PHARMACOTHERAPY

The Relationship between the Initial Anti-factor Xa Measurement and the Duration of Direct Oral Anticoagulant Influence in Patients Transitioning to Heparin

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Background Anticoagulation monitoring during transition from direct oral anticoagulants (DOAC) to heparin infusions is a significant challenge. Factor Xa inhibitors influence the heparin calibrated antifactor Xa assay. The University of Virginia (UVA) Medical Center utilized a corrected antifactor Xa assay (c-AXA) during this transition period, which removes DOAC-mediated antifactor Xa activity (d-AXA) and reflects heparin-specific activity. Currently, the duration of this influence is not well described.

Study Objective This study had two aims: to determine if the initial d-AXA is predictive of the duration of DOAC influence and to further characterize this influence among different patient populations.

Methods This retrospective study included adult patients admitted to UVA Medical Center between September 2016 and March 2017, with c-AXA measurements, who received apixaban or rivaroxaban within 48 hours before heparin initiation. A Pearson correlation test, Kaplan–Meier Survival Analysis, and multivariate linear regression were used to assess the relationship between initial d-AXA and duration of influence.

Results Sixty-eight patients met inclusion criteria and were maintained on either apixaban (85%) or rivaroxaban (15%) before heparin initiation. The initial d-AXA ranged from 0.11 to 3.27 IU/ml. The mean duration of influence was 69.3 ± 46.2 hours, with a median duration of 62.7 hours. No strong correlation was identified between initial d-AXA and duration of influence ($R^2 = 0.124$). Presence of interacting medications significantly increased duration of influence (p=0.012). No significant difference in duration of influence existed between patients with normal renal function and those with dynamic renal function (p=0.84), or with body mass index (BMI) greater than 40 kg/m^2 (p=0.16).

Conflict of interest: The authors declare no conflicts of interest for this article.

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Conclusions The initial d-AXA was not predictive of duration of influence in patients transitioning from DOACs to heparin infusion; however, the median duration of influence suggests influence may be present for longer than currently stated in the literature, especially in those taking interacting medications.

Key Words antifactor Xa assay, laboratory interference, heparin monitoring, anticoagulation, direct factor Xa inhibitors, pharmacokinetics, hematology.
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Patients often require temporary transition from oral anticoagulants to heparin infusion during hospitalization for a variety of reasons. Many institutions, such as the University of Virginia (UVA) Medical Center, utilize a heparin calibrated antifactor Xa assay (h-AXA) as the primary method of heparin monitoring.[1] Heparin binds to and produces a conformational change in antithrombin. This potentiates the action of antithrombin, leading to inactivation of unbound factors Xa and IIa (thrombin), thus preventing conversion of fibrinogen to fibrin. The h-AXA directly coincides with the mechanism of action of heparin and exclusively measures factor Xa activity. Alternatively, assays like the activated partial thromboplastin time (aPTT) are more global and account for activity in multiple parts of the coagulation cascade, such as factors XII, XI, X, IX, VIII, V, II (prothrombin), and I (fibrinogen). The aPTT is a nonspecific test that can be affected by several variables. Physiologic abnormalities, such as hyper- or hypofibrinogenemia and lupus anticoagulant, may prolong or shorten baseline aPTT, making it difficult to assess the level pharmacologic anticoagulation.[1,2] Compared with aPTT, use of the h-AXA assay has shown more rapid achievement of therapeutic anticoagulation levels for a longer duration, and with fewer dose adjustments.[2] The antifactor Xa assay (AXA) is a chromogenic assay that uses plasma and known amounts of a reagent containing factor Xa (FXa) to quantify antifactor Xa activity.[3]

Unfortunately, the use of h-AXA presents an obstacle when monitoring heparin in patients with recent administration of direct oral anticoagulants (DOACs). Specifically, direct FXa inhibitors can impact h-AXA causing an inaccurate measure of heparin-specific anticoagulation.[4–6] This creates difficulty as proper management of anticoagulation is essential to optimal patient care and clinical outcomes. Adjusting heparin infusions based on h-AXA while subtherapeutic DOAC activity is still present can lead to unwarranted rate changes and likely subtherapeutic levels of anticoagulation. Although the duration and degree of this activity remains uncharacterized, current literature recommends the use of alternative heparin monitoring methods, such as aPTT, for 48 to 72 hours after DOAC discontinuation.[5,7-12]

