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ORIGINAL RESEARCH ARTICLE

Impact of Renal Function on Anti-factor Xa Activity Concentrations with Edoxaban Use in Patients with Non-valvular Atrial Fibrillation

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Abstract

Background Chromogenic anti-factor Xa activity (AXA) assay is used to measure the pharmacodynamics of factor Xa inhibitors, including edoxaban. Although AXA concentrations in patients with non-valvular atrial fibrillation using edoxaban have been reported, the impact of renal function on AXA concentrations with edoxaban use in patients with non-valvular atrial fibrillation has not been fully assessed.

Methods Trough and peak AXA concentrations were measured in 93 patients with non-valvular atrial fibrillation taking edoxaban (73.6 ± 11.2 years, 48 were male). The patients were divided into three groups: patients with moderate renal dysfunction (creatinine clearance 15–49 mL/min), mild renal dysfunction (creatinine clearance 50–95 mL/min), and normal renal function (creatinine clearance > 95 mL/min). Both trough and peak AXA concentrations were assessed among the groups according to the edoxaban dose (30 or 60 mg).

Results At a 30-mg dose, patients with moderate renal dysfunction showed significantly higher trough AXA concentrations than patients with mild renal dysfunction or normal renal function. At a 60-mg dose, patients with mild renal dysfunction showed significantly higher trough AXA concentrations than patients with normal renal function. Peak AXA concentrations were not significantly different between the groups. Creatinine clearance was significantly and negatively correlated with trough AXA concentrations at a 60-mg dose, whereas the correlation of creatinine clearance with AXA concentrations was borderline significant at a 30-mg dose. No correlation was found between creatinine clearance and peak AXA concentrations at either dose.

Conclusions Creatinine clearance tends to be negatively correlated with trough AXA concentrations in patients with non-valvular atrial fibrillation taking edoxaban, while renal function is not correlated with peak AXA concentrations.

1 Introduction

Direct oral anticoagulants, including edoxaban, apixaban, dabigatran, and rivaroxaban, are used to prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF). Direct oral anticoagulants are characterized by convenient oral administration, rapid onset of action, fixed dosing regimens, minimal drug–drug interactions, and no dietary restrictions [1–4].

Routine coagulation monitoring of factor Xa (FXa) inhibitors is not required because their pharmacokinetic and pharmacodynamic properties are more predictable than those of warfarin; nonetheless, the chromogenic anti-FXa activity (AXA) assay is considered one of the most appropriate methods to measure the pharmacodynamics of FXa inhibitors, including edoxaban [5–10]. Edoxaban has an oral bioavailability of 62% and a plasma elimination half-life of 10–14 h, and approximately 50% of it is renally excreted [11, 12]. Previous studies on the impact of renal function on edoxaban outcomes reported that a high-dose regimen (60 mg daily or a 50% dose reduction to 30 mg daily if the patient fulfilled any of the following conditions: a creatinine clearance [CrCl] of 15–50 mL/min, body weight ≤ 60 kg, or use of a potent permeability glycoprotein inhibitor) demonstrated a lower effectiveness for the prevention of stroke

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Key Points

This study provides evidence of the impact of creatinine clearance (CrCl) on anti-factor Xa activity (AXA) concentrations with edoxaban use in patients with non-valvular atrial fibrillation.

The trough AXA concentrations for the edoxaban 30-mg intake were higher in patients with moderate renaldysfunction (CrCl 15–49 mL/min) than in those with mild renal dysfunction (CrCl 50–95 mL/min) or normal renal-function (CrCl >95 mL/min).

The trough AXA concentrations for the edoxaban 60-mg intake were higher in patients with mild renal dysfunction (CrCl 50–95 mL/min) than in those with normal renal function (CrCl >95 mL/min).

The peak AXA concentrations for the edoxaban 30-mg or 60-mg intake did not significantly differ with renal-function.

or systemic embolism than warfarin at CrCl levels > 95 mL/min [13]. Therefore, edoxaban is not recommended for patients with NVAF in the USA, who have a CrCl > 95 mL/min [14]. Meanwhile, it is widely used in Japan, even by patients with CrCl > 95 mL/min. Although AXA concentrations in patients with NVAF using edoxaban have been reported in a previous study, the impact of renal function on these patient types has not been fully assessed [15]. The purpose of this study was to evaluate the distribution of AXA concentrations depending on renal function and analyze the impact of renal function on AXA concentrations with edoxaban use.

