



Transitioning to Unfractionated Heparin in Treatment of Non-ST-Segment Elevation Myocardial Infarction Patients on Direct Oral Anti-Xa Inhibitors

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ARTICLE INFO

Original paper

Article history:

Received: January 19, 2023

Accepted: March 22, 2023

Published: March 31, 2023

Keywords:

Direct Oral Anticoagulants; Non-ST-Elevated Myocardial Infarction; Heparin Anti-Xa Assay

ABSTRACT

The heparin anti-Xa assay is affected by the use of direct oral anticoagulants (DOACs) and is utilized in the management of intravenous unfractionated heparin. Patients with non-ST-segment myocardial infarction (NSTEMI) receive intravenous unfractionated heparin with prior administration of DOACs poses challenges given these laboratory abnormalities. On this background, we evaluate if an elevated heparin anti-Xa assay may lead to the decision to delay heparin in the management of NSTEMI patients and the outcome of in-hospital mortality. This is a single-center chart review study with patients admitted between January 2019 and December 2020. Patients with a documented DOAC home medication and a diagnosis of NSTEMI were included. Data was collected for heparin anti-Xa levels at baseline, after 6 and 12 hours of hospitalization, in addition to the reason for the delay in the administration of heparin. Statistical analysis included the determination of r-squared correlation and one-way ANOVA using GraphPad Prism 8.0. A total of 44 patients were divided into three groups based on baseline Xa levels of patients. Elevated Xa level was noted more in patients who were taking apixaban. Heparin infusion was delayed among this sub-group of patients. Elevated baseline heparin anti-Xa levels were significantly improved after 12 hours. There was no correlation between elevated anti-Xa levels and activated partial thromboplastin time. No in-hospital mortality was observed among any of the subgroups. Collectively, this study demonstrates that the high sensitivity of heparin anti-Xa assay to DOACs affect assay accuracy and result in elevated heparin anti-Xa level with the use of DOACs resulting in delayed start of heparin therapy in treating NSTEMI patients.

Doi: <http://dx.doi.org/10.14715/cmb/2023.69.3.28>

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Introduction

Non-ST-segment elevation myocardial infarction (NSTEMI) has emerged as the predominant cause of hospitalization in individuals with ischemic heart disease and continues to be associated with high morbidity and mortality (1). In the United States, approximately 546,000 patients are admitted to hospitals each year due to NSTEMI, with a higher prevalence observed in males (2). The underlying pathophysiology of NSTEMI typically involves thrombus formation or progressive arterial stenosis leading to subtotal occlusion of an epicardial coronary artery (3, 4). By virtue of their ability to inhibit factors associated with thrombosis and reduce ischemic outcomes, the use of anticoagulants has contributed to the low in-hospital mortality rates observed in NSTEMI patients (2, 5).

Significant progress has been made in comprehending the molecular and cellular mechanisms underlying thrombus formation in recent decades, with anticoagulants remain the primary approach for managing and preventing thromboembolic disorders (6-8). The coagulation pathway is a complex process involving a sequence of molecular

events that eventually culminate in fibrin clot development (9, 10). The activation of the tissue factor (TF) coagulation pathway appears to be central in arterial and venous thrombosis leading to acute cardiovascular events, such as myocardial infarction (11-13). TF binds with circulating Factor VIIa to create the TF-Factor VIIa complex, which triggers Factor IX and Factor X. At the beginning phase of blood coagulation, tissue factor pathway inhibitor (TFPI) is a vital physiological inhibitor of Factor Xa. It binds with Factor Xa and blocks the TF-Factor VIIa-Factor Xa complex (14). Factor Xa converts small quantities of prothrombin into thrombin, which then boosts coagulation by activating platelets and platelet-bound Factor XI, as well as Factor V and Factor VIII (on the surface of activated platelets). The coagulation cascade is amplified by additional Factor Xa formation via the Factor IXa-Factor VIIIa-Ca²⁺-phospholipid complex. Factor Xa, along with Factor Va, binds to negatively charged phospholipid surfaces, such as activated platelets, creating the prothrombinase complex, the primary prothrombin activator that transforms prothrombin to thrombin (15). Thrombin not only transforms soluble fibrinogen to fibrin and activates

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platelets but also intensifies its generation through feedback activation of Factor VIII and Factor V, in addition to activating Factor XIII, which stabilizes the clot further (16).

