Trauma Surgery & Acute Care Open

Predictors of direct oral anticoagulant concentrations in the trauma population

Louis Perkins ,[1] Laura Adams ,[1] Dmitri Lerner,[2] Jarrett Santorelli ,[1] Alan M Smith,[1] Leslie Kobayashi [1]

[1]Department of Surgery, Division of Trauma, Surgical Critical Care, Burns and Acute Care Surgery, University of California San Diego, San Diego, California, USA
[2]Department of Pharmacy, University of California San Diego, San Diego, California, USA

Correspondence to
Dr Louis Perkins; laperkins@health.ucsd.edu

ABSTRACT

Introduction Direct oral anticoagulant (DOAC) use is becoming more prevalent in patients presenting after trauma. We sought to identify the prevalence and predictors of subtherapeutic and therapeutic DOAC concentrations and hypothesized that increased anti-Xa levels would correlate with increased risk of bleeding and other poor outcomes.

Methods A retrospective cohort study of all trauma patients on apixaban or rivaroxaban admitted to a level 1 trauma center between January 2015 and July 2021 was performed. Patients were excluded if they did not have a DOAC-specific anti-Xa level at presentation. Therapeutic levels were defined as an anti-Xa of 50 ng/mL to 250 ng/mL for rivaroxaban and 75 ng/mL to 250 ng/mL for apixaban. Linear regression was used to identify correlations between study variables and anti-Xa level, and binomial logistic regression was used to test the association of anti-Xa level with outcomes.

Results There were 364 trauma patients admitted during the study period who were documented to be on apixaban or rivaroxaban. Of these, 245 patients had anti-Xa levels measured at admission. The population was 53% woman, with median age of 78 years, and median Injury Severity Score of 5. In total, 39% of patients had therapeutic and 20% had supratherapeutic anti-Xa levels. Female sex, increased age, decreased height and weight, and lower estimated creatinine clearance were associated with higher anti-Xa levels at admission. There was no correlation between anti-Xa level and the need for transfusion or reversal agent administration, admission diagnosis of intracranial hemorrhage (ICH), progression of ICH, hospital length of stay, or mortality.

Conclusions Anti-Xa levels in trauma patients on DOACs vary widely; female patients who are older, smaller, and have decreased kidney function present with higher DOAC-specific anti-Xa levels after trauma. We were unable to detect an association between anti-Xa levels and clinical outcomes.

Level of evidence III—Prognostic and Epidemiological.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients on anticoagulation medication have worse outcomes after trauma. Direct oral anticoagulants (DOACs) are being increasingly prescribed, and measurements of DOAC concentration can guide the administration of reversal agents.

WHAT THIS STUDY ADDS

⇒ A description of the variation in DOAC-specific anti-Xa levels of trauma patients and evidence that female sex, increased age, smaller height and weight, and decreased creatinine clearance are associated with higher DOAC concentrations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Trauma and critical care providers can use our study findings to assist in clinical decision-making regarding the monitoring and treatment of patients on DOACs, particularly when drug-specific anti-Xa testing is not available. Future research should support the determination of specific anti-Xa thresholds for guiding management after trauma.

INTRODUCTION

The prescription of direct oral anticoagulants (DOACs) has increased rapidly during the last decade.[1] The first DOAC was approved in 2010 and by the end of the decade, 81% of Medicare patients on anticoagulation for atrial fibrillation and 87% on anticoagulation for venous thromboembolism were on a DOAC.[2 3] Given the increase in the prevalence of DOAC usage, as well as the increase in geriatric trauma patients who are more likely to be on anticoagulation for a comorbidity, we can expect a steady increase in trauma injuries to patients on DOACs.[4 5]

Patients on anticoagulation have longer hospital and intensive care unit lengths of stay (H-LOS, ICU-LOS), are more likely to get discharged to a facility instead of home, and have increased risk of mortality.[6] In 2015, a large prospective observational study by Kobayashi *et al*[7] concluded that DOACs did not pose a higher risk of intracranial hemorrhage (ICH), progression of bleeding, or death compared with warfarin. Since then, several studies have confirmed equivalent or improved outcomes with DOAC use in non-head injury trauma,[8] in ICH progression after a minor head injury,[9 10] in overall cost of hospital stay,[11] and in overall mortality in trauma with ICH[12–14] when compared with warfarin.

