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Assessment of Anti-Xa activity in patients receiving concomitant apixaban with strong p-glycoprotein inhibitors and statins

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Abstract

What is known and objectives: Although the apixaban Food and Drug Administration (FDA) package insert recommends dose reduction in patients administered dual strong inhibitors of p-glycoprotein (P-gp) and cytochrome P-450 (CYP) 3A4, there are limited published data regarding potential drug-drug interactions between apixaban (Eliquis) and common p-glycoprotein (P-gp) and CYP3A4 inhibitors co-administered with statins. The aim of this study was to investigate the degree of elevation relative to apixaban serum peak and trough concentration after the co-administration of amiodarone, diltiazem and statins (atorvastatin, rosuvastatin and simvastatin).

Methods: Patients prescribed apixaban 5mg twice daily for at least one week were identified from the anticoagulation clinic database and contacted for potential enrolment. A total of 117 volunteers were enrolled with eight excluded due to discontinued use, resulting in 109 volunteers (44 females and 65 males delineated into age groups 40–64 and ≥65 years old) completing the observational study. Fifty-five volunteers were administered apixaban without the P-gp inhibitors amiodarone or diltiazem, with or without statins (atorvastatin, rosuvastatin and simvastatin). Fifty-four volunteers were administered apixaban with either amiodarone or diltiazem, with or without statins (atorvastatin, rosuvastatin or simvastatin). Peak and trough concentrations were assessed for each patient utilizing an apixaban anti-Xa assay.

Results: Of the combinations studied, the mean apixaban trough concentration upon co-administration of amiodarone without a statin was elevated compared to apixaban alone (experimental 156.83 +/− 79.59 ng/ml vs. control 104.09 +/− 44.56 ng/ml; $p = 0.04$). The co-administration of diltiazem and rosuvastatin, and the administration of amiodarone without a statin led to greater than 1.5-fold increase in apixaban concentrations (peak experimental 315.19 +/− 157.53 ng/ml vs control 207.6 +/− 83.38 ng/ml; $p = 0.08$ and trough experimental 182.03 +/− 95.93 ng/ml vs control 112.32 +/− 37.78 ng/ml; $p = 0.17$) suggesting the need to assess dose adjustment for patients per the FDA package insert. In addition, the aggregated mean peak

($p = 0.0056$) and trough ($p = 0.0089$) elevation of CYP3A4 experimental groups (atorvastatin and simvastatin) co-administered apixaban and diltiazem were statistically significant compared with the aggregated non-CYP3A4 control groups (no statin and rosuvastatin).

What is new and conclusion: Herein, we report novel data regarding peak and trough apixaban concentrations after concomitant administration of P-gp and CYP3A4 inhibitors (amiodarone or diltiazem) co-administered with statins (atorvastatin, rosuvastatin or simvastatin). Providers should consider utilizing the apixaban anti-Xa assay or comparative heparin anti-Xa assay to determine if patients require dose reduction to decrease adverse events in high-risk patients prescribed apixaban and concomitant p-glycoprotein and CYP3A4 inhibitors amiodarone or diltiazem with and without a CYP3A4 or non-3A4 statin.

KEYWORDS
amiodarone, anti-Xa, apixaban, atorvastatin, CYP3A4 inhibitor, diltiazem, p-glycoprotein inhibitor, rosuvastatin, simvastatin

1 | WHAT IS KNOWN AND OBJECTIVES

Since the introduction of direct oral anticoagulants (DOACs) such as apixaban,[1] there has been debate and confusion regarding the need for therapeutic monitoring and which anticoagulation laboratory assay is appropriate.[2–4] This debate is further confounded when potential drug-drug interactions (DDIs) may occur due to polypharmacy, especially the concomitant use of drugs associated with significant patient safety warnings and precautions.

Apixaban is transported through P-glycoprotein (P-gp) and eliminated via renal and non-renal pathways primarily utilizing CYP3A4 metabolism (Table S1).[5] Therefore, the concomitant administration of CYP3A4 and P-gp inhibitors may lead to increased apixaban peak and trough plasma concentrations with subsequent risk of increased bleeding events[6,7] when prescribed for stroke prophylaxis with atrial fibrillation,[8] postoperative prophylaxis[9] and treatment of venous thrombosis and pulmonary embolism.[10] While the apixaban (Eliquis) Food and Drug Administration (FDA) package insert recommends dose reduction or avoidance of concomitant use with strong dual inhibitors or inducers of CYP3A4 and P-gp, such as clarithromycin, ritonavir, itraconazole and ketoconazole,[5] we sought further DDI data relative to concomitant prescribing within our patient population.