In the search for novel anticoagulant strategies, efforts have been directed towards identifying a singular enzyme within the coagulation pathway, and Factor Xa has emerged as a particularly encouraging target for effective anticoagulation because it is positioned at the convergence point of the intrinsic and extrinsic coagulation pathways (17), (18). Therefore, several new oral agents that selectively target Factor Xa have been developed (19, 20).

The use of direct oral anticoagulants (DOACs), rivaroxaban, apixaban, edoxaban, and dabigatran, has expanded given the increasing indications and the appealing efficacy, safety, and convenience when compared to alternative therapies (21). DOACs retain advantage primarily in two areas which include their fixed oral dosing strategies and the lack of routine laboratory monitoring (22-24). Insurance claims for anticoagulation medications increased by 30% between 2014 and 2019 propelled largely by increases in prescriptions for apixaban and rivaroxaban. Conversely, the total number of claims during this period for warfarin had decreased by approximately 40% among Medicare Part D and Medicaid beneficiaries (25).

Use of DOACs with factor Xa inhibitory effects, including apixaban, rivaroxaban and edoxaban may cause elevations in coagulation assays including thrombin time (TT), heparin anti-Xa assay, activated partial thromboplastin time (aPTT), and prothrombin time (PT) (26). Monitoring unfractionated heparin (UFH) therapy is an institutional preference, if the heparin anti-Xa assay is utilized in the monitoring of UFH, the factor Xa inhibitors can yield inaccurate or unquantifiable results while global coagulation assays measuring aPTT or PT are altered to a lesser degree (27).

In clinical practice, transitioning from oral factor Xa inhibitors to UFH in the treatment of NSTEMI has been challenging since some institutions have transitioned to the heparin anti-Xa assay to monitor therapeutic levels of UFH. Elevations in the heparin anti-Xa assay would encourage de-escalation of heparin infusion rates or cause delays in the administration of heparin. DOACs are not currently approved in the treatment of NSTEMI and guidance for the transition of DOACs to parenteral anticoagulation recommends starting the parenteral anticoagulation at the same time the next dose of DOAC would be administered (21). Under this guidance, there is the potential to delay UFH therapy for six or more hours in NSTEMI patients. The American Heart Association and American College of Cardiology guidelines for the management of patients with NSTEMI recommend initiation of dual antiplatelet therapy and anticoagulant therapy with either heparin, enoxaparin, or fondaparinux for ischemia-guided management (28). Consequently, intravenous unfractionated heparin is a cornerstone of therapy for the treatment of NSTEMI and delays in therapy should be mitigated if possible. Therefore, the purpose of this study was to assess whether there was any delay in the administration of heparin infusion in patients who were receiving DOACs in the outpatient setting. We further aimed to assess whether the delay in heparin infusion was significant in patients with elevated heparin anti-Xa levels.

Materials and Methods

Study Design

This single-center study was performed at St. Mary's Medical Center, Huntington, West Virginia (WV). The study was completed by the retrospective chart review of patients' electronic medical records (EMR). The study was approved by the institutional review board (IRB) of Marshall University Joan C. Edwards School of Medicine, Huntington, WV (IRB No: 1682796), and a waiver was obtained for informed consent.