2 Methods

2.1 Study Design and Participants

This observational study was conducted during routine clinical practice at Matsudo City General Hospital, Chiba, Japan, from April 2018 to November 2019. A total of 112 inpatients with NVAF using edoxaban were enrolled in this study. Only inpatients receiving edoxaban therapy were enrolled in this study, to ensure a proper intake of medication and management of measuring time. Patients with CrCl < 15 mL/min or those undergoing dialysis were excluded because edoxaban is contraindicated for these patients in Japan. Patients who were under 18 years of age or who received an inappropriate dose of edoxaban were also excluded. The selection of edoxaban dose was defined by Japanese prescribing information as follows: standard dose 60 mg once daily (30 mg once daily if the patient fulfills any of the following conditions: body weight ≤ 60 kg, CrCl of 15–50 mL/min, or concomitant use of a medication with P-glycoprotein interaction such as quinidine, verapamil, and dronedarone). Finally, 93 patients with NVAF receiving edoxaban therapy were analyzed (Fig. 1). This study was conducted in accordance with the ethics policies of Matsudo City General Hospital. The study protocol was approved by the Ethics Committee of Matsudo City General Hospital (Approval number 30-9 and 31-7), and all patients provided informed consent.

Characteristics of the patients, such as age, body weight, CrCl, and CHA_2DS_2-VASc scores, were recorded.

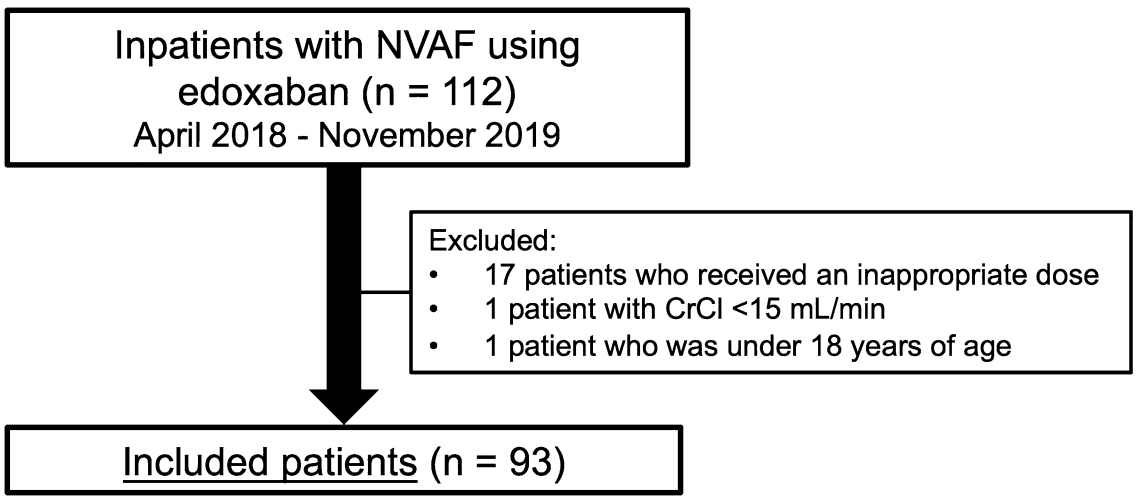

Fig. 1 Study protocol. *CrCl* creatinine clearance, *NVAF* non-valvular atrial fibrillation

Creatinine clearance was determined using the Cockcroft–Gault formula: men, [(140 − age)/(serum creatinine)] × (weight/72); women, 0.85 × [(140 − age)/(serum creatinine)] × (weight/72) [16].

We defined CrCl 15–49 mL/min as moderate renal dysfunction, CrCl 50–95 mL/min as mild renal dysfunction, and CrCl >95 mL/min as normal renal function. All enrolled patients were prescribed edoxaban, in accordance with the dose reduction criteria in Japan, as follows: standard dose 60 mg once daily (30 mg once daily if the patient fulfilled any of the following conditions: body weight ≤ 60 kg, CrCl of 15–50 mL/min, or concomitant use of a medication with P-glycoprotein interaction such as quinidine, verapamil, and dronedarone).