Although the P-gp inhibitors diltiazem[11] and amiodarone[12] have been explored in combination with apixaban, scant information is available regarding the concomitant use of these agents with statins. Herein, we discuss an observational study comparing patients prescribed apixaban in the usual course of clinical care with and without a statin to those prescribed apixaban and concomitant p-glycoprotein and CYP3A4 inhibitors amiodarone or diltiazem with and without a statin. In addition, statin CYP3A4 substrates atorvastatin and simvastatin are compared to rosuvastatin, which does not utilize the CYP3A4 metabolic pathway.

2 | METHODS

2.1 | Setting

The study was completed at the D.D. Eisenhower Army Medical Center (DDEAMC) in Ft. Gordon, Georgia USA (July 2018—October 2020). The protocol was submitted in accordance with DDEAMC policies and procedures associated with research involving human subjects. The study protocol was reviewed and approved by the U.S. Army Regional Health Command—Atlantic Institutional Review Board (IRB) (RHC-A-18–013). Written informed consent was obtained during enrolment.

2.2 | Study design

With the use of apixaban increasing in active-duty military personnel, dependents and retiree populations, an observational study was completed, whereby patients previously prescribed apixaban in the usual course of clinical care are compared to patients co-administered P-gp and CYP3A4 inhibitors (Table S1) amiodarone and diltiazem with and without a statin. Patients prescribed apixaban 5mg twice daily for at least one week were identified from the anticoagulation clinic database and contacted for potential enrolment. As shown in Figure 1 and Table 1, a total of 117 volunteers were enrolled with eight excluded due to discontinued use, resulting in 109 volunteers completing the observational study. Fifty-five volunteers were administered apixaban without amiodarone or diltiazem, with or without statins (atorvastatin, rosuvastatin and simvastatin). Fifty-four volunteers were administered apixaban with either amiodarone or diltiazem, with or without statins (atorvastatin, rosuvastatin and simvastatin). Amiodarone (100 mg and 200 mg), diltiazem (120, 180, 240, 360 mg), atorvastatin (10, 20, 40, 80 mg), rosuvastatin (10,

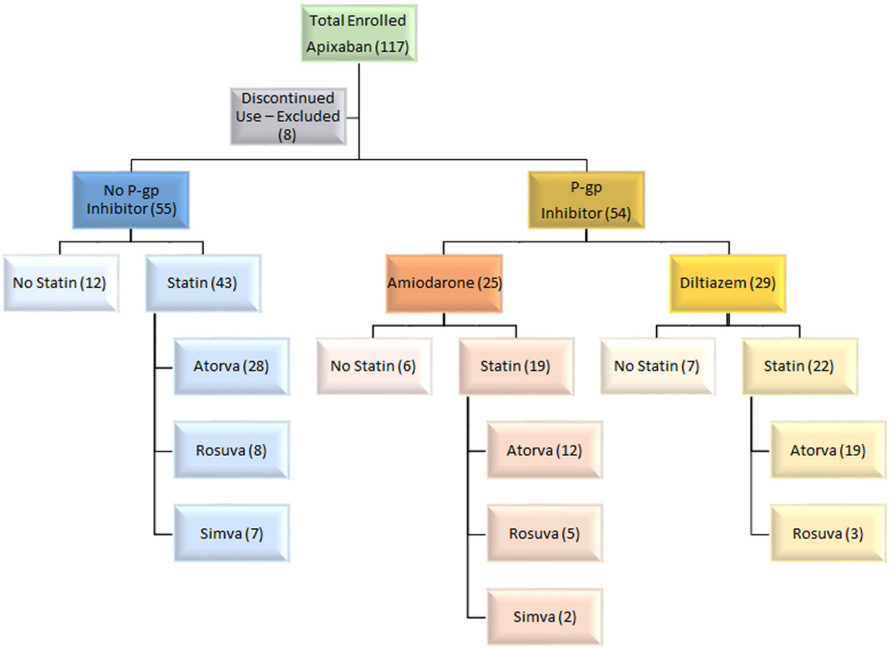

FIGURE 1 Study design

20, 40 mg) and simvastatin (10, 20, 40, 80 mg) dosage were documented. Patient medication records were reviewed to identify co-administration of P-gp and CYP3A4 (inducers and inhibitors) not specified in the study design according to the FDA package inserts and referenced databases.[5,13–19] No patients were administered both amiodarone and diltiazem.