Patient Selection and Data Collection

To ensure an appropriate selection of patients eligible for the study, trained hospital personnel examined patients' medical records with appropriate confidentiality measures and in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Specifically, patients were identified by the review of (EMR) using the search period from January 2019 to December 2020. During this search period, patients aged >18 years old, admitted to the hospital with a clinical diagnosis of NSTEMI, eligible to receive continuous UFH infusion, with documented DOAC home medication, including apixaban, rivaroxaban or edoxaban, were identified and included in the study. In addition, heparin flow chart documentation was reviewed to determine UFH administration times in concordance to heparin anti-Xa levels according to St. Mary's Medical Center's UFH dosing protocol. Consequently, patients' inclusion was also based on laboratory measurement of heparin anti-Xa assay at the hospital. Heparin anti-Xa levels were measured using automated chromogenic HemosIL® Liquid Anti-Xa assay by Warfen Instrumentation Laboratory based on the standardized protocol at the hospital. Based on the EMR review, the dose of DOACs was recorded for each patient meeting the inclusion criteria. Patient's exclusion criteria included patients less than 18 years old, those with no documented use of DOAC as a home medication, patients without baseline heparin anti-Xa level, any patient who received percutaneous coronary intervention prior to UFH infusion, or any patient presenting as an out-of-hospital cardiac arrest and patients for whom there was incomplete data. Patients were also excluded if the EMR review showed confounding factors that influence heparin anti-Xa levels, such as administration of low molecular weight heparin (LMWH) or direct thrombin inhibitors within 48 hours prior to UFH infusion.

Patients meeting the inclusion criteria were assessed for the delay in the administration of UFH infusion. Heparin anti-Xa levels were recorded prior to UFH infusion (baseline; T0), after 6 hours (T1) and after 12 hours (T2) of UFH infusion. The data was divided into three primary groups: 1) patients with baseline (T0) heparin anti-Xa levels of <0.3 IU/mL, 2) patients with baseline (T0) heparin anti-Xa levels between 0.3-0.7 IU/mL, and 3) patients with baseline (T0) heparin anti-Xa levels of >0.7 IU/mL. Demographics data was collected for each patient including sex, age, body mass index (BMI), aPTT, PT, documented DOAC home medication, and ischemic workup. Additional data that was collected included the medical history of cardiovascular diseases, history of chronic illnesses, history of renal dysfunction, including acute kidney injury (AKI) and chronic kidney disease (CKD), crea-

tinine clearance (CrCl), and level of estimated glomerular filtration rate (eGFR).

Statistical Analysis

Data were analyzed using GraphPad Prism 8.0. Demographic and clinical variables are presented as means ± standard error of the mean (SEM) or frequency/percentage. One-way ANOVA was performed to identify statistical significance in the assessed parameters between the three groups analyzed. All data comparisons are presented as no statistical significance (NSS), p<0.05 (confidence interval of 95%) and p<0.01 (confidence interval of 99%), as described previously (29).

Results

Patient Demographics

A total of 68 patients were identified during the initial screening of EMR for the patients admitted at St. Mary’s Hospital, West Virginia. Of these patients, a total of 44 patients met all inclusion criteria for diagnosis of NSTEMI and history of DOACs administration, where documented in EMR. These patients were divided among three groups based on the baseline (T0) heparin anti-Xa levels. Specifically, 34% of the patients had baseline (T0) heparin anti-Xa levels of <0.3 IU/mL (n = 15), 18% of the patients had baseline (T0) heparin anti-Xa levels between 0.3 – 0.7 IU/mL (n = 8), and 48% of the patients had baseline (T0) heparin anti-Xa levels of >0.7 IU/mL (n = 21) (Table 1 and Figure. 1A). Due to the small sample size, following statistics are mainly descriptive only. The mean age in each group was 72.8 ± 2.4 years, 68.0 ± 4.6 years and 75.9 ± 2.3 years, respectively (Table 1), which showed no statistical significance. There was also no statistical significance with regard to the BMI among the three groups (Table 1). The medical history of patients in each group, specifically