2.2 Measuring AXA, Prothrombin Time, and Activated Partial Thromboplastin Time

The HemosIL Liquid Heparin Kit (Instrumentation Laboratory, Lexington, KY, USA) was used for the chromogenic AXA assay. This single assay is based on the reaction between FXa and a synthetic chromogenic substrate. For liquid heparin, 10 µL of plasma was mixed with 100 µL of chromogenic substrate and incubated at 37 °C; thereafter, 75 µL of bovine FXa was added. The chromogenic substrate was hydrolyzed by FXa to release p-nitroaniline, and the quantity of p-nitroaniline released was determined using spectrophotometry at 405 nm on an ACL TOP 500 CTS analyzer system (Instrumentation Laboratory). Standard HemosIL heparin calibrators (Instrumentation Laboratory) were used, and AXA was expressed in heparin international units (IU)/mL. To ensure measurement at precise intervals corresponding to the trough concentration, the first blood collection was performed immediately before edoxaban intake in the morning. A second blood collection was performed 2 h later to accurately measure the peak concentration. This timing was based on reaching a peak plasma concentration in 1–2 h of taking edoxaban [11, 17]. To measure the steady state, serum creatinine level at trough and AXA concentrations at trough and peak times after repeated edoxaban intake were measured at least 72 h after the start of treatment.

2.3 Statistical Analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean ± standard deviation. Statistical analysis was performed at a significance level of 5%. To compare parameters between groups, the Mann–Whitney *U* test, Wilcoxon signed-rank test, chi-squared test, or Fisher's exact test was used. Analysis of variance was used to analyze AXA concentrations. All statistical analyses were conducted using STATA/IC version 15.1 (StataCorp, College Station, TX, USA).

3 Results

3.1 Patient Characteristics

A total of 93 inpatients (48 were male and 45 were female) with NVAF receiving edoxaban therapy were analyzed. The patients were further divided into three groups according to CrCl: moderate renal dysfunction group ($n = 38$), mild renal dysfunction group ($n = 39$), and normal renal function group ($n = 16$). Table 1 shows the baseline characteristics of the patients. Age, body weight, CrCl, and CHA_2DS_2-VASc scores were significantly different between the groups.

Table 1 Baseline characteristics

	Moderate renal dysfunction ($n = 38$)	Mild renal dysfunction ($n = 39$)	Normal renal function ($n = 16$)	*p* value
Age (years)	79.7 ± 6.3	73.8 ± 9.3	58.4 ± 9.9	< 0.01
Male sex, *n* (%)	15 (39.5)	22 (56.4)	11 (68.8)	0.11
30 mg, *n* (%)	38 (100)	29 (74.4)	5 (31.2)	< 0.01
60 mg, *n* (%)	0 (0)	10 (25.6)	11 (68.8)	< 0.01
Body weight (kg)	48.6 ± 7.7	56.6 ± 11.1	73.5 ± 16.8	< 0.01
CrCl (mL/min)	36.5 ± 8.1	70.4 ± 13.0	178.1 ± 73.3	< 0.01
CHA2DS2-VASc score	3.9 ± 1.4	3.6 ± 1.6	2.5 ± 1.5	< 0.01
Hypertension, *n* (%)	17 (44.7)	23 (59.0)	6 (37.5)	0.26
Dyslipidemia, *n* (%)	10 (26.3)	6 (15.4)	4 (25.0)	0.47
Diabetes mellitus, *n* (%)	10 (26.3)	15 (38.5)	2 (12.5)	0.14
P-glycoprotein inhibitors, *n* (%)	0 (0)	0 (0)	0 (0)	–