Venipuncture specimens were collected 2–3 h after an apixaban dose or 1–3 h before the next dose corresponding to peak and trough apixaban serum concentrations, respectfully. At the time of enrollment, patients were counselled to administer apixaban at the same time each day (+/− 30 mins) for at least one week prior to the laboratory visits. Adherence to this dosing plan was stressed at the time of enrollment and during follow-up appointments to ensure both peak and trough apixaban serum concentrations were measured for each patient. Patients were asked to maintain a dosing diary for one week prior to each venipuncture sampling. The time of last dose and blood draw was documented. Patients were reminded to abstain from grapefruit or grapefruit juice as they are taught at the initiation of apixaban therapy due to the P-gp inhibiting properties.

As outlined in Figure 1, the observational study design was based upon each cohort receiving apixaban. The control group was prescribed only apixaban (no P-gp inhibitor or statin), while the comparison cohorts were grouped by P-gp inhibitor and statin. Patients were further sorted according to age, weight, creatinine clearance (CrCl), aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

2.3 | Data collection

2.3.1 | Anticoagulation

Based upon the literature recommendations,[4,19–22] we sought to implement an anti-activated Factor Xa (anti-Xa) assay specifically calibrated for apixaban and compare that assay to the established heparin anti-Xa assay within our laboratory. The two anti-Xa assays were validated utilizing STAGO STA Compact Max coagulation analyzers and (1) Stago STA® low molecular weight heparin (LMWH) calibrators, controls and liquid anti-Xa reagents, which are FDA-cleared for clinical diagnostic use and reported as UI units[23] and (2) Stago STA® apixaban calibrator, Stago STA® apixaban control and STA® liquid anti-Xa, which are 'For Research Use Only' and utilized to quantify apixaban concentration (ng/ml).[24] Figure S1 correlates the data generated analysing specimens utilizing either the apixaban anti-Xa assay (ng/ml) or the low molecular weight heparin (LMWH) anti-Xa assay (UI/ml).

2.3.2 | Renal function

Serum Creatinine: Abbott® serum creatinine calibrators, controls and reagents were implemented and validated utilizing Architect c4000 instruments.[25] Serum creatinine reference ranges: >18 years 0.3–1.2 mg/dl. CrCl was estimated via the Cockcroft Gault equation: (140-age) × (weight in kilograms)/72 × (serum creatinine in mg/dl) multiplied by 0.85 for females. The following renal function CrCl categories were utilized per FDA guidance: Normal renal function: >90 ml/min; Mild renal impairment: 60–89 ml/min; Moderate renal impairment: 30–59 ml/min.[26]

2.3.3 | Hepatic function

Abbott® AST and ALT calibrators, controls and reagents were implemented and validated utilizing Architect c4000 instruments.[27] AST Reference Ranges: 15–41 IU/L. ALT Reference Ranges: 4–50 IU/L (male), 14–54 IU/L (female).