Given its advantages over other anticoagulants, DOAC use will likely continue to increase. The most common DOACs prescribed are apixaban and rivaroxaban.[15] Both agents work by inhibiting factor X (Xa) activity and their concentrations can be measured by specific chromogenic anti-Xa assays. A recent European trauma guideline states that DOAC plasma concentration is important in determining

To cite: Perkins L, Adams L, Lerner D, *et al*. *Trauma Surg Acute Care Open* 2024;**9**:e001208.

the need for active reversal[16]; however, there is very little guidance on how to clinically interpret the measured concentrations. The latest guidance from the International Society of Thrombosis and Hemostasis (ISTH) recommends using 50 ng/mL as a threshold for antidote administration and 30 ng/mL for invasive procedures.[17] More recent literature has described significant variability in the therapeutic anti-Xa thresholds, and this variability depends on patient factors, dosing regimens, and choice of DOAC.[18]

This single-center retrospective study evaluated apixaban and rivaroxaban plasma concentrations measured on hospital day 1 in trauma patients. We then explored possible relationships between body mass index (BMI), renal function, age, and measured DOAC concentrations. Analysis of therapeutic apixaban and rivaroxaban plasma levels and their possible association with longer ICU and hospital lengths of stay, discharge placement, or development of ICH at our institution was also investigated. We hypothesized that anti-Xa levels would be impacted by BMI, age, and renal function and that elevated levels would correlate with higher risk of ICH, bleeding, and other poor outcomes.

METHODS

At our institution, we maintain an active trauma registry and maintain a global use IRB for retrospective study of registry data. A retrospective cohort study of trauma patients on DOACs was performed. All trauma patients on apixaban or rivaroxaban admitted to our level 1 trauma center between January 2015 and July 2021 were included. Patients were excluded if they did not have an anti-Xa measured on presentation. Patient demographics, admission vitals, mechanism of injury, Injury Severity Score (ISS), BMI, and estimated creatinine clearance (eCC), as well as outcomes of ICH, bleeding requiring intervention or transfusion, transfusions, H-LOS, and ICU-LOS, progression of neurologic injury, and death were collected from the institutional trauma registry. Comorbid conditions were also evaluated and used to generate a comorbidity index assigning a value of 1 for each of the following comorbidities: myocardial infarction, congestive heart failure, stroke, chronic obstructive pulmonary disease, cirrhosis, diabetes, and chronic kidney disease. After consultation with institutional pharmacists, therapeutic levels were defined as an anti-Xa of 50 ng/mL to 250 ng/mL for rivaroxaban and 75 ng/mL to 250 ng/mL for apixaban. Any level >250 for either drug was considered supratherapeutic.

In analyzing comparisons of categorical variables, the χ^2 and Fisher exact tests were used for large and small samples, respectively. Wilcoxon and Kruskal-Wallis rank-sum testing were used for comparisons between groups with continuous variables. Bivariate and multivariate linear regression was used to identify correlations between study variables and admission anti-Xa levels. Binomial logistic regression was used to identify predictors of therapeutic group. The association between anti-Xa levels and outcomes was evaluated both by using therapeutic groupings of anti-Xa levels in Fisher exact testing and by binomial logistic regression. Statistics were conducted in R Studio (V.3.5.3; Posit, Boston, MA). For all statistical tests, the alpha value for significance was set at 0.05.

