SVMC) in Bridgeport, CT, between December 1, 2020, and June 30, 2022, based on clinical indications. The indications included non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), cerebrovascular accident, venous thromboembolic event (VTE), new-onset atrial fibrillation, or pre-operative procedure requiring bridging anticoagulation. Baseline anti-Xa plasma levels were recorded for all eligible patients. The therapeutic range for anti-Xa plasma levels in patients receiving UFH maintenance was set between 0.3 to 0.7 IU/mL.[16] Patients less than 18 or more than 90 years old who were not using apixaban or rivaroxaban, and patients who only received a bolus of UFH or prophylactic heparin were excluded from the study.

The primary outcome of this study was to assess the incidence of adverse or serious adverse events. The analysis plan is descriptive in nature, focusing on evaluating the occurrence of events and examining sample characteristics. For continuous data, normality of distribution was assessed. Continuous data that exhibited a normal distribution were presented as mean and standard deviation. Categorical data were presented as frequency and percentages. An alpha (α) value of 0.05 was used to determine statistical significance. All analyses were performed using Excel 2021.

RESULTS

A total of 48 patients were included in this study. The average age of the patients was 70.52 years. Females accounted for 40% of the study population, while males constituted 60%. The majority of the study participants were white. Among the patients, a higher proportion (83%) were maintained on apixaban compared to rivaroxaban (17%). The indications for transitioning to intravenous unfractionated heparin are displayed in **Figure 1**. The average time from admission to the initiation of intravenous UFH was 31 hours, and the average duration of UFH use during hospitalization was 61 hours.

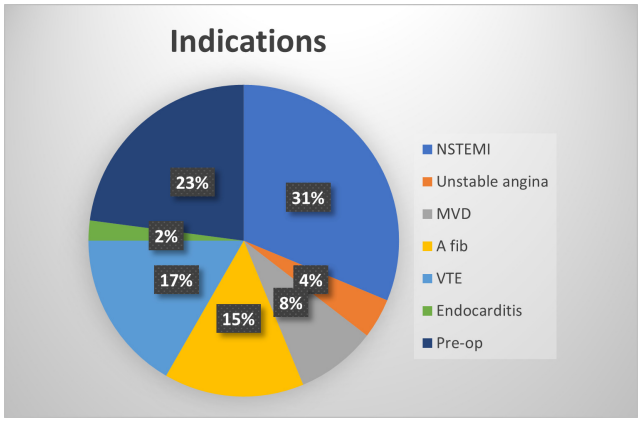

Figure 1. The indications to transition from direct factor Xa inhibitors intravenous UFH during hospitalization.

NSTEMI: Non-ST elevation myocardial infarction; MVD: Multi-vessel disease; A fib: Atrial fibrillation; VTE: Venous thromboembolic event; Pre-op: Pre-operation

A total of 13 patients experienced bleeding or thrombotic complications, with 12 cases (25%) involving bleeding and one case (2%) involving thrombosis, specifically a myocardial infarction. Half of the bleeding events were gastrointestinal (GI) bleeds, while 33.3% were soft tissue bleeds, and 16.67% were genitourinary (GU) bleeds. GI bleeds encompassed upper or lower GI bleeding, while GU bleeds included cases of hematuria. Soft tissue bleeds referred to intracompartment bleeds, such as retroperitoneal hemorrhage. Among the patients who experienced complications, 57% had baseline anti-Xa levels above the therapeutic range for UFH. The mean baseline anti-Xa level was 0.92 U/mL. There was no statistically significant difference in baseline anti-Xa levels between patients with complications and those without complications (p-value 0.26).