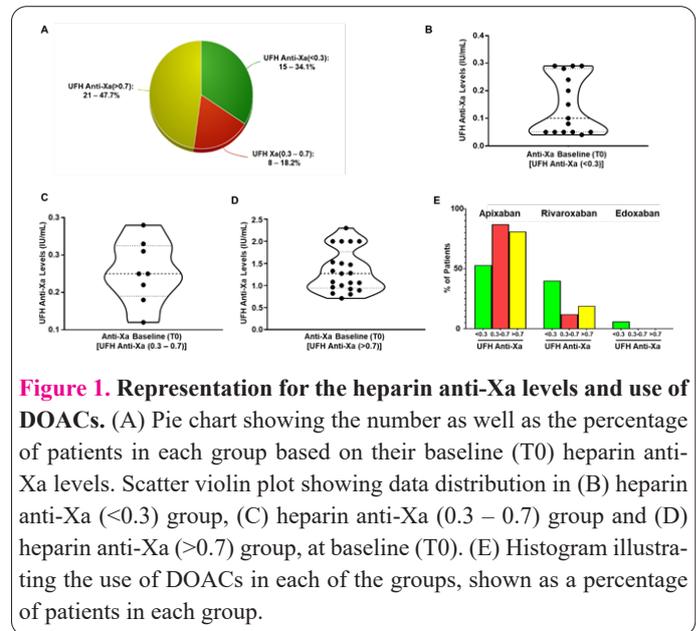


Figure 1. Representation for the heparin anti-Xa levels and use of DOACs. (A) Pie chart showing the number as well as the percentage of patients in each group based on their baseline (T0) heparin anti-Xa levels. Scatter violin plot showing data distribution in (B) heparin anti-Xa (<0.3) group, (C) heparin anti-Xa (0.3 – 0.7) group and (D) heparin anti-Xa (>0.7) group, at baseline (T0). (E) Histogram illustrating the use of DOACs in each of the groups, shown as a percentage of patients in each group.

the history of cardiovascular diseases, renal diseases, and other chronic diseases, is presented in Table 1. Most notably, the population in each group had a relatively higher percentage prevalence of atrial fibrillation, chronic kidney disease (varying stages), and comorbidities like diabetes, hypertension and dyslipidemia, as compared to other pathophysiological conditions (Table 1).

Use of DOACs

The data distribution for the baseline heparin anti-Xa levels in heparin anti-Xa <0.3 (Figure. 1B), heparin anti-Xa 0.3-0.7 (Figure. 1C), and heparin anti-Xa >0.7 (Figure. 1D), is shown as scatter violin plots, demonstrating the skewness in each group. Most of the patients in each group had a history of the use of apixaban, specifically 53% of

Table 1. Summary of patient demographics and general clinical profile. The table summarizes the basic characteristics of the study population as well as comorbidities in the population within each group. Values of age and BMI are represented as means ± SEM. The quantitative values for comorbidities are shown as a percentage of the population within each respective group. NSS: no statistical significance.

| | UFH Anti-Xa <0.3 | UFH Anti-Xa 0.3-0.7 | UFH Anti-Xa >0.7 |
|--|------------------|---------------------|------------------|
| Sample Size (n) | 15 | 8 | 21 |
| Age (yrs.) | 72.8 ± 2.4 (NSS) | 68.0 ± 4.6 (NSS) | 75.9 ± 2.3 (NSS) |
| Sex (M/F) | 6/9 | 5/3 | 14/7 |
| BMI (kg/m2) | 31.4 ± 1.2 (NSS) | 30.4 ± 1.9 (NSS) | 29.2 ± 1.2 (NSS) |
| Cardiovascular Diseases | | | |
| Atrial Fibrillation (%) | 66.6 | 75 | 85.7 |
| Atrial Flutter (%) | 13.3 | 12.5 | 9.5 |
| Venous Thromboembolism (%) | 40 | 12.5 | 28.5 |
| Stroke (%) | 20 | 0 | 23.8 |
| Peripheral Vascular Disease (%) | 13.3 | 0 | 13.3 |
| Ischemic Cardiomyopathy | 40 | 37.5 | 28.5 |
| Coronary Artery Disease | | | |
| Percutaneous coronary intervention (PCI) (%) | 20.0 | 25 | 23.8 |
| Coronary artery bypass graft (CABG) (%) | 26.6 | 37.5 | 23.8 |
| PCI and CABG (%) | 26.6 | 25 | 38.1 |
| Renal Diseases | | | |
| Acute Kidney Injury (%) | 20 | 37.5 | 23.8 |
| Hemodialysis (%) | 13.3 | 25 | 4.8 |
| Chronic Kidney Disease (%) | 73.3 | 75 | 76.2 |
| Other Chronic Diseases | | | |
| Diabetes Mellitus (%) | 80 | 87.5 | 52.4 |
| Hypertension (%) | 100 | 100 | 85.7 |
| Hypothyroidism (%) | 20 | 25 | 9.5 |
| Dyslipidemia (%) | 80 | 75 | 85.7 |

the patients in the heparin anti-Xa (<0.3) group, 87% of patients in the heparin anti-Xa (0.3 – 0.7) group, and 81% patients in heparin anti-Xa (>0.7) group (Figure. 1E). The use of DOAC, rivaroxaban, was the second most common with 40% of the patients in heparin anti-Xa (<0.3) group, 13% of patients in heparin anti-Xa (0.3 – 0.7) group, and 19% patients in heparin anti-Xa (>0.7) group (Figure. 1E). Only about 6% of the patients in heparin anti-Xa (<0.3) group had a history for the use of edoxaban (Figure. 1E).