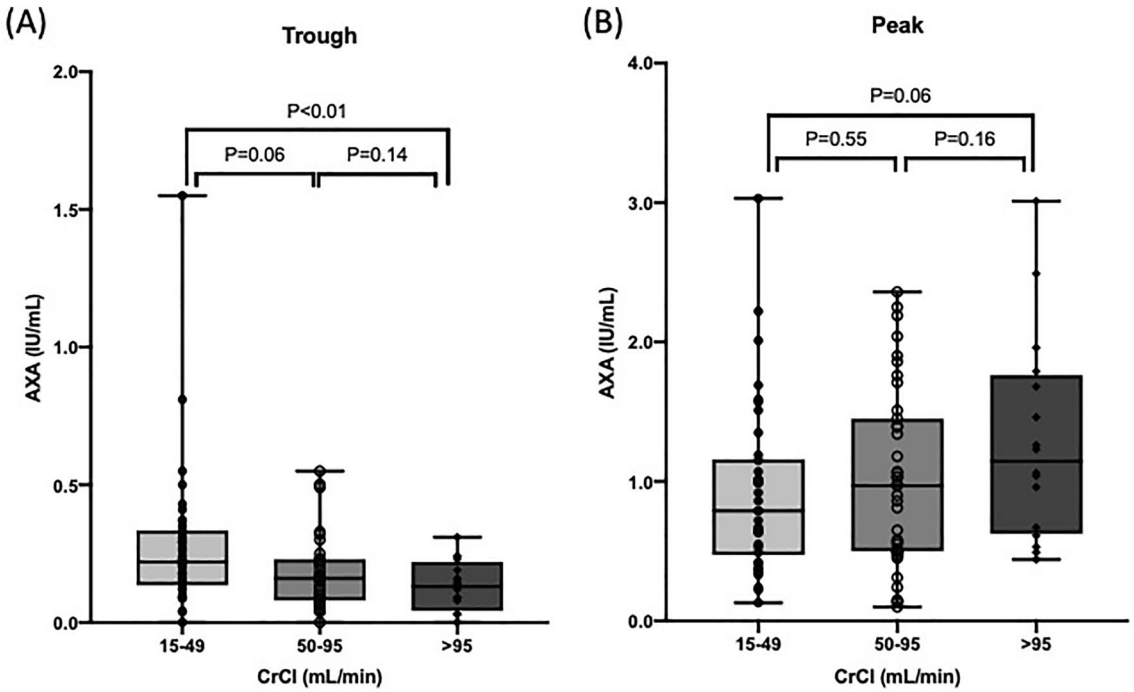

Fig. 2 Anti-factor Xa activity (AXA) concentrations in all patients at trough (**a**) and peak (**b**) times. *CrCl* creatinine clearance

Table 2 Anti-factor Xa activity concentrations according to renal functions

	Moderate renal dysfunction (CrCl 15–49 mL/min)	Mild renal dysfunction (CrCl 50–95 mL/min)	Normal renal function (CrCl >95 mL/min)	*p* value (ANOVA)
Trough (all)	0.28 ± 0.26	0.19 ± 0.13	0.13 ± 0.09	0.025
Peak (all)	0.92 ± 0.60	1.01 ± 0.64	1.29 ± 0.72	0.17
Trough (30 mg)	0.28 ± 0.26	0.16 ± 0.12	0.12 ± 0.08	0.048
Peak (30 mg)	0.92 ± 0.60	0.88 ± 0.52	0.78 ± 0.31	0.84
Trough (60 mg)	–	0.26 ± 0.13	0.14 ± 0.10	0.027
Peak (60 mg)	–	1.39 ± 0.78	1.53 ± 0.77	0.71

ANOVA analysis of variance

Patients with normal renal function were younger and had a higher body weight, better CrCl, and lower CHA_2DS_2-VASc scores than those with moderate or mild renal dysfunction. None of the patients used P-glycoprotein inhibitors. Regarding the dose of edoxaban, 77.4% (72/93) of patients received a reduced dose of 30 mg, whereas 22.6% (21/93) received a standard dose of 60 mg. In the mild renal dysfunction group, 74.4% (29/39) of patients received a reduced dose of 30 mg, whereas 25.6% (10/39) received a standard dose of 60 mg. In contrast, in the normal renal function group, 31.2% (5/16) of patients received a reduced dose of 30 mg, whereas 68.8% (11/16) received a standard dose of 60 mg. All patients in the moderate renal dysfunction group received a reduced dose of 30 mg.

3.2 AXA Concentration Analysis

The trough and peak AXA concentrations were compared among the three groups. First, all patients regardless of dose were assessed (Fig. 2, Table 2). At trough time, AXA concentrations in patients with moderate renal dysfunction (AXA 0.28 ± 0.26 IU/mL) were significantly higher than those in patients with normal renal function (AXA 0.13 ± 0.09 IU/mL) [$p < 0.01$]. Anti-factor Xa activity concentrations between patients with mild renal dysfunction and those with normal renal function, or moderate renal dysfunction and mild renal dysfunction were not significantly different ($p = 0.14$ and $p = 0.06$, respectively). At peak time, AXA concentrations were not significantly different among the groups ($p = 0.17$, analysis of variance).