DISCUSSION

Coagulation refers to a complex system that maintains the fluidity of the blood in the vascular system while allowing for the rapid formation of a solid blood clot to prevent hemorrhaging subsequent to blood vessel injury. Such system is composed of numerous vessel walls, platelets, coagulation factors, inhibitors, and the fibrinolytic systems.[17] Several techniques, including clot-based tests, chromogenic or color assays, direct chemical measurements, and ELISAs, are used for coagulation testing.[18] The activating partial thromboplastin time (aPTT) allows measurement of optimal activation of contact factors (factor XII, factor XI, prekallikrein, and high-molecular-weight kininogen).[19] Low-molecular weight heparin (LMWH) usually forms an inhibitory complex with antithrombin to inactivate activated factor X (Xa). An anti-factor Xa assay quantitatively measures the pharmacodynamic effect of the inhibition of factor Xa by LMWH.[20]

One of the benefits of anti-Xa assays is to prevent over- or under- anticoagulation which can lead to potential negative outcomes.[21] Despite the titration of UFH infusions guided by anti-Xa levels, adverse outcomes can still occur, as observed in this study. Although the baseline difference in anti-Xa levels was not statistically significant between patients experiencing adverse thrombotic/bleeding events and those without adverse events, the mean anti-Xa level was higher in patients with bleeding outcomes. This finding may suggest the need to initiate UFH infusions at a lower rate than usual or to delay UFH initiation until adequate clearance of direct factor Xa inhibitors is achieved in cases involving recent use.

Since direct factor Xa inhibitors can lead to supratherapeutic anti-Xa levels,[21,22] bleeding episodes may be expected. The incidence of bleeding events in patients with supratherapeutic anti-Xa levels in the context of recent direct factor Xa inhibitor use is estimated to be 3% for major bleeding events and 3% for non-major bleeding events.[22] However, the frequency was higher in our study. The majority of our patients underwent UFH infusion for acute thrombotic events, including NSTEMI and VTE. Studies have demonstrated a lower rate of VTE recurrence when the target therapeutic anticoagulation values are attained within 24 hours after the initiation of UFH infusion.[23] Therefore, a previous use of a direct factor Xa inhibitor, which affects baseline anti-Xa, may be a risk factor for thrombotic recurrence.

There is conflicting data regarding whether prior use of direct factor Xa inhibitors can increase the rate of in-hospital bleeding events. For instance, in patients admitted for STEMI, the use of home direct factor Xa inhibitors was not found to be associated with an increased incidence of in-hospital major bleeding.[24] On the contrary, intracranial bleeds were significantly increased among admitted patients maintained on apixaban or rivaroxaban at home, according to another study.[25] Risk factors for bleeding included age greater than 80 years, inappropriately high dosing regimens, and modest anti-Xa levels.[25]

Activated partial thromboplastin time (aPTT) assays can also be used to monitor and titrate heparin dosing, as was historically the case prior to the year 2000.[26] However, it is interesting to note that aPTT levels have been found to be more strongly associated with an increased incidence of bleeding than anti-Xa levels,[26] particularly in the pediatric population. Conversely, there was no significant difference in clinical outcomes between anti-Xa and aPTT-based monitoring of unfractionated heparin (UFH) infusion.[27] Direct factor Xa inhibitors might affect aPTT, but aPTT can often still be normal in these cases.[28]

There are several limitations to our study. Firstly, being a retrospective chart review study, it is challenging to eliminate potential confounding factors, as the data relies on existing medical records. Secondly, the diagnosis of bleeding or thrombosis was determined based on chart documentation, which is subject to potential variations in accuracy and completeness of the recorded information. Additionally, it is unclear whether bleeding events had already commenced prior to the initiation of UFH infusion, which could impact the interpretation of causality. Thirdly, the specific time elapsed since the last intake of apixaban, or rivaroxaban was not available, leading to inclusion of patients based solely on self-reporting of their use of these medications. Lastly, it is worth noting that normal anti-Xa levels observed in some cases may be attributable to medication errors or limitations in medication adherence.