The UVA Medical Center implemented an alternative method to overcome DOAC influence on h-AXA called the "corrected anti-factor Xa assay" (c-AXA).[13] The c-AXA is a laboratory method that removes DOAC influence from the assay and reflects only heparin-specific activity (detailed in Figure 1). For purposes of this study, the DOAC-mediated activity on h-AXA will be referred to as d-AXA. This result itself cannot be used to quantify anticoagulation because the assay is calibrated for heparin, not a DOAC. It is currently unknown whether or not the initial degree of anti-Xa activity on the h-AXA (the initial d-AXA) is predictive of the duration of DOAC influence with h-AXA quantification. The primary purpose of this study was to characterize the duration of DOAC influence on the h-AXA and to determine if the initial d-AXA level is predictive of this duration. Secondarily, the effects of renal function, presence of interacting medications, and body mass index (BMI) on duration of DOAC influence were analyzed.

Methods

This retrospective study was performed at the UVA Medical Center and was approved by the local institutional review board. Patients 18 years and older who were admitted and transitioned from apixaban or rivaroxaban to heparin infusion between the dates of September 1, 2016, and March 1, 2017, were eligible for inclusion. Patients were identified on the basis of past orders for c-AXA in the electronic medical record (EMR). In the case of multiple eligible admissions, patients were included separately for each encounter. Patients were excluded if they did not receive heparin long