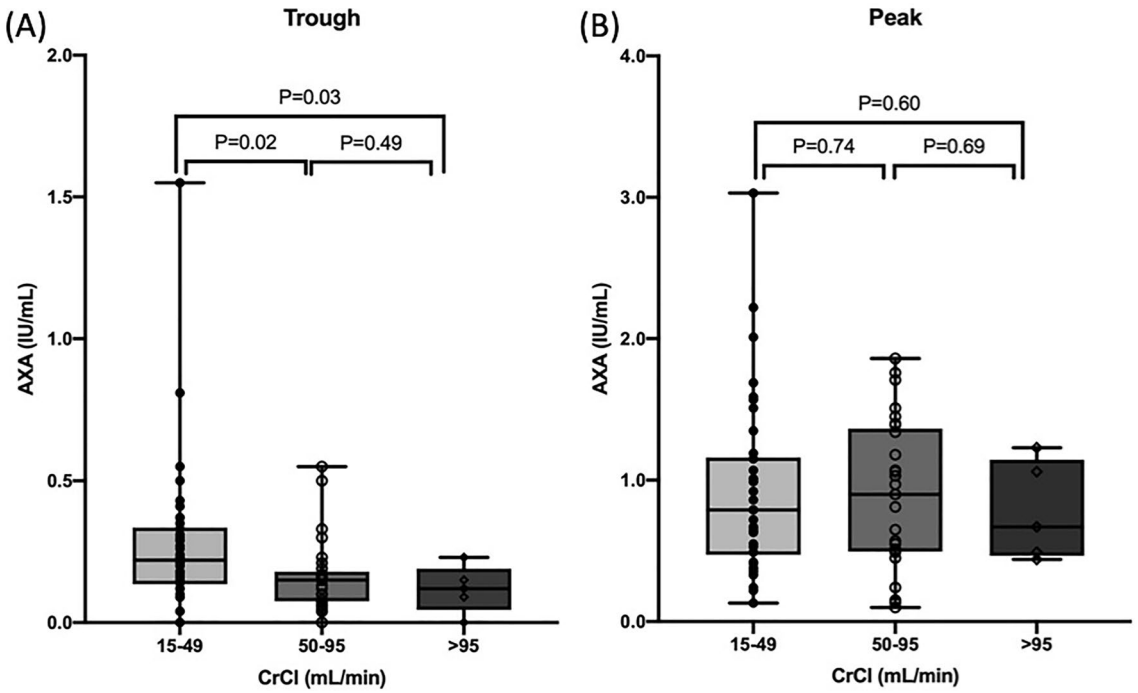

Fig. 3 Anti-factor Xa activity (AXA) concentrations in patients receiving edoxaban 30 mg at trough (**a**) and peak (**b**) times. *CrCl* creatinine clearance