RESULTS

There were 364 trauma admissions during the study period involving patients who were documented to be on a DOAC with 245 admissions (242 unique patients) meeting the inclusion criteria of having an anti-Xa level drawn at admission (table 1). The cohort was 53% woman and 56% white with median age of 78 years (IQR 68–87 years) and median ISS of 5 (IQR 4–10). Sixty-nine percent (n=168) of patients were on apixaban and 31% (n=77) of patients were on rivaroxaban with median admission anti-Xa levels of 95.3 ng/mL (IQR 38.3–221.2 ng/mL) and 78.6 ng/mL (IQR 13.0–217.7 ng/mL), respectively. The substantial variability in anti-Xa level at admission is evident in figure 1. With the drug-specific anti-Xa cutoffs, 41% (n=100) of patients had subtherapeutic, 39% (n=96) had therapeutic, and 20% (n=49) had supratherapeutic anti-Xa concentrations. Women were more likely to present with therapeutic or supratherapeutic anti-Xa levels (RR 1.27, CI 1.04 to 1.58, p=0.024) as were older, smaller patients with lower eCC. There was no difference in the calculated comorbidity index between groups. The 119 patients who were excluded due to not having an admission anti-Xa level drawn did not differ in age, sex, race, injury severity, BMI, or comorbidities. They did have a lower rate of ICH (10.1% vs 20.8%, p=0.016) resulting in a shorter ICU-LOS. Mortality, H-LOS, and discharge disposition were not different.

Bivariate and multivariate regression analysis

Bivariate regression analyses were conducted to identify correlations between patient age, admission creatinine, eCC, height, weight, and BMI, and admission anti-Xa levels (tables 2 and 3, figure 2). Older age was positively correlated with anti-Xa levels (Pearson's r=0.21, p=0.001), whereas creatinine clearance (Pearson's r=−0.22, p≤0.001), weight (Pearson's r=−0.14, p=0.037), and height (Pearson's r=−0.24, p<0.001) were negatively correlated. Admission creatinine and BMI were not correlated. Multivariate analysis of age, BMI, eCC, and sex showed that only female sex was correlated with increased admission anti-Xa levels (p=0.038) (table 3). Given these findings, a review of a subset of 59 female patients older than 65 years of age with eCC less than 50 mL/min was conducted and showed that 27% had subtherapeutic, 41% had therapeutic, and 32% had supratherapeutic anti-Xa levels.

Outcomes

Overall, six patients (2.4%) died during the index admission. Six patients received blood transfusions (2%), and 10 patients received prothrombin complex for reversal (4%). Fifty-one (21%) had ICH diagnosed on presentation and seven patients (3%) experienced ICH progression. The median H-LOS and ICU-LOS was 3 and 2 days, respectively. There was no difference between groups in mortality, transfusion, or reversal agent requirement, or diagnosis and progression of ICH. Compared with the therapeutic group, patients in the subtherapeutic group had longer LOS (median 3 vs 2 days, p=0.014), but there was no difference in LOS in comparison with the supratherapeutic group. Compared with the therapeutic and supratherapeutic groups, patients in the subtherapeutic group were more likely to be discharged to a place other than home (RR 1.36, CI 1.09 to 1.71, p=0.008) (table 4). In binomial logistic regression accounting for anti-Xa level as a continuous variable, there was no association between anti-Xa level and mortality, need for transfusion or reversal, or progression of ICH. Of the 10 patients who received a reversal agent, eight had a diagnosis of ICH of which four experienced progression of bleed, one had intraabdominal bleeding from solid organ injury, and one had a thigh hematoma from a femur fracture.

DISCUSSION

DOACs are being increasingly prescribed and seen in the medical history of trauma patients. Therapeutic effects of these drugs

