



Relationship between the degree of renal dysfunction and the safety and efficacy outcomes in patients with atrial fibrillation receiving direct oral anticoagulants

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Abstract

Background: The clinical evaluation of a direct oral anticoagulant (DOAC) treatment for atrial fibrillation (AF) patients with renal dysfunction has not been sufficiently studied. This study aimed to evaluate the safety and efficacy of DOACs for patients with a severely impaired renal function.

Methods: This was a retrospective and observational study in a single center. We enrolled 894 consecutive AF patients who were prescribed DOACs, and divided them into three groups based on their creatinine clearance (CrCl) value: CrCl \geq 50 mL/min group (n = 634), CrCl 30-49 mL/min group (n = 207), and CrCl 15-29 mL/min group (n = 53). We evaluated the occurrence of major bleeding (MB) as the safety outcome and thromboembolic events (TEs) as the efficacy outcome during the follow-up.

Results: The incidence of MB in the CrCl 15-29 mL/min group was significantly higher than in the other groups (CrCl \geq 50 mL/min group, 0.8/100 person-years; CrCl 30-49 mL/min group, 1.2/100 person-years; CrCl 15-29 mL/min group, 9.0/100 person-years, log rank test, $P < .001$). On the other hand, there was no significant difference in the incidence of TEs among the three groups. A multivariate analysis using a Cox proportional hazard model adjusted for the age revealed that the CrCl 15-29 mL/min group was significantly associated with increased MB compared to the CrCl \geq 50 mL/min group (hazard ratio: 9.76, 95% confidence interval: 2.69-35.5, $P < .001$). Similar results were observed when adjusting for other multiple clinical factors.

Conclusion: This study demonstrated that the degree of renal dysfunction was a significant prognostic factor for MB in AF patients receiving DOACs.

KEYWORDS

atrial fibrillation, direct oral anticoagulants, renal dysfunction

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1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and is more common among patients with renal dysfunction.¹ This leads to important anticoagulant therapeutic challenges as both the bleeding and stroke risk increase in patients with comorbid AF and renal dysfunction.²⁻⁴ Although warfarin is often prescribed in these patients to reduce the risk of ischemic strokes, the benefit for thromboembolisms without an effect on bleeding events using warfarin has been controversial.^{2,5,6} The Japanese guidelines document that rivaroxaban, apixaban, and edoxaban are viable options even in patients with a severely impaired renal function, that is, a creatinine clearance (CrCl) of 15-29 mL/min.⁷ All direct oral anticoagulants (DOACs) are dependent on the kidney for elimination. Thus, the decision-making process to initiate them for a DOAC treatment should be done while carefully considering the risk-benefit ratio. Prior meta-analyses of randomized and Phase III trials have well demonstrated that DOACs were at least as safe and effective as dose-adjusted warfarin for the management of AF. However, the clinical evaluation of a DOAC treatment in patients with a CrCl of 15-29 mL/min is still limited.^{8,9} The objective of this study was to evaluate the safety and efficacy of DOACs in patients with a severely impaired renal function as compared to those with a mildly or moderately impaired renal function.

2 | METHODS

2.1 | Study population

This was a retrospective and observational study of 894 consecutive patients who were diagnosed with AF and treated with DOACs (rivaroxaban, apixaban, or edoxaban) between August 2014 and December 2017 at our hospital (Toho University Omori Medical Center, Tokyo, Japan). The patient observation began at the time of initiation of the anticoagulant treatment. The start date of the DOACs was considered the date the prescription was dispensed. Since the prescription of dabigatran in patients with a CrCl of <30 mL/min is regarded as a contraindication by the current dosing recommendations of the Japanese Ministry of Health, Labour and Welfare,^{7,10} we excluded those patients receiving dabigatran from the present study.

