

Influence of Direct Oral Anticoagulants on Anti-Factor Xa Measurements Utilized for Monitoring Heparin

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Abstract

Background: Unanticipated drug-laboratory interactions may occur between **direct oral anticoagulants (DOACs)** and anti-factor Xa (AXA) levels used to monitor parenteral heparin infusions. Characterization of the extent and duration of DOAC effect on AXA levels may reduce complications with transition to heparin infusions. **Objective:** To evaluate the impact of oral factor Xa inhibitors on AXA levels with and without concurrent heparin. **Methods:** This retrospective descriptive study was approved by institutional review board waiver and included patients with AXA levels drawn on a heparin calibrated assay who had received a factor Xa inhibitor. Participants were divided on the basis of whether AXA levels were drawn with concurrent parenteral heparin. If transitioned to heparin, number of AXA draws required until AXA level was within therapeutic range was recorded. **Results:** A total of 50 patients (60% rivaroxaban, 40% apixaban) met inclusion criteria. When AXA levels were drawn within 12 hours of apixaban without concurrent heparin ($n = 7$), 71% were greater than 1 IU/mL, and 29% were below suggested trough levels (0.7–1.1 IU/mL). For AXA levels drawn within 24 hours of rivaroxaban without concurrent heparin ($n = 11$), 55% were greater than 1 IU/mL, 9% were within suggested trough (0.6–1 IU/mL), and 36% were below 0.6 IU/mL. In patients ($n = 28$) who were initiated on heparin infusion prior to AXA monitoring, administration of the DOAC within the prior 72 hours resulted in supratherapeutic initial AXA levels 69% of the time. **Conclusion:** DOACs may cause elevations in heparin-calibrated AXA assays; this creates problematic challenges in using the AXA level to optimize heparin management.

Keywords

anticoagulants, anticoagulation, cardiology, clinical practice, drug monitoring, hematology, heparin, interactions

Since the approval of the first direct oral anticoagulant (DOAC) dabigatran, this class has grown in size and popularity. With the subsequent addition of rivaroxaban, apixaban, and edoxaban, there are now multiple alternatives to warfarin for oral anticoagulation for nonvalvular atrial fibrillation and venous thromboembolism (VTE). Preference is given to the DOAC agents over vitamin K antagonist therapy for non-cancer patients with deep-vein thrombosis (DVT) or pulmonary embolism (PE) in the 2016 CHEST Guidelines for Antithrombotic Therapy for VTE Disease and for atrial fibrillation patients in the 2012 CHEST Guidelines for Antithrombotic Therapy for Atrial Fibrillation.^{1,2} As a result of these updated guideline recommendations and typical patient preference to avoid routine laboratory monitoring, DOAC prescribing has increased.³

Although DOACs are marketed as unmonitored medications, clinical situations exist where it may be necessary to detect and quantify the presence of residual anticoagulant effect.^{4–6} This includes situations such as overdose, suspected

patient nonadherence, renal failure, need for emergent surgery, and transition to alternate anticoagulation. Despite this, there are limited data for correlation of existing laboratory coagulation tests with therapeutic DOAC levels.

In response, a small number of studies have investigated the most useful laboratory tools for DOAC monitoring. Collectively, these publications suggest that the anti-factor Xa (AXA) laboratory assay has quantitative utility for measurement of DOACs in the factor Xa inhibitor class.^{7–15} Factor Xa inhibitors include edoxaban, apixaban, and rivaroxaban; dabigatran is unique as an oral direct thrombin inhibitor. Standard unfractionated heparin (UFH)– and low-molecular-weight heparin (LMWH)–calibrated AXA assays

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measure inhibition of activated coagulation factor X by the heparin-antithrombin complex.¹⁶ Although methods to directly measure AXA activity using calibrators for the factor Xa inhibitors exist, these methods are not currently FDA approved and, therefore, have limited availability.^{7,12} As such, correlation of DOAC concentrations with available heparin-calibrated AXA assays may offer certain clinical benefits. All further references to AXA levels within this publication refer to AXA levels drawn on a heparin hybrid calibrated machine.