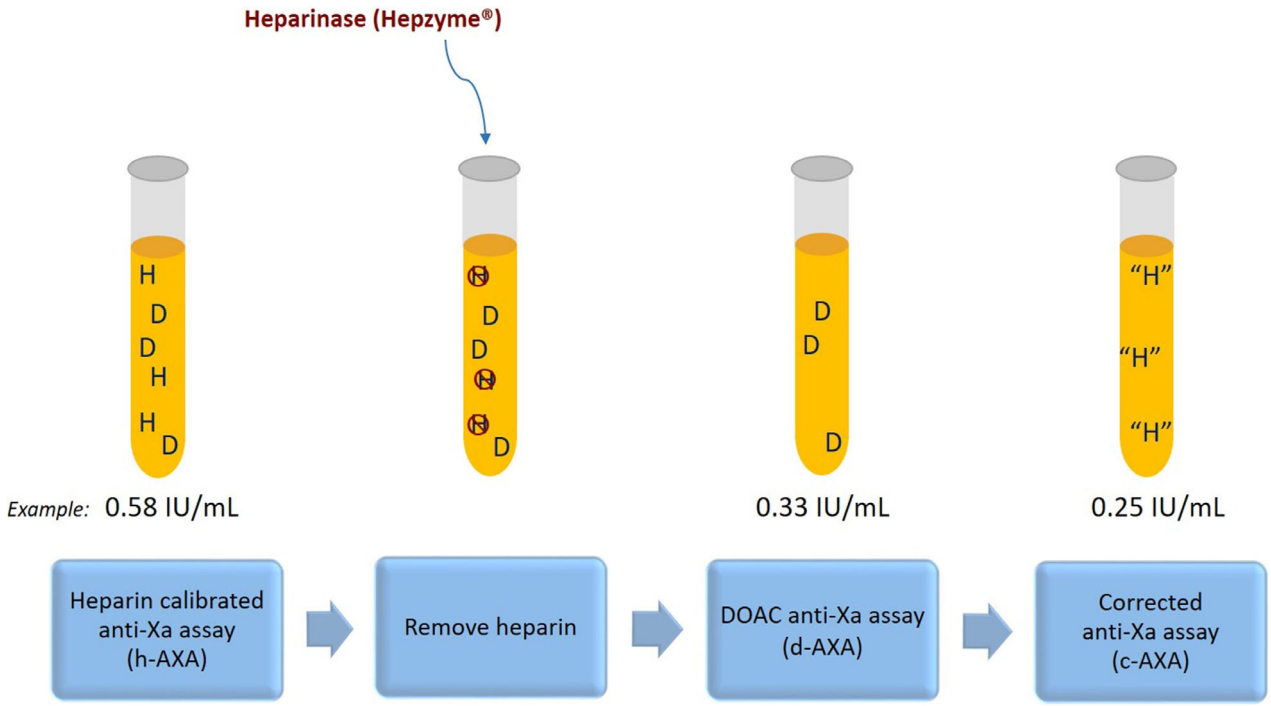

Figure 1. Corrected anti-factor Xa assay (c-AXA) laboratory method. The letter D represents presence of a direct oral anticoagulant (DOAC) in the blood sample, whereas H represents presence of heparin in the sample. An initial heparin calibrated anti-factor Xa assay (h-AXA) is measured. The sample is then treated with heparinase (Hepzyme) to neutralize heparin. The h-AXA is remeasured and the resulting level is referred to as the DOAC anti-factor Xa assay (d-AXA), which represents the magnitude of DOAC influence present on the h-AXA. The d-AXA is subtracted from the h-AXA, resulting in the c-AXA. The c-AXA is reflective of heparin-specific activity, absent DOAC influence. The c-AXA continues to be ordered for these patients until the laboratory determines DOAC influence no longer exists, defined as when d-AXA measures less than 0.1 international units per milliliter (IU/ml). Standard h-AXA levels resume thereafter. [Color figure can be viewed at wileyonlinelibrary.com]

enough to achieve an h-AXA free of DOAC influence, or if the initial d-AXA did not exhibit DOAC influence (< 0.1 IU/dl heparin units). Pregnant and/or incarcerated patients were excluded. Some patients were included in a previous publication about development of the laboratory method.[14]

Data were analyzed to determine if a correlation was present between the magnitude of the initial d-AXA level and the total duration of DOAC influence on h-AXA using a Pearson Correlation test to determine the coefficient of determination, R^2. Total duration of influence was measured from time zero (defined as the time from the last DOAC dose documented in the EMR), to the time when no DOAC anti-Xa activity was present (defined as d-AXA ≤ 0.1 IU/ml). A series of Kaplan–Meier curves with log rank tests were used to determine the total duration of influence and if renal dysfunction, interacting medications, or BMI ≥ 40 kg/m^2 impacted prevalence of DOAC influence at different time points. Normally distributed data were reported as average and standard deviation (SD), whereas nonnormally distributed data were reported as median and interquartile range (IQR).

To evaluate the impact of renal function on the duration of influence, patients were stratified into three groups designated as: "normal renal function," "stable chronic kidney disease (CKD)," or "dynamic renal function." Patients were included in the normal renal function group if serum creatinine remained at baseline (± 50%) of previous laboratory values in the EMR throughout the period when c-AXA levels were assessed. Presence of CKD was determined based upon previous diagnosis documented in the EMR and was considered stable if serum creatinine remained at their patient-specific baseline (± 50%) throughout the period of DOAC influence.[15] The dynamic renal function group included patients receiving peritoneal dialysis, hemodialysis, continuous renal replacement therapy (CRRT), or with acute kidney injury (AKI) during the period of DOAC influence based on serum creatinine elevations per the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[16]

Additional secondary analyses included the impact of interacting medications and BMI on the duration of influence. Moderate and strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) and/or p-glycoprotein (P-gp) were considered interacting medications per the apixaban and rivaroxaban package inserts.[17,18] BMI was calculated based on patient weight at the time of admission. Presence of liver disease was assessed using the EMR "search" function. The search terms, "hepatic," "cirrhosis," and "liver" were used to help identify presence of a liver disease diagnosis.

A multivariate linear regression was used to assess if the following eight patient factors impacted our result: age, gender, race, BMI, history of liver disease, initial d-AXA, interacting medications, and renal dysfunction. All statistical analysis was performed using IBM SPSS software and Microsoft Excel.