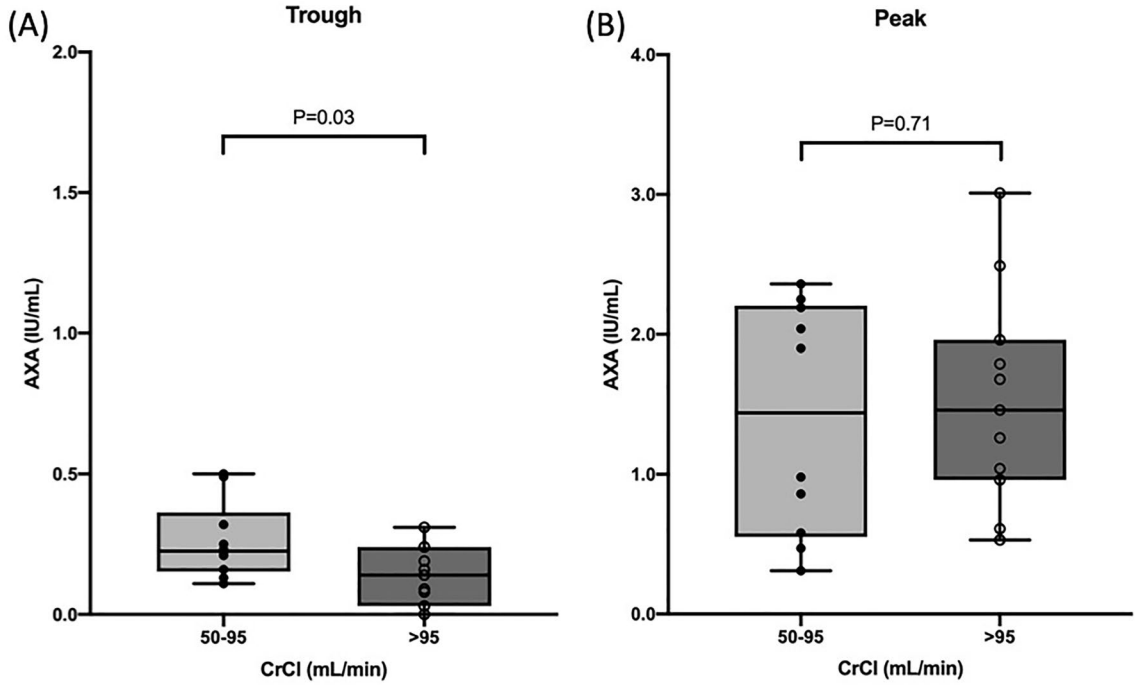

Fig. 4 Anti-factor Xa activity (AXA) concentrations in patients receiving edoxaban 60 mg at trough (**a**) and peak (**b**) times. *CrCl* creatinine clearance

Second, patients taking edoxaban 30 mg were assessed (Fig. 3, Table 2). At trough time, AXA concentrations in patients with moderate renal dysfunction (AXA 0.28 ± 0.26 IU/mL) were significantly higher than those in patients with mild renal dysfunction (AXA 0.16 ± 0.12 IU/mL) or patients with normal renal function (AXA 0.12 ± 0.08 IU/mL) [*p*