Wendte et al¹⁷ describe an average AXA level of 1.8 IU/mL in patients taking apixaban, as reported in personal communication from Bristol-Meyers Squibb; however, peak and trough ranges are not provided. To this end, Beyer et al⁷ tested apixaban and rivaroxaban concentrations in both spiked and patient-treated samples against heparin-calibrated AXA assays. By the use of serial dilution, they correlated apixaban steady-state peak and trough concentrations with AXA ranges of 1.8 to 2.2 IU/mL and 0.7 to 1.1 IU/mL, respectively. Rivaroxaban concentrations were associated with AXA levels of 3.8 to 6.2 IU/mL (peak) and 0.6 to 1 IU/mL (trough).⁷ These data corroborate earlier findings by Osanai et al⁸ in 124 patients with nonvalvular atrial fibrillation on apixaban. Steady-state AXA levels were similar to that found by Beyer et al, with an average of 2.05 IU/mL at the peak and 1 IU/mL at the trough.

Although the above-referenced publications provide baseline expectations for the effect of factor Xa inhibitors on AXA levels, they do not address the complexities that arise when transitioning from these agents to parenteral UFH infusions. Historically, UFH infusions have been adjusted on the basis of activated partial thromboplastin time (aPTT). However, aPTT reagents can exhibit significant variability, and values can be influenced by underlying disease states, such as lupus and antiphospholipid antibody syndromes.¹⁶ Because of this, the study institutions switched from the use of aPTT to AXA for the monitoring of UFH infusions. The AXA monitoring protocol is similar to standard aPTT protocols, with serial monitoring of AXA levels and subsequent infusion rate adjustment every 6 hours until the level is within the defined therapeutic range (0.3 to 0.7 IU/mL). However, an increase in supratherapeutic AXA levels has been noted in recent years and was found to be related to DOAC use.

Thus, our primary objective was to quantify the extent and duration of AXA effect attributable solely to recent DOAC administration. Additionally, in DOAC patients transitioned to an UFH infusion, our secondary objectives were to determine the influence of DOAC administration within the prior 72 hours on the initial AXA level drawn on an UFH infusion and to evaluate the number of AXA lab draws necessary before the value fell within therapeutic range.

Methods

Study Design

This study was a retrospective chart review of the electronic medical record (EMR) of 3 affiliated community hospitals. An institutional review board waiver was obtained for the purposes of completion of this retrospective review.

Patient Selection and Data Collection

A search of the EMR from October 1, 2015, to June 1, 2016, was conducted to identify patients who had one or more laboratory AXA levels drawn and had received apixaban, rivaroxaban, or edoxaban immediately prior to admission or while inpatients. Charts that met these criteria were assessed for a temporal relationship between last administered dose of DOAC and timing of AXA draw. The timing of the last administered dose of DOAC was determined by either EMR documentation or patient self-reporting. If the last dose of DOAC was given within 72 hours prior to collection of the AXA level, there was considered to be a potential for DOAC residual effect, and these patients met study inclusion criteria. A cutoff point of 72 hours was chosen based on the half-life of up to 13 hours for rivaroxaban and 12 hours for apixaban and the assumption of near complete elimination after 5 half-lives.^{4,5}

Demographic data were collected on all patients meeting inclusion criteria. Reported data included age, weight, height, baseline and admission serum creatinine, international normalized ratio, DOAC dosing, and indication for anticoagulation.

Confounding factors with potential to influence AXA levels or DOAC concentration were also recorded. Cases were screened for administration of medications known to independently elevate AXA levels, including UFH, LMWH, and parenteral factor Xa inhibitors. Factors expected to elevate or prolong DOAC serum concentrations were reviewed, including development of acute renal failure (defined as acute rise in serum creatinine of 0.5 mg/dL or greater) and concomitant use of interacting drugs with the potential to slow DOAC elimination. These were reviewed during data analysis as potential contributors to outliers and variability.