Laboratory Method: Corrected Anti-factor Xa Assay

The c-AXA was determined using a multistep process.[14] An initial h-AXA was performed on an ACL TOP analyzer using the HemosIL anti-Xa assay, produced by Instrumentation Laboratory. The plasma sample was then treated with heparinase, the Dade Hepzyme reagent for heparin neutralization. An h-AXA is remeasured and the resulting level is referred to as the d-AXA, which represents the magnitude of DOAC influence in heparin units (IU/ml). The d-AXA is subtracted from the h-AXA, resulting in the c-AXA. The c-AXA is reflective of heparin-specific activity. The c-AXA continues to be ordered for these patients until the laboratory determines DOAC influence no longer exists, specifically when d-AXA measures less than 0.1 IU/ml (heparin units). Standard h-AXA levels resume thereafter (Figure 1). Further details describing the c-AXA laboratory method can be found in Strickland and colleagues.[14]

The h-AXA detects the presence of a DOAC in the blood, but this result has not been correlated to the level of anticoagulation or clinical efficacy. Therefore, the c-AXA is not used to determine how much anticoagulation the DOAC is providing, but rather how much it is altering the h-AXA, which is used for anticoagulation adjustment. This method allows for continued use of the h-AXA to monitor heparin-mediated anticoagulation in the setting of recent DOAC use, rather than switching to alternative assays for unclear durations.

Results

Patients

Of 141 patients screened, 68 were eligible for inclusion. Patients were excluded if heparin therapy was completed before reaching "no DOAC influence" with d-AXA $\leq$ 0.1 IU/ml (76%), DOAC activity was not present on initial d-AXA level (17%), incarceration (6%), and one patient was switched to aPTT monitoring (1%). Before heparin infusion initiation, the majority of included patients were maintained on apixaban (85.3%), followed by rivaroxaban (14.7%), and no patients had received edoxaban or betrixaban. The mean age was 58 $\pm$ 18.23 years (Table 1).

Primary Outcome

No strong correlation was observed between the magnitude of the initial d-AXA level and the total duration of DOAC influence on h-AXA

Table 1. Baseline Characteristics (N=68)

Gender, n (%)	
Female	35 (51.5)
Race, n (%)	
White	53 (77.9)
African American	13 (19.1)
Other	2 (2.9)
Age, years $\pm$ SD	58 $\pm$ 18.23
DOAC, n (%)	
Apixaban	58 (85.3)
Rivaroxaban	10 (14.7)
DOAC indication, n (%)	
History VTE	36 (52.9)
Atrial fibrillation	24 (35.3)
Coagulation disorder[a]	3 (4.4)
Malignancy	2 (2.9)
Other[b]	3 (4.4)
DOAC dosing, n (%)	
Apixaban	
5 mg twice daily	47 (69.1)
2.5 mg twice daily	11 (16.2)
Rivaroxaban	
20 mg daily	7 (10.3)
15 mg daily	3 (4.4)
Liver disease, n (%)	4 (5.9)
BMI, mean $\pm$ SD, kg/m^2	30.6 $\pm$ 10.1
> 40 kg/m^2, n (%)	8 (11.8)

BMI = body mass index; DOAC = direct oral anticoagulant; kg/m^2 = kilogram per meter squared; SD = standard deviation; VTE = venous thromboembolism.

[a]Includes antiphospholipid syndrome, factor 5 Leiden, antithrombin 3 mutation.

[b]Includes congenital heart defect, renal artery stenosis, and inferior vena cava graft.

levels (R^2 = 0.124; p=0.003). Higher degrees of DOAC influence were not predictive of longer durations of influence (Figure 2).

Regarding the total duration of influence, the prevalence of continued influence was 73% and 33% at 48 and 72 hours after the last documented DOAC dose, respectively (Figure 3). The median duration of influence was 62.74 hours (IQR = 35.23). However, one patient continued to exhibit apixaban influence for 390.9 hours in the presence of interacting medications (amiodarone and diltiazem infusions) and AKI requiring new start CRRT.

Secondary Outcomes

Thirty-eight patients (55.9%) demonstrated some degree of renal dysfunction at baseline or during the study period. Dynamic renal function was the most common type and was found in 39.7% of the study population (Table 2). When patients were categorized into groups based on renal function, there was no significant difference in duration of influence between groups (p=0.84; Figure 4).