UFH infusion and heparin anti-Xa levels

Next, the administration of UFH was evaluated among each of the groups. While all patients in heparin anti-Xa (<0.3) group received heparin infusion, more than 90% patients also received heparin bolus (Figure. 2A). Similarly, all patients in heparin anti-Xa (0.3 – 0.7) group received heparin infusion, however, only about 50% of the patients also received heparin bolus (Figure. 2B). Finally, about 95% (20 out of 21 patients) in heparin anti-Xa (>0.7) group received heparin infusion, about 52% (11 out of 21 patients) also received heparin bolus, while 5% (1 out of 21 patients) received no heparin (Figure. 2C). Our review of patients’ chart in heparin anti-Xa (>0.7) group also showed significant decline in the heparin anti-Xa levels at 12 hours (0.69 ± 0.08 IU/mL), as compared to baseline (initial measurement) (1.33 ± 0.10 IU/mL) and at 6 hours (1.05 ± 0.09 IU/mL) (Figure. 2D). Despite a significant decline in the mean heparin anti-Xa levels at 12 hours, a large number of patients in heparin anti-Xa (>0.7) group still had elevated heparin anti-Xa levels with an overall range between 0.22 to 1.45 IU/mL at 12 hours.

Delay in administration of UFH infusion

Each group of patients showed a delayed start in the administration of continuous UFH infusion. Specifically, about 40% patients (6 out of 15) had a delayed start of UFH infusion in the heparin anti-Xa (<0.3) group, 75% patients (6 out of 8) had a delayed start of UFH infusion in heparin anti-Xa (0.3 - 0.7) group, and approximately 71% patients (15 out of 21) had a delayed start of UFH infusion in heparin anti-Xa (>0.7) group (Figure. 3A).

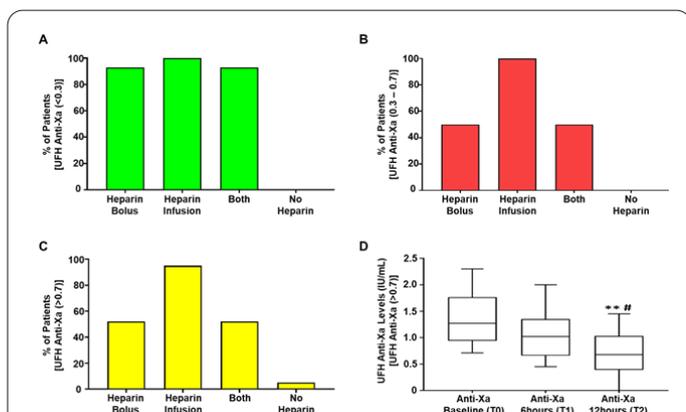


Figure 2. UFH infusion and heparin anti-Xa levels. Histograms illustrating the continuous administration of UFH by heparin bolus, heparin infusion, both or none in (A) heparin anti-Xa (<0.3) group, (B) heparin anti-Xa (0.3 – 0.7) group and (C) heparin anti-Xa (>0.7) group. (D) Heparin anti-Xa levels at baseline (T0), 6 hours (T1) and 12 hours (T2) in the heparin anti-Xa (>0.7) group. Data is shown as a box and whiskers plot with means and range of heparin anti-Xa levels. Significance is shown as **p<0.01 vs baseline (T0), #p<0.05 vs. 6 hours (T1).