TABLE 1 Study Population Demographics, Indication and Co-Medication Screen

(Number of Volunteers)	Indication	Age (years)	Weight (kg)	Ethnicity	Gender	Co-medication Screen
Apixaban with No P-gp Inhibitor (55 Volunteers)						
No Statin (12)	AF(12)	≥65(9), 40–64(3)	<65(1), 65–85(4), 86–119(7)	AA(5); C(7)	M(5); F(7)	CVD(1)
Atorvastatin (28)	AF(27), DVT(1)	≥65(22), 40–64(6)	<65(1), 65–85(6), 86–119(21)	AA(8); C(19); H(1)	M(18); F(10)	CVD(3); NIF(1); FEL(1)
Rosuvastatin (8)	AF(8)	≥65(6), 40–64(2)	<65(1), 65–85(1), 86–119(6)	AA(4); C(4)	M(5); F(3)	
Simvastatin (7)	AF(7)	≥65(5), 40–64(2)	65–85(1), 86–119(6)	C(7)	M(5); F(2)	CVD(4)
P-gp Inhibitor—Amiodarone (25 Volunteers)						
No Statin (6)	AF(6)	≥65(6)	<65(1),65–85(1), 86–119(4)	C(6)	M(4); F(2)	
Atorvastatin (12)	AF(6), DVT(4), PE(2)	≥65(10), 40–64(2)	65–85(1), 86–119(11)	AA(3); C(9)	M(11); F(1)	CVD(2); FEL(2)
Rosuvastatin (5)	AF(5)	≥65(3), 40–64(2)	<65(1), 86–119(4)	AA(2); C(3)	M(4); F(1)	
Simvastatin (2)	AF(2)	≥65(2)	65–85(1), 86–119(1)	C(2)	F(2)	
P-gp Inhibitor—Diltiazem (29 Volunteers)						
No Statin (7)	AF(7)	≥65(5), 40–64(2)	65–85(4), 86–119(3)	AA(2); C(5)	M(2); F(5)	CVD(1)
Atorvastatin (19)	AF(15), DVT(2), PE(2)	≥65(13), 40–64(6)	<65(1), 65–85(5), 86–119(13)	AA(6); H(1); C(12)	M(10); F(9)	CVD(3); NIF(1); FEL(1)
Rosuvastatin (3)	AF(3)	≥65(3)	<65(1), 65–85(1), 86–119(1)	C(3)	M(1); F(2)	CVD(1)

Abbreviations: AA, African American; AF, Atrial Fibrillation; C, Caucasian; CVD, Carvedilol; DVT, Deep Vein Thrombosis; F, Female; FEL, felodipine; H, Hispanic; M, Male; NIF, nifedipine; PE, Pulmonary Embolism.

2.3.4 | Patient demographics

Age, weight and sex were collected from military electronic healthcare records.

2.3.5 | Data analysis

Data and statistical analyses were performed using 2020 O365 Microsoft Excel with the data analysis add-on package and R-Studio (version 4.0.2; 20200622) with tidyverse, forestplot, reshape2 and ggplot2 packages. The difference (increase or decrease) of anti-Xa activity was determined by comparing the experimental and control groups at each sampling time (peak/trough). *t* test: The *F*-test was employed to determine the appropriate *t* test (equal vs. unequal variances) based upon comparing *F*-test and *F*-critical values. *Critical value* and *p-value* (0.05 alpha) were utilized to assess Type 1 error for the normally distributed continuous parameters. The control group was compared to two or more experimental groups utilizing single factor *Analysis of variance (ANOVA)*. The fold difference and per cent difference between experimental and control groups were calculated based upon the means of the experimental and control groups (fold difference = experimental mean/control mean) and (percent difference = ((experimental-control)/control)*100).

3 | RESULTS

The observational study cohorts based upon the volunteers within our patient population are outlined in Table 1 and Figure 1. A total of 117 volunteers were enrolled, eight were excluded from data analysis. One volunteer stopped apixaban, one volunteer stopped amiodarone and six volunteers did not complete the specified blood draws. Approximately equal enrolment was accomplished in the 'no P-gp inhibitor' cohort (55 volunteers) and the 'P-gp inhibitor' cohort (54 volunteers). It should be noted that amiodarone and diltiazem are P-gp and CYP3A4 substrates, but for simplicity Figure 1 and Table 1 indicates with or without a P-gp inhibitor since two statins (atorvastatin and simvastatin) are also CYP3A4 substrates. Within the 'no P-pg inhibitor' cohort, twelve volunteers were not prescribed a statin and the 'statin' cohort consisted of 43 volunteers co-administered apixaban and a CYP3A4-statin (atorvastatin, simvastatin) or non-CYP3A4-statin (rosuvastatin). Similarly, the 'P-gp inhibitor' cohort is categorized based upon patients co-administered apixaban and amiodarone (25 volunteers) or diltiazem (29 volunteers), coupled with further delineation whether a statin was prescribed. No volunteers had a history of bleeding during anticoagulant therapy.