DOAC regimens were also reviewed for dose appropriateness per manufacturer labeling, based on indication for anticoagulation and patient-specific variables, including age, weight, and renal function.

AXA levels were analyzed on the STA-Multi-Hep Calibrator with STA-Liquid Anti-Xa hybrid reagent (Diagnostics Stago, Parsippany, NJ) and were reported up to the upper limit of detection of the heparin-calibrated assay of 1 IU/mL. These values were categorized into 2 groups based on the presence or absence of heparin administration in the immediate time period prior to AXA lab retrieval. In the absence of concurrent heparin use, AXA

Table 1. Baseline Patient Characteristics.

| | Apixaban (n = 20) | | | Rivaroxaban (n = 30) | | |
|--|--------------------------------|----------|-----------|----------------------|-----------|----------|
| Age (range) | 75 (63-91) | | | 66 (39-95) | | |
| Male | 45% | | | 57% | | |
| Acute renal failure (ie, SCr increase by 0.5 mg/dL or greater) | 25% | | | 23% | | |
| Drug-drug inhibitory interactions | 65% (PGP or CYP3A4 inhibitors) | | | 0% | | |
| Inappropriate dose | 35% | High: 0% | Low: 100% | 13% | High: 75% | Low: 25% |
| Indication | Afib | | | 57% | | |
| | PE/DVT | | | 30% | | |
| | Afib + DVT/PE | | | 13% | | |
| | Other | | | 0% | | |
| | 5% (CVA) | | | | | |

Abbreviations: Afib, atrial fibrillation; CVA, cerebrovascular accident; CYP, cytochrome P450; DVT, deep-vein thrombosis; PE, pulmonary embolism; PGP, P-glycoprotein; SCr, serum creatinine.

levels drawn within the 72-hour cutoff were assessed as a function of the DOAC dose alone and were classified as being either within or beyond the DOAC dosing interval. DOAC dosing interval was defined as 12 hours for apixaban and 24 hours for rivaroxaban. Alternatively, in those patients who were transitioned to UFH, the initial AXA level was obtained approximately 6 hours after UFH initiation per the institution's protocol, and the total number of AXA measurements required until the value reached the desired therapeutic range (0.3-0.7 IU/mL) was recorded. Finally, total hours elapsed from time of administration of DOAC dose to time of therapeutic AXA level on UFH was calculated to estimate the potential duration of the confounding effect.

Results

A total of 161 patients were identified on initial screening who had laboratory AXAs and orders for a factor Xa inhibitor. Of these patients, a total of 50 met all inclusion criteria for temporal association between DOAC administration and AXA collection. Participants were divided into 60% on rivaroxaban (n = 30), 40% apixaban (n = 20), and 0% edoxaban. Because of the small sample size and inherent inability to adhere to standardized protocols with a retrospective review, statistics listed as follows are descriptive only.

Baseline characteristics were evenly divided by gender (52% male, 48% female) with an average age of 70 years (range = 39-95 years) and average weight of 88 kg (range = 52-137 kg). Approximately a quarter of patients in both groups (Table 1) developed acute renal failure while inpatients. All apixaban patients were on a renally adjusted dose if indicated by serum creatinine, age, and weight. However, 35% of apixaban patients were on an off-label reduced dose. This included patients on renal dosing of apixaban 2.5 mg twice daily despite an indication of PE/DVT (for which no renal adjustment is recommended) or for atrial fibrillation despite meeting only 1

or none of the criteria for dose reduction. Conversely, the majority of rivaroxaban patients on dosing that varied from the package insert (13%) were on an inappropriately high dose, comprising patients for whom renally reduced dosing was indicated but the dose was not appropriately adjusted. Only 1 patient was on an inappropriately low dose (prophylaxis dose of 10 mg daily) when treatment dosing was indicated.