Table 1 Cohort comparison

	Subtherapeutic N=100	Therapeutic N=96	Supratherapeutic N=49	Total N=245	P value
Sex					0.026
Female	44%	54%	67%	53%	
Male	56%	46%	33%	47%	
Race					0.469
Asian	2%	6%	6%	5%	
African American	6%	6%	0%	5%	
Caucasian	55%	59%	53%	56%	
Other race	36%	26%	39%	32%	
Unknown	1%	2%	2%	2%	
Age (years)					0.004
Median (IQR)	73 (63–86)	80 (72–87)	83 (75–87)	78 (68–87)	
BMI (kg/m^2)					0.431
Median (IQR)	25.9 (22.6–30.0)	25.8 (22.2–29.1)	27.0 (24.0–30.5)	26.0 (22.5–30.0)	
Height (m)					0.003
Median (IQR)	1.70 (1.63–1.75)	1.69 (1.60–1.78)	1.6 (1.57–1.68)	1.68 (1.58–1.75)	
Weight (kg)					0.342
Median (IQR)	73.9 (63.2–90.0)	73.4 (60.7–88.9)	70.3 (59.8–79.9)	73.0 (61.2–88.9)	
Admission Cr (mg/dL)					0.189
Median (IQR)	0.96 (0.77–1.17)	0.92 (0.77–1.11)	1.04 (0.84–1.46)	0.95 (0.78–1.21)	
eCC (mL/min)					0.014
Median (IQR)	67.5 (47.8–98.3)	57.3 (39.3–79.4)	46.9 (33.9–75.7)	58.0 (39.3–85.5)	
Comorbidity index					0.108
Median (IQR)	1 (0–2)	0 (0–1)	1 (0–2)	1 (0–1)	
ISS					0.399
Median (IQR)	6 (4–13)	5 (4–10)	5 (4–10)	5 (4–10)	
Head AIS					0.552
Median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	2 (2–3)	
DOAC					0.972
Apixaban	69%	68%	69%	69%	
Rivaroxaban	31%	32%	31%	31%	
Admission anti-Xa					–
Apixaban—median (IQR)	18.7 (0–51.4)	140.0 (99.0–181.7)	327.2 (288.1–398.9)	95.3 (38.3–221.2)	
Rivaroxaban—median (IQR)	6.1 (0–17.1)	127.3 (79.3–168.3)	346.2 (282.7–384.4)	78.6 (13.0–217.7)	

AIS, Abbreviated Injury Scale; BMI, body mass index; Cr, creatinine; DOAC, direct oral anticoagulant; eCC, estimated creatinine clearance; ISS, Injury Severity Score.

can be measured by specific anti-Xa assays, which can guide decision-making.[16] We sought to analyze what patient factors are predictive of DOAC-specific anti-Xa levels and whether higher anti-Xa levels were associated with worse outcomes after trauma. Our data indicates that there is substantial variability in anti-Xa levels on trauma admission, but female sex, increased age, decreased creatinine clearance, and lower height and weight are correlated with higher anti-Xa levels and, theoretically, more therapeutic effects from DOACs. We were not able to detect a correlation between DOAC-specific anti-Xa level and increased risk of transfusion, reversal, or complications.

Interestingly, patients in the subtherapeutic group were more likely to be discharged to a facility than those in the therapeutic and supratherapeutic groups. Given that the ISS and the prevalence of comorbidities between the groups were similar, it is unclear about the mechanism behind this difference. Patients in the subtherapeutic group also had longer LOS compared with the therapeutic group, but there was no difference when including supratherapeutic patients in the analysis. These differences are likely not clinically relevant.

DOACs, as anticoagulants, confer an increased risk of bleeding and plasma DOAC-specific anti-Xa levels can be used to monitor the level of risk. The variation in anti-Xa levels and relationships with patient characteristics in the trauma population has not been described previously to the authors' knowledge. DOAC-specific anti-Xa testing is not available at all institutions, and the turnaround time may limit their use, especially in the time-sensitive domain of trauma.[18] We have identified several predictors of anti-Xa levels that can guide clinical decision-making in the acute trauma setting, particularly if a DOAC plasma concentration is not readily available. We have also investigated bleeding and other trauma-related outcomes and, although we