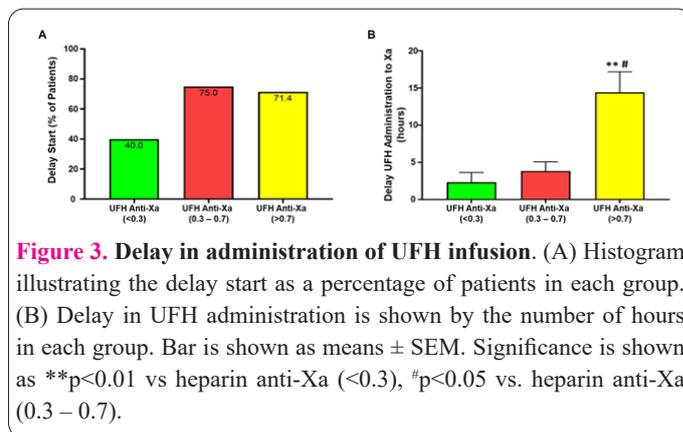


Figure 3. Delay in administration of UFH infusion. (A) Histogram illustrating the delay start as a percentage of patients in each group. (B) Delay in UFH administration is shown by the number of hours in each group. Bar is shown as means ± SEM. Significance is shown as **p<0.01 vs heparin anti-Xa (<0.3), #p<0.05 vs. heparin anti-Xa (0.3 – 0.7).

Although, there was a delay in the administration of UFH in all groups, there was a most significant delay (14.4 ± 2.8 hours) in heparin anti-Xa (>0.7) group, as compared to heparin anti-Xa (<0.3) and heparin anti-Xa (0.3 - 0.7) group having mean delay of approximately less than 4 hours (Figure. 3B).

Ischemic assessment

Next, we evaluated the ischemic work up among the patients in each group. About 13% of the patients in the heparin anti-Xa (<0.3) group, 12% of the patients in the heparin anti-Xa (0.3-0.7) group and about 24% of the patients in the heparin anti-Xa (>0.7) group underwent no left heart catheterization. For the patients that underwent left heart catheterization, almost 47% of the patients in the heparin anti-Xa (<0.3) group had undergone percutaneous coronary intervention (PCI), 20% with coronary artery bypass graft (CABG) surgery and about 20% of patients subjected to only medical management. Assessment in the heparin anti-Xa (0.3-0.7) group showed while none of the patients had CABG surgery, about 63% of patients underwent PCI, and about 25% of patients were subjected to medical management. Consequently, about 47% of patients in the heparin anti-Xa (>0.7) group underwent PCI while 10% of patients underwent CABG surgery with about 19% of patients with left heart catheterization medically managed.

Correlation analysis in patients with elevated heparin anti-Xa levels

There was no significant correlation between the BMI and heparin anti-Xa levels in the heparin anti-Xa (>0.7) group. There was also no significant positive correlation noted between the baseline aPTT and baseline heparin anti-Xa levels in the heparin anti-Xa (>0.7) group. We also aimed to assess the correlation between the decreased creatinine clearance as well as eGFR levels and increased heparin anti-Xa levels. However, our results showed no significant correlation between creatinine clearance and eGFR levels in patients with elevated heparin anti-Xa levels.

Discussion

Institutions that use the heparin anti-Xa assay as the only method to monitor and titrate UFH creates a dilemma for patients on DOACs as home therapy with a diagnosis of NSTEMI. The American Heart Association and American College of Cardiology recommended the use of dual antiplatelet therapy for Non-ST elevation-acute coronary

syndrome (NSTEMI-ACS) as well as anticoagulation therapy (28, 30). DOACs are not currently indicated in the treatment of NSTEMI-ACS. In the setting of NSTEMI management, to our knowledge, the literature has not addressed the outcome and concerns of residual effects of recent DOAC use in transitioning to UFH infusions in this subset of the population. Approximately 10-16% of patients with the acute coronary syndrome (ACS) that required stenting have pre-existing conditions necessitating the use of therapeutic anticoagulation, which includes the use of DOACs (31). In the present study, the highest prevalence of atrial fibrillation of 85.7% was observed among patients with elevated anti-Xa level assays.