Figure 2 outlines the data indicating the extent apixaban peak and trough concentrations were altered in our patient population during concomitant administration of P-gp and CYP3A4 inhibitors (amiodarone or diltiazem) and statin CYP3A4 substrates (atorvastatin and simvastatin). In the absence of a statin, apixaban concentration increased greater than 1.5-fold when amiodarone was

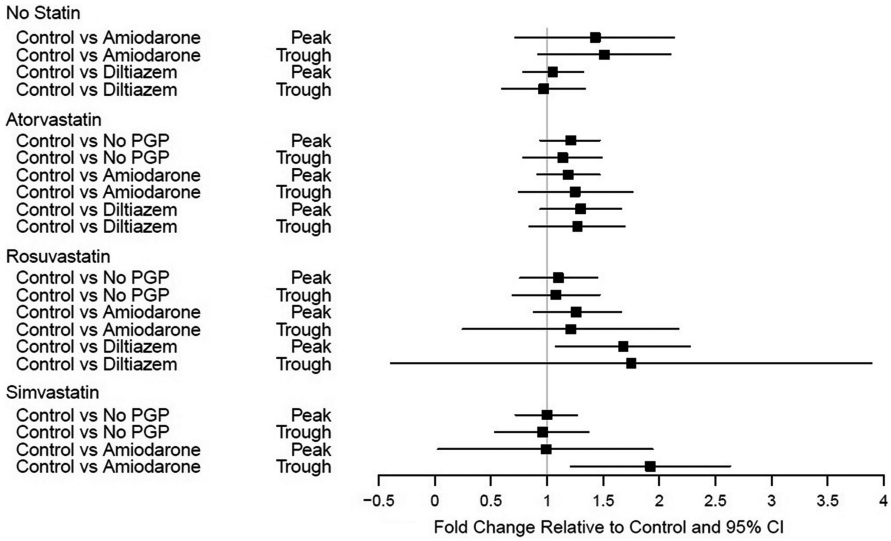

FIGURE 2 Fold change comparing control (apixaban mono-administration) versus co-administration of P-gp inhibitors (amiodarone or diltiazem) categorized by concomitant use of a statin cohorts (atorvastatin, rosuvastatin and simvastatin)

co-administered (mean 268.5 ng/ml peak; 156.83 ng/ml trough) compared to control (mean 188.06 ng/ml peak; 188.06 ng/ml trough for apixaban with no P-gp inhibitor or CYP3A4 substrate) (Figure 2 and Table S2). Within the rosuvastatin cohort, the largest fold increases (> 1.5-fold) relative to control (mean 207.6 ng/ml peak; 112.32 ng/ml trough) were observed with the co-administered of apixaban and diltiazem (mean 315.19 ng/ml peak; 182.03 ng/ml trough). Conversely, negligible fold differences were observed for the other cohorts as indicated in Figure 2.

The varying dosage of amiodarone (100mg and 200mg) and diltiazem (120, 180, 240, 360mg) were randomly dispersed throughout the statin cohorts yielding insufficient data for dose-response analysis within this observational study. A co-medication screen was performed to identify potential confounding DDIs from medications not associated with the study cohorts.[18,19] As indicated in Table 1, two patients were co-administered nifedipine and four felodipine (CYP3A4 substrates), and fifteen patients were administered carvedilol (literature precedence of P-gp inhibition[28] although not noted in the FDA package insert[29]), but a statistically significant change in apixaban concentration was not observed in the cohorts that included these volunteers.

Subsequent cohort analyses (Tables S2-S4) yielded mixed results regarding statistical significance. Table S2 indicates the p-values upon comparing the P-gp substrates to control (no amiodarone or diltiazem) within each statin cohort. A statistically significant increase in apixaban trough concentration was observed within the cohort co-administered simvastatin and amiodarone ($p = 0.01$) or amiodarone with no statin ($p = 0.04$) Table S3 outlines the ANOVA p-values upon comparing each stain cohort within the amiodarone, diltiazem and no P-gp groups, which did not indicate statistically significant elevations in peak and trough apixaban concentrations. Further analysis was completed comparing the statins metabolized via CYP3A4 (atorvastatin and simvastatin) to the non-CYP3A4 metabolized cohorts (no statin and rosuvastatin). As shown in Table S4, the aggregated mean peak ($p = 0.0056$) and trough ($p = 0.0089$) elevation of CYP3A4 experimental groups (atorvastatin and simvastatin) co-administered apixaban and diltiazem were statistically significant compared with the aggregated non-CYP3A4 control groups (no statin and rosuvastatin).