2.2 | Administration of DOACs

The type of DOAC was selected by the patient's primary physician based on the Japanese recommendations in the drug package insert, either rivaroxaban with a dose of 15 mg/d (at a reduced dosage of 10 mg/d in patients with a CrCl of 15-49 mL/min), apixaban with a dosage of 10 mg/d (at a reduced dosage of 5 mg/d in patients with more than two of the following criteria: an age \geq 80 years, body weight (BW) \leq 60 kg, and serum creatinine \geq 1.5 mg/dl), or edoxaban with a dosage of 60 mg/d (at a reduced dosage of 30 mg/d in patients

with a BW \leq 60 kg or CrCl of 15-49 mL/min).¹¹ An inappropriate dose of the DOACs was defined as patients with an over- or under-dose as compared to an appropriate dose of DOACs.

2.3 | Clinical data

In the present study, the baseline clinical data for each patient at the time of the initial DOAC prescription was retrieved from the medical history. The CHADS₂ and CHA₂DS₂-VASc scores, which reflect the risk of an ischemic stroke, and HAS-BLED score for the risk of bleeding were assessed. The CrCl was calculated using the Cockcroft-Gault formula.^{12,13} Cancer included a past history of cancer and active cancer. Active cancer was defined as evidence of a neoplasm on imaging or ongoing cancer therapy.

2.4 | Safety and efficacy outcomes

The primary safety outcome of the present study was represented by the incidence rate of major bleeding (MB). The primary efficacy outcome included the incidence of thromboembolic events (TEs) consisting of ischemic strokes and systemic embolisms (SEs). MB was defined as fatal bleeding, bleeding in a critical area or organ, a transfusion of two or more units of whole blood or red cells, or a decreased hemoglobin level of 2 g/dL while on the DOAC treatment.¹⁴ Ischemic strokes were defined as a loss of neurological function with a sudden onset lasting \geq 24 hours. SEs were defined as thromboembolisms outside the brain.¹⁵ The time until their first bleed or TE, discontinuation of the treatment, treatment switch to a different OAC, patient death, or the end of the study period (August 31st, 2018) was used in the calculations. The patients enrolled for the analysis were divided into three groups based on their CrCl value (CrCl \geq 50 mL/min group, CrCl 30-49 mL/min group, and CrCl 15-29 mL/min group).

2.5 | Statistical analysis

Data were analyzed using EZR on R-commander version 1.24 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). The data were expressed as the mean \pm SD for normally distributed variables, and as the median (quartile: 25%-75%) for continuous variables with a non-normal distribution. The incidence rate was calculated using the person-year method (events per 100 person-years). The relationship between the renal function and incidence rate of MB or TEs was analyzed using the Kaplan-Meier method, and the curves were compared using a log-rank test. As sub-analyses, we compared the incidence rate of MB or TEs grouped by the renal function in each DOAC group using a log-rank test. In addition, we compared the incidence rate of MB among the three DOAC groups based on the renal function using a log-rank test. Moreover, the enrolled patients were

divided into three groups: appropriate dose of DOACs ($n = 744$), inappropriate under-dose of DOACs ($n = 138$), and inappropriate over-dose of DOACs ($n = 12$) groups. We compared the incidence rate of MB among the three treatment groups based on the renal function by means of a log-rank test. We investigated the comparisons between the patients with and without MB by a univariate logistic regression analysis (Fisher's exact test, Unpaired t test, or Mann-Whitney test). A multivariate analysis using a Cox proportional hazard model was constructed to identify the predictors of the occurrence of MB. This model was adjusted by the CrCl value and other multiple factors including the age (Model 1), BW (Model 2), history of coronary artery disease (CAD) (Model 3), HASBLED score (Model 4), and history of cancer (Model 5). In this study, a value of $P < .05$ was considered statistically significant.

2.6 | Ethical considerations

This study was performed in accordance with the Code of Federal Regulations and the Declaration of Helsinki. The present study was approved by the Ethics Committee of Toho University Omori Medical Center (approval number: M19122). Comprehensive agreement was obtained from all patients and informed consent was obtained in the opt-out form on the web-site of Toho University Omori Medical Center.

3 | RESULTS

3.1 | Patient characteristics

The baseline characteristics are shown in the Table 1. Seventy percent of the patients ($n = 634$) were in the CrCl ≥ 50 mL/min group, and 23.2% ($n = 207$) and 5.9% ($n = 53$) were in the CrCl 30-49 mL/min and CrCl 15-29 mL/min groups, respectively. The lower CrCl value groups included more elderly and female patients, and they had a lower BW. Those groups also had more comorbidities including HF, ischemic strokes, and cancer. The CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores in the CrCl 30-49 mL/min group and CrCl 15-29 mL/min group were comparable, while those in the CrCl ≥ 50 mL/min group were significantly lower than that in the other two groups.