Seventeen patients (25%) received concomitant medications with documented interactions with apixaban or rivaroxaban. Of this subgroup, 16 patients received a CYP 3A4 and/or P-gp inhibitor, whereas one patient received phenytoin, a strong CYP 3A4 and P-gp inducer. Amiodarone was the most common inhibitor (68.8%), followed by azithromycin (25%), and diltiazem (6.3%). Patients receiving concomitant inhibitors had a significantly longer duration of influence as compared with those without interacting medications (p=0.012; Figure 4).

The mean BMI for all patients was 30.6 ± 10.1 kg/m^2. Eight patients had a BMI of greater

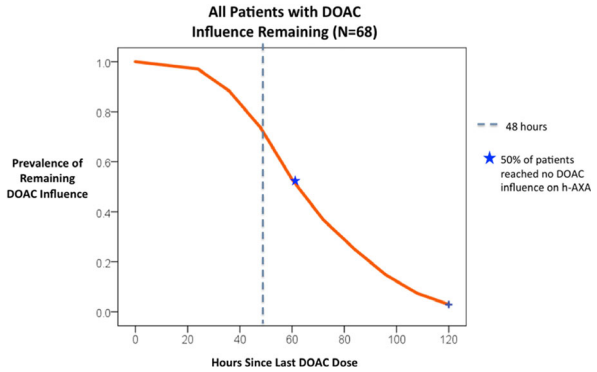

Figure 3. Prevalence of direct oral anticoagulant (DOAC) influence remaining after DOAC discontinuation. According to the above Kaplan–Meier curve, greater than 75% of patients still experienced DOAC influence on the heparin calibrated antifactor Xa assay (h-AXA) at 48 hours after the last DOAC dose. It took greater than 100 hours for 90% of patients to reach no DOAC influence. [Color figure can be viewed at wileyonlinelibrary.com]