Drug-drug interactions were identified in 65% of apixaban patients; however, these were caused by diltiazem or carvedilol with only moderate effects on CYP3A4 and P-glycoprotein inhibition, respectively. No relevant drug-drug interactions with potential to slow elimination were identified in those on rivaroxaban.

Seven patients on apixaban had AXA levels drawn within the dosing window (within 12 hours after the last dose) that were not affected by prior administration of heparin. Of these patients, a total of 5 (71%) had AXA levels >1 IU/mL. The remaining patients (n = 2) had AXA levels reported below the suggested trough range as per Beyer et al.⁷ An AXA level of 0.68 was reported 8 hours post-apixaban dose in a 66-year-old patient with no pertinent distinguishing factors, and an AXA level of 0.26 was reported 11 hours post-apixaban dose in a patient with conversely confounding factors of obesity (124 kg) and acute renal failure. Interestingly, 1 patient had an AXA level drawn 27 hours after an apixaban 5-mg dose that remained detectable at 0.51 IU/mL despite no renal impairment.

AXA levels drawn within 24 hours of a rivaroxaban dose in patients not currently on alternate anticoagulation were above 1 IU/mL 55% of the time (6 out of 11 total patients). Four patients in this group had AXA levels below the suggested trough range of 0.6 to 1 IU/mL, per Beyer et al.⁷ However, one of these AXA levels was drawn only 1 hour post-drug administration, and, thus, likely does not represent full absorption and distribution of the drug. Another AXA level resulted as undetectable (<0.1 IU/mL) 13 hours postdose; however, the patient was on an inappropriate dose

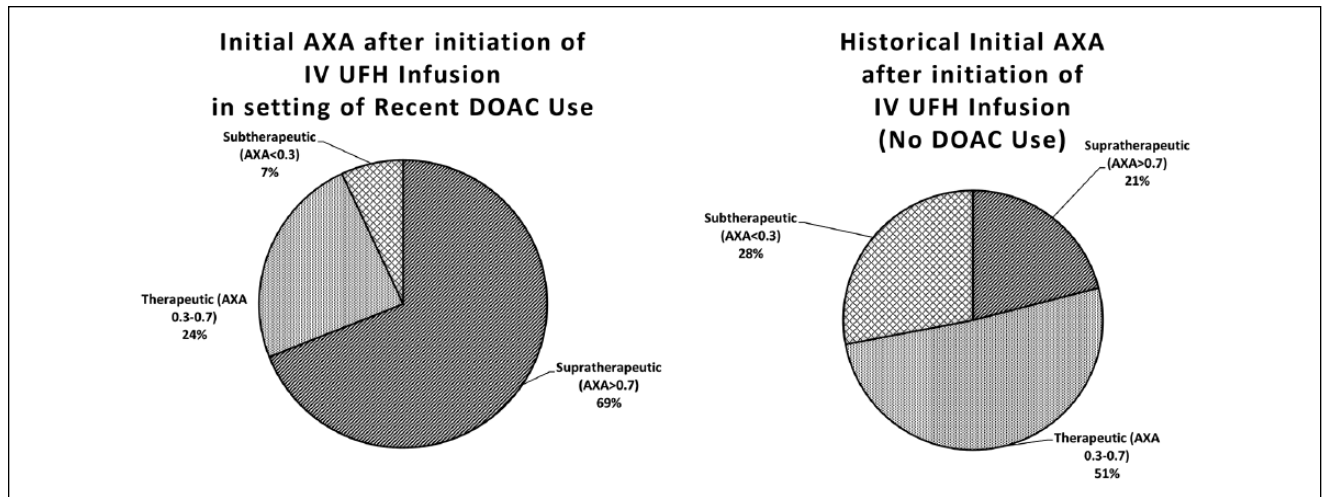


Figure 1. Influence of DOAC Therapy on Initial AXA Levels.