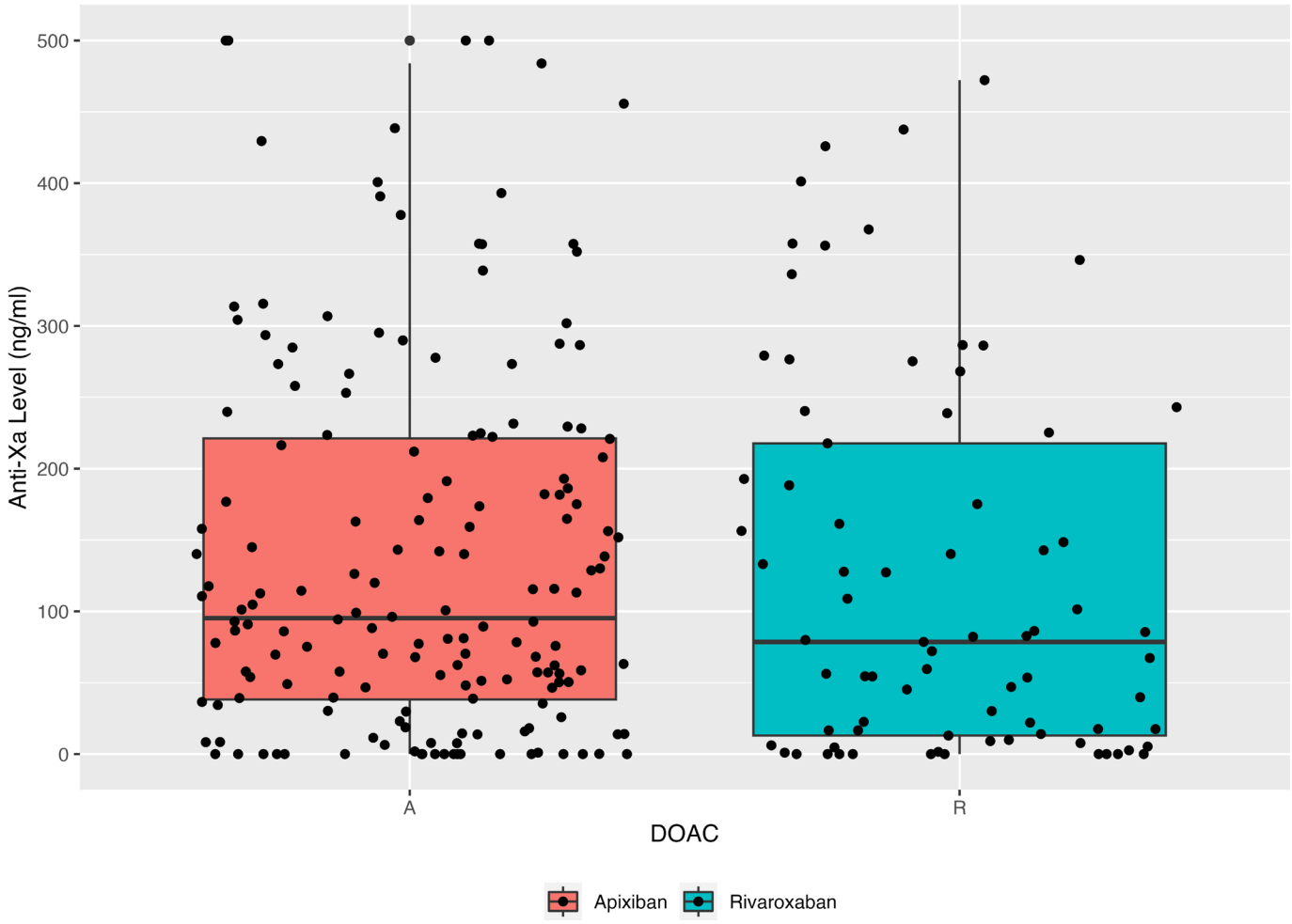

Figure 1 Admission drug-specific anti-Xa levels by direct oral anticoagulant (DOAC).

did not have the power to detect true differences, the overall low incidence of complications for trauma patients on DOACs further demonstrates the relative safety of these drugs.

Our study does have limitations. It is a retrospective single-center study, and 33% of patients on DOACs who were admitted after trauma during the study period were excluded due to not having an anti-Xa level drawn at admission. It is unclear as to why so many patients did not have a level drawn; however, given the lower incidence of ICH in this group, it may be related to a lower initial suspicion of head trauma and intracranial bleeding by the treatment team. Additionally, we did not have data on the time since the last dose of medication, which would certainly affect the concentration. However, given that this information would likely be unavailable in many clinical scenarios, our study reflects the variables most readily available. Lastly, the study group primarily sustained relatively minor injuries, as indicated by a median ISS of 5. This low injury severity, coupled with a lack of power, likely limited our ability to find a correlation between DOAC-specific anti-Xa levels and complications such as the need for transfusion and reversal agent administration. This prevents us from being able to make recommendations on specific clinical interventions on the basis of anti-Xa level. Future

Table 2 Bivariate analysis results

	Regression coefficient	95% CI	Pearson's r coefficient	P value
Age (years)	2.02	0.81 to 3.22	0.207	0.001
Creatinine (mg/dL)	11.18	−1.18 to 23.55	0.114	0.076
eCC (mL/min)	−0.75	−1.18 to −0.33	−0.222	<0.001
Weight (kg)	−0.86	−1.67 to −0.05	−0.135	0.037
Height (cm)	−2.65	−4.04 to −1.26	−0.242	<0.001
BMI (m/kg^2)	0.33	−2.53 to 3.19	0.015	0.821
ISS	−0.32	−2.86 to 2.22	−0.016	0.806

BMI, body mass index; eCC, estimated creatinine clearance; ISS, Injury Severity Score.