CONCLUSION

Patients who are on direct factor Xa inhibitors as part of their home medication regimen may require bridging to unfractionated heparin (UFH) when they are admitted to the hospital. This bridging is often necessary for various reasons, including myocardial infarction or venous thromboembolic events. Monitoring the bridging process is crucial, and anti-Xa assays are available to assess the extent of anticoagulation. However, it should be noted that the use of apixaban and rivaroxaban, which are direct factor Xa inhibitors, can potentially impact anti-Xa levels, increasing the risk of bleeding or thrombotic events. Therefore, it is essential to establish baseline anti-Xa levels to guide the subsequent use of UFH or determine the suitability of alternative assays, such as the activated partial thromboplastin time (aPTT).

Author Contributions

All authors have reviewed the final manuscript prior to submission. All the authors have contributed significantly to the manuscript, per the International Committee of Medical Journal Editors criteria of authorship.

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosures/Conflicts of Interest

The authors have no conflicts of interest to disclose.

Corresponding Author

Georges El Hasbani MD
Department of Internal Medicine
St. Vincent's Medical Center
Bridgeport, CT 06606
Email: george.hasbany@lau.edu

REFERENCES

1. Daliri S, Bouhnouf M, van de Meerendonk HWPC, et al. Longitudinal medication reconciliation at hospital admission, discharge and post-discharge. *Research in Social and Administrative Pharmacy*. 2021;17(4):677-684. doi:10.1016/j.sapharm.2020.05.022

2. Comerota AJ, Ramacciotti E. A Comprehensive Overview of Direct Oral Anticoagulants for the Management of Venous Thromboembolism. *The American Journal of the Medical Sciences*. 2016;352(1):92-106. doi:10.1016/j.amjms.2016.03.018

3. Gilchrist IC. Heparin, bivalirudin, or the best of both for STEMI interventions. *Catheter Cardiovasc Interv*. 2019;93(2):248-249. doi:10.1002/ccd.28091

4. Dorobantu M, Bogdan S. Unfractionated heparin or low-molecular-weight heparin in the elderly. *Int J Cardiol*. 2016;222:1084-1090. doi:10.1016/j.ijcard.2016.07.208

5. Centeno EH, Militello M, Gomes MP. Anti-Xa assays: What is their role today in antithrombotic therapy? 2019;86:417-425.

6. Whitman-Purves E, Coons JC, Miller T, et al. Performance of Anti-Factor Xa Versus Activated Partial Thromboplastin Time for Heparin Monitoring Using Multiple Nomograms. *Clin Appl Thromb Hemost*. 2018;24(2):310-316. doi:10.1177/1076029617741363

7. Kalaria SN, Zhu H, Liu Q, Florian J, Wang Y, Schwartz J. Influence of age on the relationship between apixaban concentration and anti-factor Xa activity in older patients with non-valvular atrial fibrillation. *Int J Cardiol*. 2021;331:109-113. doi:10.1016/j.ijcard.2021.01.025

8. Perzborn E, Roehrig S, Straub A, Kubitza D, Mueck W, Laux V. Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol*. 2010;30(3):376-381. doi:10.1161/atvbaha.110.202978

9. Byon W, Garonzik S, Boyd RA, Frost CE. Apixaban: A Clinical Pharmacokinetic and Pharmacodynamic Review. *Clin Pharmacokinet*. 2019;58(10):1265-1279. doi:10.1007/s40262-019-00775-z

10. Schmitz EMH, Boonen K, van den Heuvel DJA, et al. Determination of dabigatran, rivaroxaban and apixaban by ultra-performance liquid chromatography – tandem mass spectrometry (UPLC-MS/MS) and coagulation assays for therapy monitoring of novel direct oral anticoagulants. *J Thromb Haemost*. 2014;12(10):1636-1646. doi:10.1111/jth.12702

11. Billoir P, Elie T, Levy JH, et al. Anticoagulation Monitoring with Activated Partial ThromboPlastin Time and Anti-Xa Activity in Intensive Care Unit Patients: Interest of Thrombin Generation Assay. *Int J Mol Sci*. 2022;23(19):11219. doi:10.3390/ijms231911219