Regarding the type of DOAC used, rivaroxaban, apixaban, and edoxaban were used in 321 (35.9%), 482 (53.9%), 91 (10.2%) patients, respectively. The prescription rates of apixaban increased as the CrCl decreased. In contrast, the prescription rates of rivaroxaban decreased as the CrCl decreased. In the CrCl 15-29 mL/min group, the most frequently used DOAC was apixaban (64.2%, $n = 34$), followed by rivaroxaban (26.4%, $n = 14$) and edoxaban (9.4%, $n = 5$), respectively. The proportion of patients receiving appropriate doses of DOACs was higher in the CrCl 15-29 mL/min group (92.5%, 49/53) than the CrCl 30-49 mL/min group (74.4%, 154/207) and CrCl ≥ 50 mL/min group (85.3%, 541/634). There were no significant

differences in the baseline characteristics among the three DOAC groups in the CrCl 15-29 mL/min group.

3.2 | Primary safety outcome

During the median follow-up period of 15.6 (4.3-26.8) months, 16 patients had MB while on a DOAC treatment (1.4/100 person-years). The MB events involved gastrointestinal bleeding ($n = 9$), cerebral hemorrhages ($n = 2$), intramuscular bleeding ($n = 2$), hemoptysis ($n = 1$), and unknown causes ($n = 2$). An increased risk of MB was observed in the CrCl 15-29 mL/min group ($n = 6$, 9.0/100 person-years) as compared to the CrCl 30-49 mL/min group ($n = 4$, 1.2/100 person-years) and CrCl ≥ 50 mL/min group ($n = 6$, 0.8/100 person-years). The Kaplan-Meier curve demonstrated that the incidence rate of MB was significantly higher in the CrCl 15-29 mL/min group than the CrCl 30-49 group and CrCl ≥ 50 mL/min group (log rank test, $P < .001$) (Figure 1).

The incidence rate of MB in each DOAC group based on the renal function is presented in Table 2. In the rivaroxaban and edoxaban groups, the incidence rate of MB in the CrCl 15-29 mL/min group was significantly higher than that in CrCl 30-49 and CrCl ≥ 50 mL/min groups. On the other hand, in the apixaban group, the incidence rate of MB among the three groups according to the renal function was comparable. In the CrCl 15-29 mL/min group, the incidence rate of MB tended to be lower in the patients receiving apixaban than in those receiving rivaroxaban or edoxaban (log rank test, $P = .17$). In the CrCl ≥ 50 mL/min group and 30-49 mL/min group, the incidence rate of MB among the three DOAC groups was comparable (log rank test, $P = .062$, $P = .063$, respectively).

The enrolled patients were divided into three groups: appropriate dose of DOACs ($n = 744$), inappropriate under-dose of DOACs ($n = 138$), and inappropriate over-dose of DOACs ($n = 12$) groups. The incidence rate of MB (1.5/100 person-years vs 1.0/100 person-years vs 0.0/100 person-years, log-rank test, $P = .99$) did not differ among the three treatment groups. In any of the CrCl ≥ 50 , 30-49, and 15-29 mL/min groups, the incidence rate of MB among the three treatment groups was comparable (log rank test, $P = .99$, $P = 1.0$, $P = .99$, respectively).