Table 3 Multivariate regression results

	Regression coefficient	95% CI	SE	P value
Constant	−1.53	−165.25 to 162.20	83.08	0.985
Age (years)	0.97	−0.73 to 2.67	1.12	0.263
eCC (mL/min)	−0.60	−1.25 to 0.05	1.84	0.070
BMI (m/kg^2)	3.07	−0.21 to 6.34	−1.83	0.070
Female sex	36.64	2.04 to 71.24	2.09	0.038

BMI, body mass index; eCC, estimated creatinine clearance.

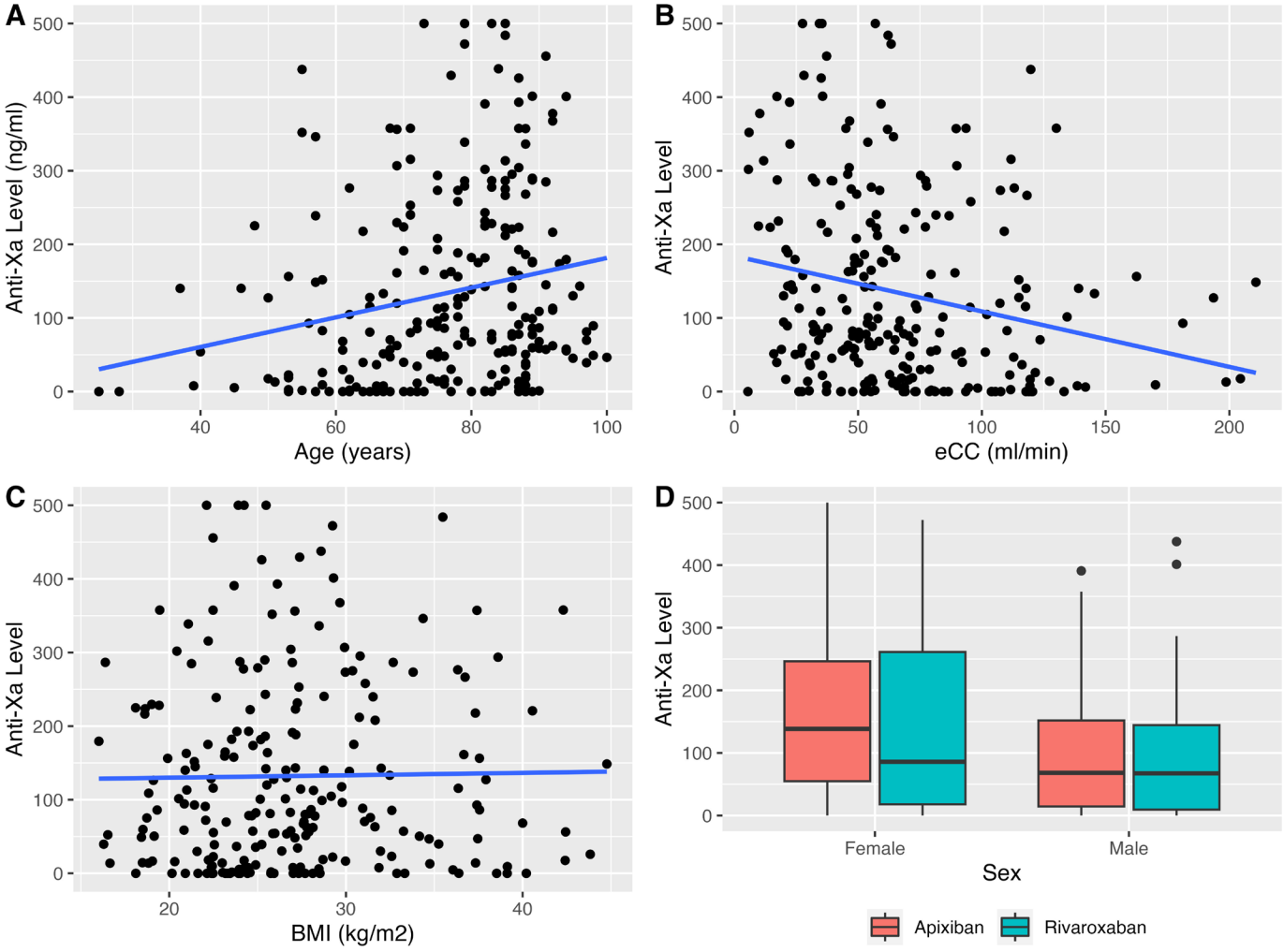

Figure 2 Patient characteristics and anti-Xa levels. (A) Age versus anti-Xa, (B) estimated creatinine clearance (eCC) versus anti-Xa, (C) body mass index (BMI) versus anti-Xa, and (D) sex versus anti-Xa.

studies should aim to expand our work to a greater population of more severely injured patients.

Trauma and critical care providers can use our study findings to assist in clinical decision-making regarding the monitoring and reversal of patients on DOACs. Although we cannot suggest specific anti-Xa cutoffs based on this study, providers can have a higher index of suspicion of the risk for bleeding complications in older female patients with decreased kidney function, given they are more likely to have higher concentration levels. Further studies should focus on large, preferably prospective groups of trauma patients on DOACs with more robust capture of admission anti-Xa levels and injury severities to detect differences in outcomes and generate guidelines on when to administer reversal agents for specific patient groups and anti-Xa levels.

CONCLUSION