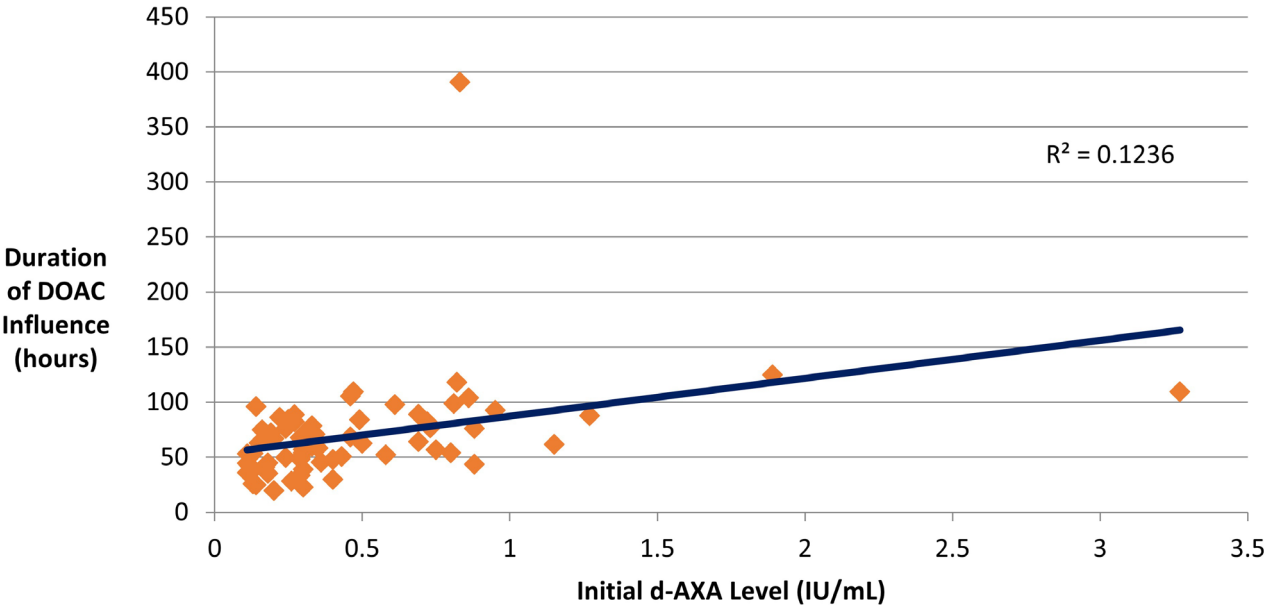

Figure 2. Duration of direct oral anticoagulant (DOAC) influence based on initial DOAC-mediated antifactor Xa activity (d-AXA) level. The initial d-AXA is plotted for each patient. A Pearson test was applied to the data and returned an R^2 value of 0.124, which is representative of no correlation. Statistical significance was present (p=0.003) but is unlikely clinically significant due to the low R^2 value. Based on this data, one can conclude that the magnitude of the initial DOAC influence (the initial d-AXA) is not predictive of total duration of influence. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2. Degree of Renal Dysfunction (n=38), n (% of total study population)

Stable CKD	11 (16.2)
Dynamic renal function	27 (39.7)
AKI on CKD	13 (19.1)
AKI without CKD	8 (11.8)
HD	3 (4.4)
PD	2 (2.9)
CRRT	1 (1.5)

AKI = acute kidney injury; CKD = chronic kidney disease; CRRT = continuous renal replacement therapy; HD = hemodialysis; PD = peritoneal dialysis.

than 40 kg/m^2 (11.8%). There was no significant difference in duration of influence when those with BMI less than 40 kg/m^2 were compared with those with BMI greater than 40 kg/m^2 (Figure 4). The mean BMI of each group was 28.0 kg/m^2 and 50.6 kg/m^2, respectively.

Multivariate Linear Regression

A multivariate linear regression model was run to evaluate the influence of eight variables (age, gender, race, BMI, history of liver disease, initial d-AXA, interacting medications, and renal dysfunction), on the total duration of DOAC influence on h-AXA. The overall model was found to be significantly associated with total duration of influence (p=0.03) based on analysis of variance (ANOVA). Three of the eight variables, BMI, renal dysfunction, and initial d-AXA, were found to be significantly associated, but weakly correlated (R^2 = 0.149), with duration of influence. Details of the multivariate analysis can be found in Table 3.

Discussion

Primary Outcome

Current literature recommends against use of h-AXA for monitoring heparin within the first 48 hours after DOAC discontinuation, and for up to 72 hours in patients with renal or hepatic impairment.[13] A recent study by Macedo and colleagues suggested DOAC influence could be present for 18 to 117 hours.[19]

The results of this study were similar, with the majority of cases exhibiting DOAC influence for greater than 60 hours and some for greater than 120 hours. The majority of cases suggest DOAC influence with the h-AXA assay beyond 48 hours, raising concerns about the length of time an alternative heparin monitoring method should be used. The current recommendations