12. Billoir P, Barbay V, Joly LM, Fresel M, Chrétien MH, Le Cam Duchez V. Anti-Xa Oral Anticoagulant Plasma Concentration Assay in Real Life: Rivaroxaban and Apixaban Quantification in Emergency With LMWH Calibrator. *Ann Pharmacother*. 2019;53(4):341-347. doi:10.1177/1060028018811657

13. Ten Cate H, Henskens YM, Lancé MD. Practical guidance on the use of laboratory testing in the management of bleeding in patients receiving direct oral anticoagulants. *Vasc Health Risk Manag*. 2017;13:457-467. doi:10.2147/vhrm.s126265

14. Frost C, Nepal S, Wang J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol*. 2013;76(5):776-786. doi:10.1111/bcp.12106

15. Coons JC, Iasella CJ, Thornberg M, et al. Clinical outcomes with unfractionated heparin monitored by anti-factor Xa vs. activated partial Thromboplastin time. *Am J Hematol*. 2019;94(9):1015-1019. doi:10.1002/ajh.25565

16. Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. *J Thromb Thrombolysis*. 2016;41(1):165-186. doi:10.1007/s11239-015-1315-2

17. Chan AKC, Paredes N. The coagulation system in humans. *Haemostasis*. 2013;992:3-12. doi:10.1007/978-1-62703-339-8_1

18. Walenga JM, Hoppensteadt DA. Monitoring the new antithrombotic drugs. *Semin Thromb Hemost*. 2004;30(6):683-695. doi:10.1055/s-2004-861511

19. Colman RW. *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. Lippincott Williams & Wilkins; 2006.

20. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):e24S-e43S. doi:10.1378/chest.11-2291

21. Macedo KA, Tatarian P, Eugenio KR. Influence of Direct Oral Anticoagulants on Anti–Factor Xa Measurements Utilized for Monitoring Heparin. *Ann Pharmacother*. 2018;52(2):154-159. doi:10.1177/1060028017729481

22. Ahuja T, Yang I, Huynh Q, Papadopoulos J, Green D. Perils of Antithrombotic Transitions: Effect of Oral Factor Xa Inhibitors on the Heparin Antifactor Xa Assay. *Ther Drug Monit*. 2020;42(5):737-743. doi:10.1097/ftd.0000000000000774

23. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. *Arch Intern Med*. 1997;157(22):2562-2568. doi:10.1001/archinte.1997.00440430038005

24. Feldman DN, Wang TY, Chen AY, et al. In-Hospital Bleeding Outcomes of Myocardial Infarction in the Era of Warfarin and Direct Oral Anticoagulants for Atrial Fibrillation in the United States: A Report From the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry. *Journal of the American Heart Association*. 2019;8(8):e011606. doi:10.1161/jaha.118.011606

25. Jakowenko N, Nguyen S, Ruegger M, Dinh A, Salazar E, Donahue KR. Apixaban and rivaroxaban anti-Xa level utilization and associated bleeding events within an academic health system. *Thromb Res*. 2020;196:276-282. doi:10.1016/j.thromres.2020.09.002

26. Oladunjoye OO, Sleeper LA, Nair AG, et al. Partial thromboplastin time is more predictive of bleeding than anti-Xa levels in heparinized pediatric patients after cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery*. 2018;156(1):332-340.e1. doi:10.1016/j.jtcvs.2018.02.101

27. Coons JC, Iasella CJ, Thornberg M, et al. Clinical outcomes with unfractionated heparin monitored by anti-factor Xa vs. activated partial Thromboplastin time. 2019;94:1015-1019.

28. Adcock DM, Gosselin RC. The danger of relying on the APTT and PT in patients on DOAC therapy, a potential patient safety issue. 2017;39:37-40.