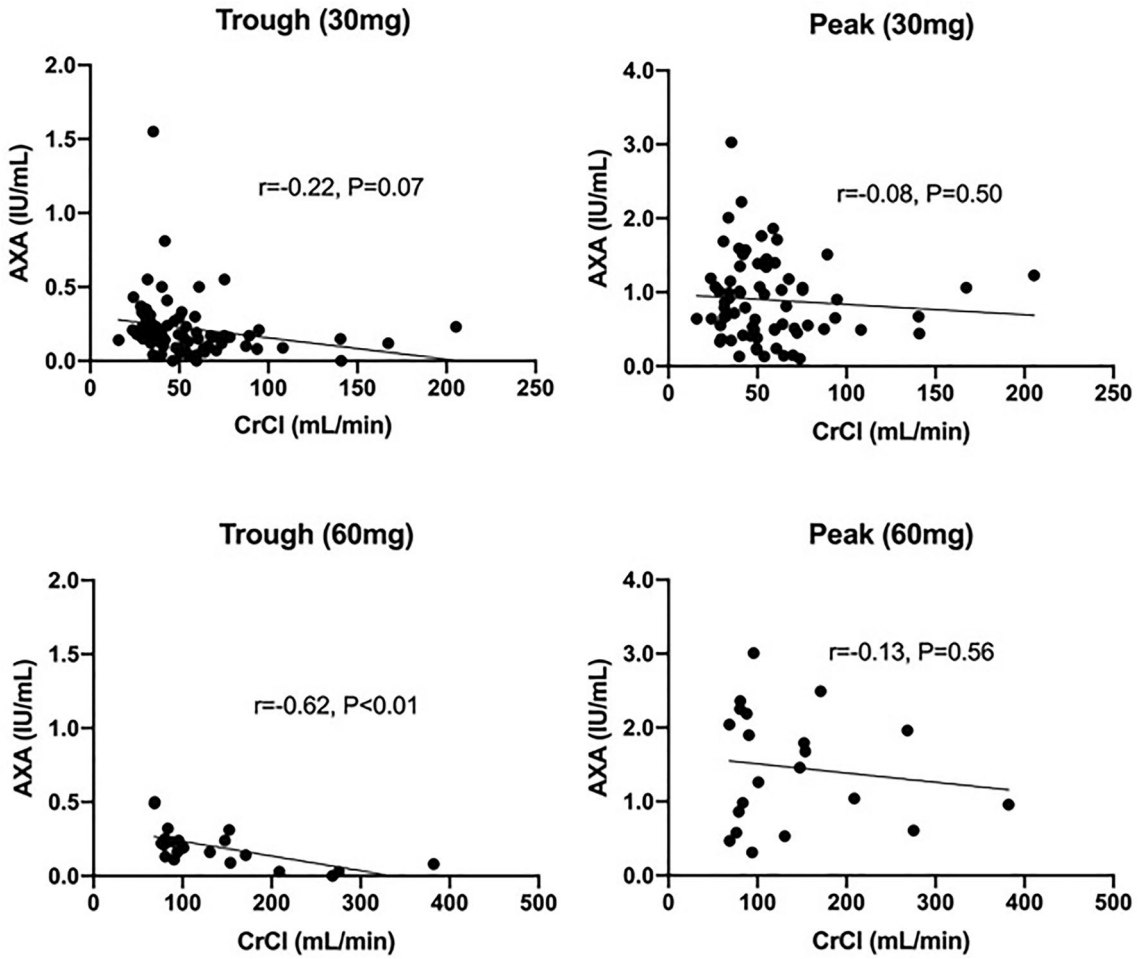

Fig. 5 Correlation between renal function and anti-factor Xa activity (AXA) concentrations. *CrCl* creatinine clearance

= 0.02 and $p = 0.03$, respectively). Anti-factor Xa activity concentrations between patients with mild renal dysfunction and those with normal renal function were not significantly different ($p = 0.49$). At peak time, AXA concentrations were not significantly different among the groups ($p = 0.84$, analysis of variance).

Last, patients taking edoxaban 60 mg were assessed (Fig. 4, Table 2). At trough time, AXA concentrations in patients with mild renal dysfunction (AXA 0.26 ± 0.13 IU/mL) were significantly higher than those in patients with normal renal function (AXA 0.14 ± 0.10 IU/mL) [$p = 0.03$]. At peak time, AXA concentrations were not significantly different between patients with mild renal dysfunction and those with normal renal function ($p = 0.71$).

3.3 Correlation Between Renal Function and AXA Concentrations

Creatinine clearance was significantly and negatively correlated with AXA concentrations ($r = -0.62$, $p < 0.01$) at a trough dose of 60 mg. The correlation of CrCl with AXA concentrations was borderline significant ($r = -0.22$, $p = 0.07$) at a trough dose of 30 mg. No significant associations were found between CrCl and AXA concentrations at peak times at each dose (30 mg: $r = -0.08$ and $p = 0.50$; 60 mg: $r = -0.13$ and $p = 0.56$) [Fig. 5].

4 Discussion

In this study, we evaluated the impact of renal function on AXA concentrations in Japanese patients with NVAF taking edoxaban at different doses by differentiating baseline renal function. Japanese prescribing information for edoxaban provides the following dose reduction criteria: standard dose 60 mg once daily (30 mg once daily if the patient fulfills any of the following conditions: body weight ≤ 60 kg, CrCl of 15–50 mL/min, or concomitant use of a medication with P-glycoprotein interaction); however, there is no contraindication for CrCl > 95 mL/min.

The main findings of this study were as follows: (1) the trough AXA concentrations for the edoxaban 30-mg intake were higher in patients with moderate renal dysfunction than in those with mild renal dysfunction or normal renal function; (2) the trough AXA concentrations for the edoxaban 60-mg intake were higher in patients with mild renal dysfunction than in those with normal renal function; (3) the peak AXA concentrations for the edoxaban 30-mg or 60-mg intake did not significantly differ with renal function; and (4) CrCl had a tendency to be negatively correlated with AXA concentrations at trough times.

In a previous study, Tobe et al. [15] reported the AXA concentrations in patients with NVAF with renal impairment and compared them between 21 patients with moderate renal dysfunction and nine patients with mild renal dysfunction who took edoxaban 30 mg. They found that the trough AXA concentrations were higher in moderate dysfunction, and peak AXA concentrations were not significantly different between the groups; these results are consistent with those of our study. Our study is novel in terms of comparing AXA concentrations to normal renal function and evaluating AXA concentrations in patients with the edoxaban 60-mg intake.