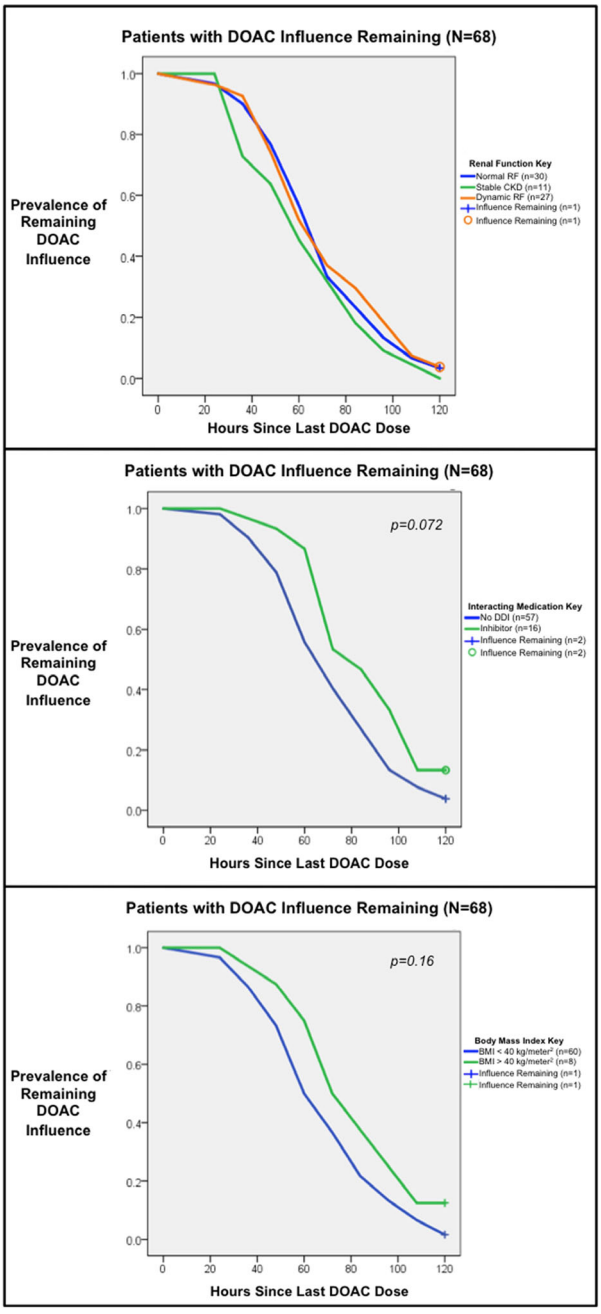

Figure 4. Secondary outcomes. Each of the above Kaplan–Meier curves represents prevalence of remaining direct oral anticoagulant (DOAC) influence at hourly time points after the last DOAC dose. Patients were stratified into cohorts based on renal function, interacting medications, and body mass index to assess for differences in duration of influence. [Color figure can be viewed at wileyonlinelibrary.com]

to use alternative measures of heparin monitoring during the first 48 hours may risk subtherapeutic anticoagulation after transition back to h-AXA monitoring. The results of this study suggest that at the 48-hour time point, DOAC influence likely remains, thus the h-AXA will

Table 3. Multivariate Linear Regression (N=68)

Variable	Unstandardized B	Significance (p)	95% Confidence interval
Age	0.66	0.06	−0.01–1.33
Gender	−10.30	0.36	−32.57–11.97
Race	−1.45	0.88	−19.96–17.06
BMI	1.22	0.04	0.09–2.36
History of liver disease	−2.66	0.91	−50.08–44.764
Initial d-AXA	34.68	0.01	11.07–58.28
Interacting medication	5.36	0.45	−8.78–19.49
AKI Stage (KDIGO)	−16.65	0.04	−32.64–(−0.67)
CKD Stage (NKF KDOQI)	−1.80	0.61	−8.83–5.23

AKI = acute kidney injury; BMI = body mass index; CKD = chronic kidney disease; d-AXA = DOAC anti-factor Xa assay; KDIGO = Kidney Disease, Improving Global Outcomes (guideline); NKF KDOQI = National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (guideline).

not be reflective of heparin-specific activity 48 hours after DOAC discontinuation. Based on the results of the current study, it may be prudent to consider alternative methods to h-AXA for heparin monitoring for an extended period of time after the last DOAC dose. Using alternative monitoring for 96 hours after the last dose would be expected to avoid greater than 80% of the observed DOAC influence. The c-AXA has been a reliable and practical option at our institution.

Although significantly correlated, the initial DOAC level is unlikely to be clinically useful in predicting the total duration of DOAC influence on the h-AXA. The overall variance in duration was only weakly explained by changes in the initial DOAC level based on a low R^2 value.

Secondary Outcomes

Categorization of renal function was not associated with the duration of DOAC influence. Available data suggest that apixaban demonstrates a relatively modest level of renal elimination (27%), and our sample was predominantly composed of patients maintained on apixaban.[18] A potential difference may exist with a larger sample of patients who received rivaroxaban or edoxaban, as they are more dependent on renal elimination, 66% and 50%, respectively.[17,20] The predominance of apixaban in this study is likely due to institution-specific prescribing preferences.