The two most common strategies that are used to monitor the therapeutic effects of UFH include the heparin anti-Xa and aPTT assays. The aPTT is an overall assessment of coagulation that reflects both intrinsic and common pathways of the clotting cascade. On the other hand, the heparin anti-Xa assay is a chromogenic assay that measures the inhibition of clotting factor Xa, which reflects plasma heparin concentration. The heparin calibrated anti-Xa assay is suggested to be the preferred method for monitoring and titrating UFH compared to the aPTT due to improved time to therapeutic anticoagulation and fewer dosage adjustments (32). The use of either monitoring assay protocol is based on institutional preference.

Since the heparin anti-Xa assay is highly sensitive in the presence of DOACs, the assay accuracy is affected and results in elevated levels which are not specific enough to distinguish between UFH and DOACs neutralizing the factor Xa, which poses a challenge for transitioning to UFH infusions (33, 34). It has been shown that, the prevalence of initially elevated heparin anti-Xa assay in the absence of DOAC use was 21% compared to 69% with recent use of a DOAC (35). Reports have indicated the residual effect of DOACs may persist for more than 48 hours from the last administered dose. In our study, the residual effect of DOACs were observed in approximately 71% of patients with elevated heparin anti-Xa levels of > 0.7 IU/mL. According to our institution's protocol, the anti-Xa level of > 0.7 IU/mL is within the supratherapeutic range and the recommendation is to hold UFH therapy, thereby causing a significant delay of 14.4 hours to initiate UFH therapy. Interestingly, the delay in initiating UFH was also observed within the considered subtherapeutic range of heparin anti-Xa < 0.3 IU/mL and therapeutic range of heparin anti-Xa $0.3 - 0.7$ IU/mL according to our institutional protocol as well as based on provider decision and level of comfort to initiate heparin therapy outside of the protocol. A mean delay of approximately less than 4 hours was observed in 40% of patients and 75% of patients, respectively. The discrepancy in the delay of starting UFH among these subgroups can be explained by the use of heparin anti-Xa assay protocol for UFH infusion therapy in our institution as the only method of monitoring, and the package insert recommendation of transitioning to UFH at the next DOAC administration time. Although the package insert recommendations are rigorously followed, it is based on known pharmacokinetics in healthy subjects during the clinical trials and not based on proof of an optimal transition strategy (33).

It has been shown that the cut-off point is 72 hours from the last administered DOAC dose based on the assumption of near-complete elimination after 5 half-lives (35).

In our study, it was noted that the lack of documentation of the last administered home dose of DOACs on admission limited the statistical correlation with the heparin anti-Xa assay. However, the last administered dose of DOACs should not interfere with the decision to initiate NSTEMI management. Even though, clinical decisions had been made to start UFH at the next scheduled dose of DOACs on an individualized basis. Further analysis showed no statistical correlation of the elevated heparin anti-Xa assay with BMI, creatinine clearance, or eGFR.

Rivaroxaban and apixaban are oral medications that are directly selective, reversible factor Xa inhibitors (36). There is no clear guidance for using the heparin anti-Xa assay during the transition from DOACs to monitor UFH infusions. The transitioning to UFH from rivaroxaban should theoretically require less time for the decrease in heparin anti-Xa levels when compared to apixaban due to the shorter half-life and longer interval between doses. Pharmacokinetic studies have demonstrated similar peak-specific heparin anti-Xa levels for apixaban and rivaroxaban, but significantly lower rivaroxaban through heparin anti-Xa levels (34). The documented elevated heparin anti-Xa assay was observed in 81 % of apixaban, as compared to 19% of rivaroxaban which can be explained by the pharmacokinetics of medications. Nevertheless, in our study more patients were on apixaban as an outpatient, therefore correlating with the observational finding of elevated heparin anti-Xa assays.

It is described that in patients with recently administered DOACs, more down-titrations occurred in the initial 6 hours of UFH infusion and subsequently more up-titrations occurred after 36 hours when titrated based on heparin anti-Xa assays. Infusions held due to elevated heparin anti-Xa assays in patients previously receiving DOACs occurred on average 0.841 times per patient. The rate of the UFH infusion was changed an average of 2.65 times per patient (33). In another study, Macedo et. al showed the average time for the heparin anti-Xa assay to reach the level of ≤ 0.7 IU/mL for apixaban and rivaroxaban was 52 hours and 39 hours respectively (35). In our study, consequently, monitoring the heparin anti-Xa assay according to the institutional protocol showed a significant decline in the heparin anti-Xa assay at 12 hours, as compared to baseline and at 6 hours. Despite a significant decline in the mean heparin anti-Xa assays, the residual effect of DOAC was still observed at 12 hours with an elevated heparin anti-Xa assay ranging from 0.22 to 1.45 IU/mL, which supports our observational findings of delayed initiating UFH therapy due to continue observing the residual effect of DOACs.