There is high variability of drug concentrations in patients on DOACs. Female patients who are older, smaller, and have decreased kidney function present with higher DOAC-specific

Table 4 Outcomes

	Subtherapeutic N=100	Therapeutic N=96	Supratherapeutic N=49	Total N=245	P value
Transfusion	3% (3)	2% (2)	2% (1)	2% (6)	1
Reversal agent	2% (2)	5% (5)	6% (3)	4% (10)	0.371
ICH at admission	22% (22)	20% (19)	20% (10)	21% (51)	0.927
Progression of ICH	1% (1)	3% (3)	6% (3)	3% (7)	0.124
Mortality	1% (1)	3% (3)	4% (2)	2% (6)	0.380
Hospital LOS (days), median (IQR)	3 (2–6)	2 (1–4)	3 (2–5)	3 (1–5)	0.033
ICU LOS (days), median (IQR)	3 (2–3)	2 (2–5)	2 (2–4)	2 (2–4)	0.997
Discharge to facility	64% (64)	49% (47)	43% (21)	54% (132)	0.024

ICH, intracranial hemorrhage; LOS, length of stay; TBI, traumatic brain injury.

anti-Xa levels after trauma. Future large, prospective studies should seek to identify differences in trauma-related outcomes attributed to DOAC-specific anti-Xa levels to offer better guidelines on the management of trauma patients on DOACs.

Contributors LP, LA, DL, and LK conceived the project. LP, DL, and AMS conducted the data analysis. LP, LA, JS, and LK wrote the manuscript. LK is the guarantor of the project.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon request.

ORCID iDs
Louis Perkins http://orcid.org/0000-0002-3136-5104
Laura Adams http://orcid.org/0000-0001-6227-6764
Jarrett Santorelli http://orcid.org/0000-0001-6450-6164
Leslie Kobayashi http://orcid.org/0000-0002-9063-0908