Abbreviations: AXA, anti-factor Xa; DOAC, direct oral anticoagulant; IV, intravenous; UFH, unfractionated heparin.

Table 2. AXA Level Monitoring on UFH with Recent DOAC Use.

| DOAC | Number of AXA Draws After UFH Initiation Until AXA Level Within Therapeutic Range ^a (Average) | Hours After Last DOAC Dose Until First AXA Level ≤0.7 (Average) |
|-------------|--|---|
| Apixaban | 1-8 (3.25) | 18-117 (52) |
| Rivaroxaban | 1-5 (1.7) | 19-62 (39) |

Abbreviations: AXA, anti-factor Xa; DOAC, direct oral anticoagulant; UFH, unfractionated heparin.

^aTherapeutic range = 0.3-0.7 IU/mL.

of rivaroxaban 10 mg daily for DVT. The remaining 2 AXA levels that were less than 0.6 IU/mL within the first 24 hours postdose were drawn on patients in whom the last dose was administered prior to admission with some concerns about adherence and accuracy of last dose reported. Finally, 2 AXA levels were found to be detectable beyond the dosing window of rivaroxaban but within the 72-hour review cut-off. One patient had an AXA level of 0.86 IU/mL 63 hours post-rivaroxaban 20-mg dose in the setting of acute renal failure (serum creatinine rise from 0.5 to 1.1 mg/dL), whereas another had an AXA level of 0.36 IU/mL 33 hours post-15-mg dose in the absence of acute changes in renal function but with a baseline estimated creatinine clearance of 30 mL/min.

In the separate group of patients transitioned from DOACs to UFH infusions ($n = 28$), initial AXA levels were supratherapeutic for the institution's goal range (0.3 to 0.7 IU/mL) 69% of the time (Figure 1). A minority (7%) were less than 0.3 IU/mL in the setting of DOAC administration prior to initiation of the heparin drip, whereas approximately a quarter fell within the therapeutic range on first check. On average, patients who had received an apixaban dose prior to starting a heparin drip required 3.25 serial AXA draws before the level fell to 0.7 IU/mL or less, with a maximum of 8 draws required (Table 2). For rivaroxaban,

the average number of serial AXA levels drawn prior to reaching a therapeutic level was lower at 1.7, with 5 being the maximum drawn on any 1 patient.

Discussion

The real-world findings of this study provide support that heparin-calibrated AXA levels are elevated by rivaroxaban and apixaban to at least the minimums reported previously by Beyer et al⁷ and Osanai et al.⁸ Notably, the majority of AXA levels within the dosing window of these agents were above or within the trough levels previously suggested, validating previously published findings. Furthermore, outliers in both the apixaban and rivaroxaban groups remained detectable beyond the dosing window, up to 63 hours post-dose. This suggests that in certain patient scenarios, the confounding effect on AXA levels may be prolonged considerably beyond the dosing interval and corroborates the findings reported by Wendte et al¹⁷ and Faust et al¹⁸ of AXA elevation for up to 96 hours in the setting of renal failure.

This study also highlights logistical concerns in the transition from a DOAC to an UFH infusion in institutions where UFH infusions are titrated to AXA ranges. In the absence of baseline monitoring of AXA values, this study found that UFH infusions were initiated at variable time

points post-DOAC dose and, in some cases, were sequentially reduced or shut off entirely because of elevated AXA values. Ongoing supratherapeutic values led to redundant AXA monitoring (every 6 hours per protocol), with negative implications on cost and patient convenience. When compared with historical data at our institution, there is a striking difference in the prevalence of initial supratherapeutic AXA levels on UFH infusions (Figure 1). In the absence of DOAC use, a minority (21%) of initial AXA levels were supratherapeutic. With recent DOAC use, however, supratherapeutic AXA levels are the majority at 69%.