Patients who were taking medications that could potentially inhibit the metabolism of apixaban or rivaroxaban required c-AXA levels for significantly longer than those who were not. This finding is particularly of interest because DOACs are rarely dose adjusted for interacting medications outside of apixaban for dual strong CYP3A4 and P-gp inhibitors. No concomitant medications in this study are classified as both strong and dual inhibitors.

The use of DOACs in patients with a BMI greater than 40 kg/m^2 is not recommended per International Society of Thrombosis and Hemostasis (ISTH) 2016 guidelines due to lack of clinical data for their safety and efficacy in this patient population.[21] Although current recommendations do not support use in these patients, DOACs are used due to limited alternative options. In order to utilize DOACs in those with BMI greater than 40 kg/m^2 at UVA Medical Center, hematology must be consulted and mass spectrometry levels may be obtained at the prescribing physician's discretion. It was not apparent that the 8 patients in this study with BMI greater than 40 kg/m^2 had any differences in DOAC clearance compared with patients with a lower BMI. However, rivaroxaban likely distributes to the tissues more extensively than apixaban with a volume of distribution of 50 liters, compared with 21 L for apixaban.[17,18] Conversely, past studies have found that DOAC half-lives are reduced in patients with BMI greater than 40 kg/m^2.[21]

When analyzed with a multivariate model, BMI, renal dysfunction, and initial d-AXA were statistically significant contributors to the prediction of the total duration of DOAC influence on the h-AXA. However, despite statistical significance, only a weak correlation exists based on a low R^2 value; therefore, it is unlikely clinically significant and is unlikely to improve our ability to predict the duration of influence. The multivariate model was not more predictive of total duration of influence than the univariate model. The results of the multivariate analysis are hypothesis generating and further research would be helpful to further characterize the influence of these variables on DOAC clearance.

Limitations and Future Directions

Limitations of the current study include the following: retrospective design, small sample size, and the population predominantly received

apixaban as opposed to other DOACs. The sample size was lower than predicted as many patients completed heparin therapy before reaching "no DOAC influence." This resulted in exclusion because total duration of influence could not be calculated. The smaller sample size limited the ability for subgroup comparison of the different levels of renal dysfunction and different DOAC agents. The current study is largely reflective of apixaban given the limited number of rivaroxaban patients included, and no eligible patients who received edoxaban or betrixaban. Therefore, we recommend using caution when generalizing the results to all FXa inhibitors. This is an area that warrants future research in order to evaluate individual DOACs.

Other approaches could be used to neutralize the effect of the DOAC. There are available materials, such as DOAC Stop, which are marketed as removing DOACs. However, there are studies suggesting that not all of the DOAC is removed[22] and that there can be residual inhibition from the DOAC in the anti-Xa assay.[23] The method presented herein allows for using the aPTT to ensure that the heparin has been removed. There is not a laboratory test that could be used as a quality measure to ensure removal of DOAC with heparin present.

Last, patients who had taken a DOAC in greater than 48 hours preceding a heparin infusion were not included in this study. In order to be included, c-AXA levels must have been collected. The current heparin infusion order at UVA Medical Center determines if c-AXA or standard h-AXA will be used depending on if a DOAC was taken in the last 48 hours. However, the results of this study suggest that DOAC influence typically remains for longer than 48 hours. The UVA Medical Center heparin infusion order has now been updated to reflect this increased duration of influence.

While we continue to gain understanding of the DOACs and their effects on traditional anticoagulation assays, there are many areas yet to be explored. A comparison of DOAC influence on h-AXA between individual DOACs could be useful due to their differing levels of renal elimination and volumes of distribution. In addition, the effect of interacting medications, specifically CYP3A4 and/or P-gp inducers, could be further described as the patients included in this study were predominantly taking inhibitors. Pharmacokinetic modeling of the d-AXA could potentially provide further insight into the duration of DOAC influence on the h-AXA.

Conclusion

Based on the results of the current study, it is reasonable to utilize alternative methods to h-AXA for heparin monitoring for 72 to 96 hours after DOAC discontinuation in order to minimize the risk of influence on the h-AXA in a majority of patients. This window of influence may be further extended in patients receiving interacting inhibitors. The c-AXA is a novel approach to manage this challenge by attempting to quantify ongoing DOAC influence.

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