The degree of variation within the cohorts is indicated in Figures 3 and 4 along with the trends associated with apixaban mono-administration or co-administration with amiodarone, diltiazem or a statin. Despite the dispersion, Figures 3 and 4 indicate an increasing trend with respect to the apixaban peak and trough serum concentration for patients co-administered apixaban, diltiazem and a statin (atorvastatin or rosuvastatin). The effect of specific population demographics relative to the peak and trough concentrations of apixaban is indicated in Figure 5 (comparing aggregated P-gp to non-P-gp cohorts) and Figure 6 (comparing aggregated statin to non-statin cohorts).

4 | DISCUSSION

While the apixaban FDA package insert[5] indicates specifically avoiding clarithromycin, ritonavir, itraconazole and ketoconazole co-administration, data regarding the polypharmacy applicable to our patient population was not available as highlighted in a recent review article.[30] Therefore, the apixaban peak and trough concentrations were determined during concomitant administration of P-gp and CYP3A4 inhibitors amiodarone or diltiazem and statin non-CYP3A4 (rosuvastatin) and CYP3A4 substrates (atorvastatin and simvastatin).

As shown in Figure 2 and Table S2, mean apixaban concentrations were increased greater than 1.5-fold by the combination of amiodarone without a statin relative to control (peak experimental 268.5 +/− 126.41 ng/ml vs. control 188.06 +/− 55.90 ng/ml; $p = 0.09$ and trough experimental 156.83 +/− 79.59 ng/ml vs control 104.09 +/- 44.56 ng/ml; $p = 0.04$). The co-administration of diltiazem and rosuvastatin, and the administration of amiodarone without a statin led to greater than 1.5-fold increases in apixaban concentrations (peak experimental 315.19 +/− 157.53 ng/ml vs

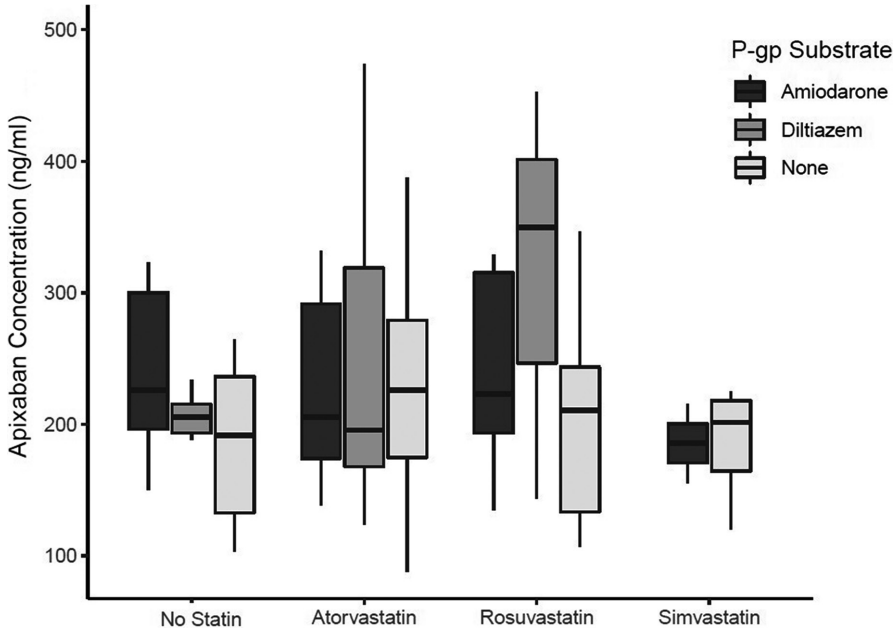

FIGURE 3 Apixaban peak concentration (ng/ml) categorized by mono-administration or co-administration with P-gp inhibitor (amiodarone or diltiazem) and categorized by statin cohorts (atorvastatin, rosuvastatin and simvastatin)