In clinical practice, due to the residual effect of DOACs, some institutions have implemented a dual protocol to monitor UFH specifying the use of aPTT monitoring for patients with recent use of DOACs and elevated heparin anti-Xa assay, otherwise, the heparin anti-Xa assay would be considered the primary protocol by default. The use of an aPTT monitoring protocol requires maintenance and up-to-date calibration according to available aPTT reagents. In institutions where aPTT is the monitoring protocol for UFH infusions, it has a significantly lower risk of laboratory confounding by recent DOAC use (35).

However, both assays have limitations. The aPTT lacks standardization and the sensitivity of reagents and coagulation factors varies among manufacturers. The heparin

anti-Xa assay has demonstrated less variability but is more likely to be affected by the use of LMWH, fondaparinux, DOACs, hyperbilirubinemia, and even hypertriglyceridemia (37). There are significant issues with the standardization of aPTT to heparin anti-Xa assays, given the variability between reagents and laboratory detection equipment used in the aPTT assay. Discordance occurred in 49% of cases between aPTT and heparin anti-Xa levels. In addition, it was noted that the aPTT was therapeutic only 35% of the time while the heparin anti-Xa level was therapeutic (32).

Despite advances in anticoagulation therapy in recent years, continuous intravenous UFH remains a cornerstone for inpatient anticoagulation management of NSTEMI. It is practical and advantageous in the acute care setting due to its rapid onset, short half-life, and reversibility (32).

Limitation

Overall, as a single-center, retrospective, observational study, we observed a significant delay in the initiation of UFH infusions for NSTEMI patients with recent use of DOACs. We are aware that our study population has a small sample size being a single-center study looking at a subset of the NSTEMI population on DOACs, which could be a limitation in observing the immediate outcome on a larger scale. The lack of an aPTT protocol and subsequent measurements in conjunction with the heparin anti-Xa assay limited the input of DOACs effect on aPTT and the management of UFH.

Conclusion

Monitoring UFH therapy by chromogenic heparin anti-Xa assay in patients with recent DOAC use posed a delay in treating NSTEMI at our institution. However, no immediate adverse outcomes were observed during the hospital stay. Literature addressed the challenge of transitioning from DOACs to UFH, but to our knowledge, it has not been documented in the NSTEMI population. Therefore, long-term outcomes of delayed management with UFH still remain obscure and close follow-up should be considered, especially in patients who are denied further ischemic evaluation.

Further studies should be considered to validate a single medication-specific assay protocol in monitoring UFH therapy with the recent use of DOACs for safe anticoagulation transition. Since heparin anti-Xa assay is the solo method of monitoring UFH in our institution, upcoming changes will be implementing an aPTT protocol to monitor UFH therapy in patients with recent use of DOACs, specifically those patients presenting with NSTEMI-ACS, as well as evaluating the risk of bleeding and thrombosis. We are only observing the tip of the iceberg and long-term effects are unknown. We hope for our concerns to be addressed in upcoming guidelines to provide further recommendations.

Acknowledgements

We would like to acknowledge Brittany Riley, Pharm.D, who is a Clinical Associate Professor and Director of the Center for Pharmacy Education at Cabell Huntington Hospital for her overall guidance.

Interest conflict

The authors declare no competing interests.

Author Contribution

Conceptualization: M.A.T.; writing-original draft prepara-

tion: M.A.T., R.A.S. and H.V.L.; investigation/methodology: M.A.T and R.A.S.; formal analysis and data curation: H.V.L.; writing-review and editing: M.A.T., R.A.S., H.V.L., S.E.J, L.G., R.S., T.D., E.T., K.S., B.S.G., R.T.S., M.E., M.D.L and M.A.S.; supervision: J.P.M.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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