Testa et al. reported no significant correlation was found between edoxaban plasma concentrations and CrCl > 17.8 mL/min both at trough and at peak times [18]. This result seems to contradict ours, but the difference was that we separately analyzed based on the dose and Testa analyzed regardless of the dose. In addition, the difference between AXA and edoxaban concentration may impact on the results.

Renal elimination of apixaban, rivaroxaban, and edoxaban has been reported to be 27%, 33–36%, and 50% of the total clearance, respectively [19, 20], with edoxaban exhibiting a higher renal clearance than apixaban and rivaroxaban. Consequently, altered renal elimination of direct oral anticoagulants impacts drug exposure, and decreased drug exposure is associated with better renal function [20]. This renal clearance may be involved in improved pharmacological clearance in patients with normal renal function (CrCl > 95 mL/min), leading to lower AXA concentrations.

In real-world practice, concerns have been raised about an excess of strokes among patients with CrCl > 95 mg/mL who were being treated with edoxaban. Bohula et al. reported that a high-dose edoxaban regimen (60 mg daily or a 50% dose reduction to 30 mg daily) had a lower effectiveness for the prevention of stroke or systemic embolism than warfarin at high levels of CrCl > 95 mL/min [13]. However, in this study, the warfarin comparator group had a higher time in the therapeutic range in the patients with CrCl > 95 mL/min, which was thought to contribute to the lower event rate in the warfarin group in this sub-analysis. Additionally, absolute event rates were very low in the group with CrCl > 95 mL/min, making it hard to draw any conclusions in this population. In a recent study, according to the Korean National Health Insurance Service data, Yu et al. reported that patients taking edoxaban 30 mg had a lower effectiveness for the prevention of stroke or systemic embolism than warfarin at high levels of CrCl > 95 mL/min [21]. However, this large retrospective study was not able to confirm if patients were receiving appropriate doses based on the package labeling, nor is body weight of the patients described in the paper; therefore, we cannot conclude about the efficacy in the case with CrCl > 95 mL/min.

A multinational phase II stroke study comparing edoxaban with warfarin revealed that bleeding correlated better with trough edoxaban concentrations than with peak concentrations, suggesting that the trough concentration is an important factor associated with the safety and efficacy of edoxaban [22]. In our study, the peak AXA concentrations were not significantly different among the groups, while AXA concentrations in patients with normal renal function were significantly lower than in those with renal impairment. These results are consistent with real-world outcomes, as stated above.

This study has several limitations. First, this was a non-randomized single-center observational study with a relatively small number of patients. Second, the peak time was defined as 2 h after the intake of edoxaban; however, the actual peak time might differ among individual patients. The peak plasma concentration of edoxaban has been reported as 1–2 h after ingestion [11, 17], thus we defined the peak time as 2 h after the intake of edoxaban. Finally, the present study enrolled only Japanese individuals; therefore, whether the results extrapolated to other populations remains uncertain.

5 Conclusions

This study provides evidence of the impact of renal function on AXA concentrations with edoxaban use in patients with non-valvular atrial fibrillation. Creatinine clearance had a significant tendency to be negatively correlated with AXA concentrations at trough times, while renal function did not reveal a correlation with AXA concentrations at peak times.

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Declarations

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Conflicts of interest/competing interests Yoshio Kobayashi received lecture fees and a research grant from Daiichi Sankyo Co., Ltd. Yoshio Kobayashi does not have any other relation with this funder, including employment, consultancy, patents, products in development, or marketed products. Other authors have no conflicts of interest to declare.

Ethics approval This study was approved by the Ethics Committee of Matsudo City General Hospital (Approval number 30-9 and 31-7). This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate All participants provided informed consent prior to their participation.

Consent for publication Not applicable.

Availability of data and material The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Code availability Not applicable.

Authors' contributions All authors contributed to the statistical analysis and writing of the study. R.O., K.F., and K.N. participated in the study design, acquisition of the data, and critical review and writing of the manuscript; H.T. and Y.H. participated in the acquisition of the data and designed the research; Y.K. critically revised the manuscript.

Disclosures Part of this article was presented in the ACC.22 conference abstract.

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