Moreover, one must consider potential bleeding and clot risks that arise with confounded laboratory values during an overlap of duplicate anticoagulation. While the addition of a baseline AXA level prior to starting an UFH infusion will help identify those patients in whom residual DOAC effect remains, one must also consider how low that value must be for it to be appropriate to start the UFH infusion. Although AXA elevation caused by DOAC agents cannot be compared on an IU/mL basis against therapeutic ranges set for UFH infusions, a potential for overanticoagulation exists with the addition of heparin to an unquantifiable DOAC effect (eg, in cases where baseline AXA levels are reported to a maximum of “greater than 1”). Certainly, a baseline AXA level of 6.2 IU/mL (as with rivaroxaban peaks) would warrant more pause than a level of 1.2 IU/mL, but this distinction may not be available to clinicians because of laboratory constraints.

Alternatively, holding or reducing an UFH infusion because of a DOAC-induced elevated AXA level may also pose undue harm to patients undergoing an acute thrombotic event. This dilemma is accentuated by the absolute difference between the upper limit of suggested “trough” values for apixaban and rivaroxaban, at 1 to 1.1 IU/mL^{7,8} (at which time alternative anticoagulation should be started), and the upper limit of the therapeutic range for UFH (0.7 IU/mL at our institution). Thus, risk versus benefit must be assessed on a patient-by-patient basis. In reaction to these findings, our institution considers initiation of UFH infusion without initial bolus once the AXA level falls to <1 IU/mL (high clot risk) or 0.7 IU/mL (lower clot risk), with the caution that lower infusion rates may initially be needed if starting with an already elevated AXA level. Notably, use of aPTT monitoring during the period of residual DOAC effect may be considered. However, this requires maintenance of an alternative aPTT monitoring protocol and up-to-date calibration of aPTT ranges based on available aPTT reagents.

In institutions where aPTT remains the monitoring parameter for UFH infusions, there is considerably lower risk of laboratory confounding by recent DOAC use. However, based on data that DOAC influence may extend beyond the normal dosing interval when drug clearance is slowed, further consideration should be given to whether

these patients are receiving duplicate anticoagulation if an UFH infusion is empirically started 12 to 24 hours post-dose, without assessment of residual DOAC effect.

It should be acknowledged that this retrospective chart review has several limitations that impede its widespread applicability. First of all, given its retrospective nature, it is inherently lacking in ability to control patient baseline characteristics and confounding factors such as concurrent medications. Timing of drug administration and AXA collection was also variable, and data were not always complete because of the limitations of a chart review. Given that some of the information collected on timing of DOAC administration was patient reported, it is also possible that the estimation of dose administration time may be somewhat inaccurate. Furthermore, sample size was restricted by our community setting, which does not capture patients of high acuity requiring a level-one trauma center, and our institution’s recent implementation of a new EMR (limiting the number of patients captured on screening reports).

Reproduction of any linear correlation between DOAC concentrations and AXA levels was hindered by our laboratory’s upper limit of detection (with AXA levels reported to a maximum of 1 IU/mL only) and our inability to directly measure serum drug concentrations.

Conclusion

Although routine monitoring of DOAC agents is not encouraged, there exist extenuating scenarios in which clinician knowledge of the extent and duration of DOAC anticoagulation is necessary. In these circumstances, the AXA level can alert to residual apixaban and rivaroxaban effect when drug concentration measurements are not widely available or financially feasible. In particular, this study highlights the difficulties with transition from a DOAC agent to an UFH infusion that is monitored by AXA levels. Institutions should be aware of the confounding effect of factor Xa inhibitors on AXA levels and make appropriate plans for when to delay UFH initiation versus use alternative monitoring (ie, aPTT) or anticoagulation (ie, unmonitored LMWH).

Further research is recommended to more clearly define therapeutic drug levels of these agents. Improved AXA monitoring parameters (with greater upper limits of detection) and DOAC-specific AXA assays will also allow for an improved understanding of safe anticoagulation transition.

Authors’ Note

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Declaration of Conflicting Interests

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