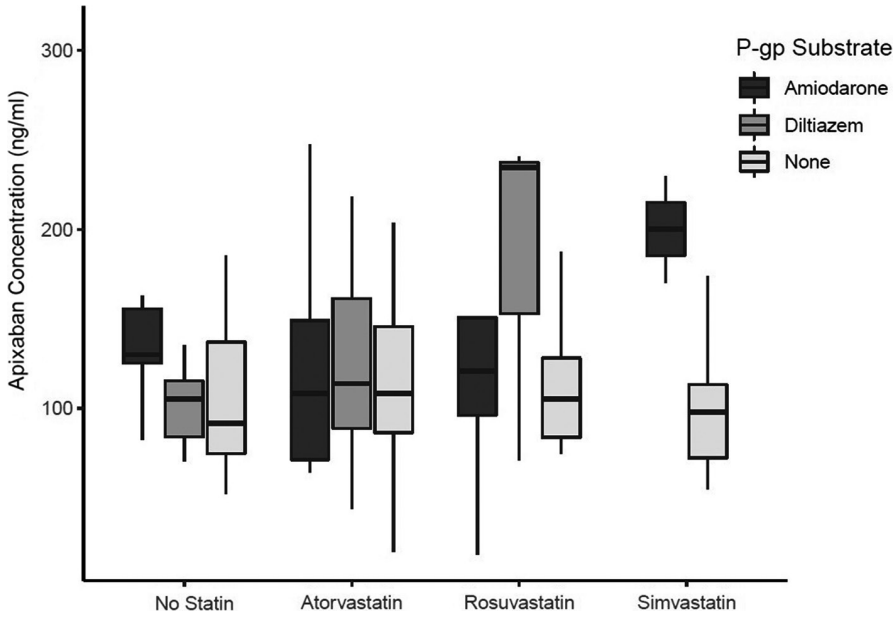

FIGURE 4 Apixaban trough concentration (ng/ml) categorized by mono-administration or co-administration with P-gp inhibitor (amiodarone or diltiazem) and categorized by statin cohorts (atorvastatin, rosuvastatin and simvastatin)

control 207.6 +/− 83.38 ng/ml; $p = 0.08$ and trough experimental 182.03 +/− 95.93 ng/ml vs control 112.32 +/− 37.78 ng/ml; $p = 0.17$) suggesting the need to assess dose adjustment for patients per the FDA package insert.[5]

These findings agree with a recent publication outlining a cohort of 358 Caucasian patients with AF prescribed apixaban (2.5 mg or 5.0 mg twice daily) with amiodarone (8% of volunteers).[12] Data were aggregated for peak and trough apixaban concentrations to develop a multiple linear regression model that was subsequently applied to predict apixaban concentrations after concomitant amiodarone administration.[12] The predicted peak and trough concentrations at steady state associated with <400 mg amiodarone[12] are commensurate with the elevation relative to control observed in our clinical data presented in Figure 3 (peak) and Figure 4 (trough) associated with amiodarone (100 mg and 200 mg). Examination of the effect of diltiazem on the pharmacokinetics of apixaban, reveals a similar trend to the literature of increased apixaban concentration,[11] which is further exacerbated with concomitant use of rosuvastatin (Table S2; >1.5-fold increase peak ($p = 0.08$) and trough ($p = 0.17$) apixaban concentrations).

Despite the lack of statistical significance associated with each cohort, the elevated apixaban concentration observed in patients indicates the importance of individual therapeutic monitoring to assess dose adjustments given the potential for increased bleeding due to the combined use of P-gp and CYP3A4 inhibitors.[67] While liquid chromatography-tandem mass spectrometry (LC-MS/MS) is considered the gold standard for DOAC quantification,[22] it less likely to be available within on-site hospital laboratories for monitoring patients.