REFERENCES

1 Costa LS da, Alsultan MM, Hincapie AL, Guo JJ. Trends in utilization, reimbursement, and price for Doacs and warfarin in the US Medicaid population from 2000 to 2020. *J Thromb Thrombolysis* 2023;55:339–45.
2 Munir MB, Hlavacek P, Keshishian A, Guo JD, Mallampati R, Ferri M, Russ C, Emir B, Cato M, Yuce H, *et al*. Oral anticoagulant Underutilization among elderly patients with atrial fibrillation: insights from the United States Medicare database. *J Interv Card Electrophysiol* 2023;66:771–82.
3 Iyer GS, Tesfaye H, Khan NF, Zakoul H, Bykov K. Trends in the use of oral anticoagulants for adults with venous thromboembolism in the US, 2010-2020. *JAMA Netw Open* 2023;6:e234059.
4 Kozar RA, Arbabi S, Stein DM, Shackford SR, Barraco RD, Biffl WL, Brasel KJ, Cooper Z, Fakhry SM, Livingston D, *et al*. Injury in the aged: geriatric trauma care at the crossroads. *J Trauma Acute Care Surg* 2015;78:1197–209.
5 Horst MA, Morgan ME, Vernon TM, Bradburn EH, Cook AD, Shtayyeh T, D'Andrea L, Rogers FB. The geriatric trauma patient: A neglected individual in a mature trauma system. *J Trauma Acute Care Surg* 2020;89:192–8.
6 Nguyen RK, Rizor JH, Damiani MP, Powers AJ, Fagnani JT, Monie DL, Cooper SS, Griffiths AD, Hellenthal NJ. The impact of anticoagulation on trauma outcomes: an national trauma data bank study. *Am Surg* 2020;86:773–81.
7 Kobayashi L, Barmparas G, Bosarge P, Brown CV, Bukur M, Carrick MM, Catalano RD, Holly-Nicolas J, Inaba K, Kaminski S, *et al*. Novel oral anticoagulants and trauma: the results of a prospective American Association for the surgery of trauma multi-institutional trial. *J Trauma Acute Care Surg* 2017;82:827–35.
8 van Erp IA, Mokhtari AK, Moheb ME, Bankhead-Kendall BK, Fawley J, Parks J, Fagenholz PJ, King DR, Mendoza AE, Velmahos GC, *et al*. Comparison of outcomes in non-head injured trauma patients using pre-injury warfarin or direct oral anticoagulant therapy. *Injury* 2020;51:2546–52.
9 Riccardi A, Spinola B, Minuto P, Ghinatti M, Guiddo G, Malerba M, Lerza R. Intracranial complications after minor head injury in patients taking vitamin K antagonists or direct oral anticoagulants. *Am J Emerg Med* 2017;35:1317–9.
10 Savioli G, Ceresa IF, Luzzi S, Gragnaniello C, Giotta Lucifero A, Del Maestro M, Marasco S, Manzoni F, Ciceri L, Gelfi E, *et al*. Rates of intracranial hemorrhage in mild head trauma patients presenting to emergency Department and their management: a comparison of direct oral anticoagulant drugs with vitamin K antagonists. *Medicina (Kaunas)* 2020;56:308.
11 Lamb LC, DiFiori M, Comey C, Feeney J. Cost analysis of direct oral anticoagulants compared with warfarin in patients with blunt traumatic intracranial hemorrhages. *Am Surg* 2018;84:1010–4.
12 Feeney JM, Santone E, DiFiori M, Kis L, Jayaraman V, Montgomery SC. Compared to warfarin, direct oral anticoagulants are associated with lower mortality in patients with blunt traumatic intracranial hemorrhage: A TQIP study. *J Trauma Acute Care Surg* 2016;81:843–8.
13 Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, Schöchl H. The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. *Scand J Trauma Resusc Emerg Med* 2018;26.
14 Nishimura T, Guyette FX, Naito H, Nakao A, Brown JB, Callaway CW. Comparison of direct oral anticoagulant and vitamin K antagonists on outcomes among elderly and Nonelderly trauma patients. *J Trauma Acute Care Surg* 2020;89:514–22.
15 Wheelock KM, Ross JS, Murugiah K, Lin Z, Krumholz HM, Khera R. Clinician trends in prescribing direct oral anticoagulants for US Medicare beneficiaries. *JAMA Netw Open* 2021;4:e2137288.
16 Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, Komadina R, Maegele M, Nardi G, Riddez L, *et al*. The European guideline on management of major bleeding and Coagulopathy following trauma. *Crit Care* 2019;23:98.
17 Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI, Subcommittee on Control of Anticoagulation. When and how to use Antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost* 2016;14:623–7.
18 Douxfils J, Ageno W, Samama CM, Lessire S, Ten Cate H, Verhamme P, Dogné JM, Mullier F. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for Clinicians. *J Thromb Haemost* 2018;16:209–19.