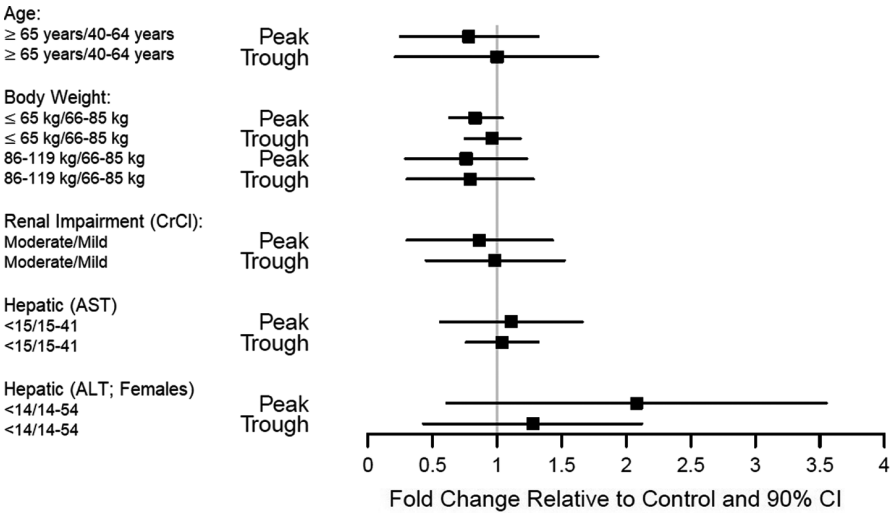

FIGURE 5 Fold change comparing population parameters of control (apixaban mono-administration) cohort versus P-gp cohorts (all P-gp regardless of statin). The renal function CrCl are as follows: Normal renal function: >90 ml/min; Mild renal impairment: 60–89 ml/min; Moderate renal impairment: 30–59 ml/min.[26] The hepatic enzyme reference ranges are as follows: AST: 15–41 IU/L; ALT: 4–50 IU/L (male), 14–54 IU/L (female)

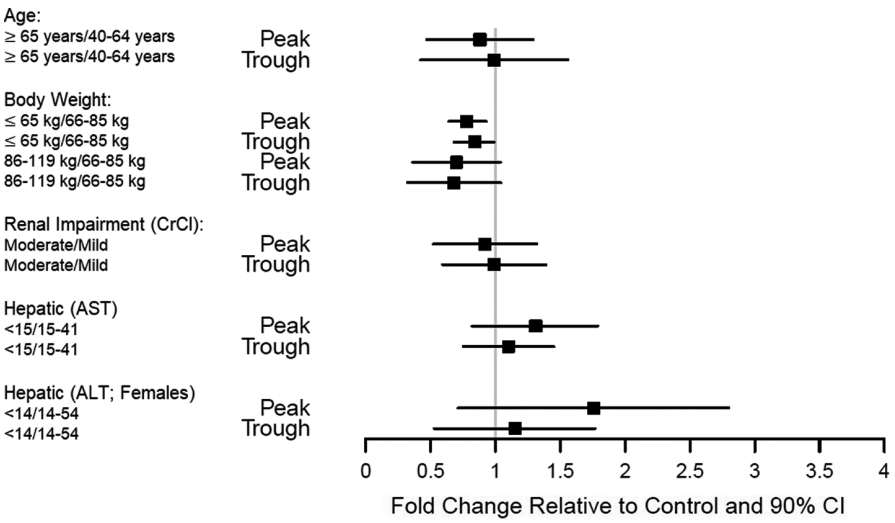

FIGURE 6 Fold change comparing population parameters of control (apixaban mono-administration) cohort versus statin cohorts (all statins regardless of P-gp). The CrCl renal function categories are as follows: Normal renal function: >90 ml/min; Mild renal impairment: 60–89 ml/min; Moderate renal impairment: 30–59 ml/min.[26] The hepatic enzyme reference ranges are as follows: AST: 15–41 IU/L; ALT: 4–50 IU/L (male), 14–54 IU/L (female)

The anti-Xa chromogenic assay,[3,23] which is commonly available in clinical laboratories and utilized within this study, has been shown to correlate to LC-MS/MS.[31] Further correlations of the anti-Xa assay calibrated for apixaban (ng/ml) versus heparin (IU) are presented in Figure S1. In addition to therapeutic monitoring, clinicians should consider reviewing the co-medication of patients administered apixaban to identify P-gp and CYP3A4 inhibitors which reportedly lead to increased bleeding events.[67] While this study was designed to investigate DDIs within our patient population, the small sample sizes for each cohort limited the ability to delve into the impact of dose response for the P-gp and CYP3A4 inhibitors and precluded statistically significant differences. Future, larger studies investigating impaired hepatic and renal function in the context of specific dosing cohorts would be beneficial.

5 | WHAT IS NEW AND CONCLUSION

Herein, we report novel data regarding peak and trough apixaban concentrations after concomitant administration of P-gp and CYP3A4 inhibitors (amiodarone or diltiazem) co-administered with statins (atorvastatin, rosuvastatin or simvastatin). The elevated peak and trough apixaban concentrations observed in patients indicates the importance of individual therapeutic monitoring to assess dose adjustments.

CONFLICT OF INTEREST

The authors declare no competing interests for this work.

DISCLAIMER

The views expressed herein are those of the authors and do not reflect the position of the United States Military Academy, Dwight D. Eisenhower Army Medical Center, the Department of the Army, the Defense Health Agency or the Department of Defense.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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