Table 3 shows that the patients with MB had a lower CrCl value, lower BW, and included more cases that were elderly and had CAD and cancer than those with no-MB. There was no significant difference in the HASBLED score, type of DOAC used, and prevalence of patients taking an inappropriate dose of the DOACs between the two groups. The multivariate analyses using a Cox proportional hazard model after adjusting for multiple clinical factors to predict MB are presented in Table 4. After adjusting for the age, the CrCl 15-29 mL/min group (reference to CrCl ≥ 50 mL/min group) was determined to be the most significant prognostic factor for MB (Hazard ratio [HR]: 9.76, 95% confidence interval [CI]: 2.69-35.5, $P < .001$) (Model 1). Similarly, the CrCl 15-29 mL/min group was significantly associated with an increased risk of MB after adjusting for the BW

TABLE 1 Baseline characteristics

	Overall	CrCl ≥ 50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	P value
Number of patients	N = 894	N = 634	N = 207	N = 53	
Age (y)	69.6 (62.0-79.0)	65.8 (59.0-75.0)*†	77.7 (74.0-83.0)*	82.3 (76.0-87.0)	<.001 ^{##}
Male (%)	598 (66.9)	438 (69.1)*	135 (65.2)	25 (47.2)	.005 [#]
Body weight (kg)	60.6 (50.9-69.5)	64.2 (54.9-72.5)*†	55.4 (46.4-60.9)*	45.2 (37.0-53.3)	<.001 ^{##}
Body mass index (kg/m ²)	23.2 (20.3-25.5)	24.1 (21.5-26.3)*†	21.4 (18.9-23.6)*	18.9 (16.1-21.3)	<.001 ^{##}
Non-paroxysmal AF (%)	371 (41.5)	244 (38.5)†	102 (49.3)	25 (47.2)	.002 [#]
Hypertension (%)	501 (56.0)	345 (54.4)	128 (61.8)	28 (52.8)	.15 [#]
Diabetes mellitus (%)	195 (21.8)	130 (20.5)	57 (27.5)	8 (15.1)	.06 [#]
History of heart failure (%)	183 (20.5)	94 (14.8)*†	63 (30.4)	26 (49.1)	<.001 [#]
History of coronary artery disease (%)	101 (11.3)	62 (9.8)	33 (15.9)	6 (11.3)	.06 [#]
History of stroke (%)	96 (10.7)	56 (8.8)†	32 (15.5)	8 (15.1)	.02 [#]
Cancer (%)	164 (18.3)	98 (15.5)*†	49 (23.7)	17 (32.1)	.001 [#]
CHADS ₂ score (mean)	1.7 (1.0-2.0)	1.5 (1.0-2.0)*†	2.2 (1.0-3.0)	2.1 (1.0-3.0)	<.001 ^{##}
CHA ₂ DS ₂ -VASc score (mean)	2.8 (2.0-4.0)	2.4 (1.0-3.0)*†	3.5 (3.0-4.0)	3.6 (3.0-4.0)	<.001 ^{##}
HASBLED score (mean)	1.6 (1.0-2.0)	1.5 (1.0-2.0)*†	2.0 (1.0-2.0)	2.0 (1.0-3.0)	<.001 ^{##}
Laboratory data					
Hemoglobin level (g/L)	13.4 (12.2-14.7)	13.6 (12.4-14.8)*†	12.0 (10.6-13.3)	12.7 (11.2-14.3)	<.001 ^{##}
Creatinine level (μmol/L)	0.90 (0.7-1.0)	0.80 (0.7-0.9)*†	1.07 (0.8-1.2)*	1.36 (1.0-1.6)	<.001 ^{##}
CrCl value (mL/min)	68.6 (47.0-85.2)	81.3 (60.9-95.0)*†	40.9 (36.3-45.8)*	24.9 (22.7-28.2)	<.001 ^{##}
Echocardiography findings					
LVEF (%)	62.0 (55.1-71.7)	63.4 (57.4-72.2)*†	59.7 (51.2-70.8)	54.6 (44.3-67.5)	<.001 ^{##}
Left atrial distance (mm)	40.6 (35.1-45.2)	40.4 (35.1-44.7)	40.9 (35.2-46.7)	42.7 (36.7-45.7)	.09 ^{##}
Medication history					
Using anti-platelet agent (%)	166 (18.6)	108 (17.0)	45 (21.7)	13 (24.5)	.25 [#]
Previous catheter ablation (%)	241 (27.0)	207 (32.6)*†	28 (13.5)	6 (11.3)	<.001 [#]
DOACs					
Rivaroxaban (%)	321 (35.9)	242 (38.2)	65 (31.4)	14 (26.4)	.07 [#]
Apixaban (%)	482 (53.9)	325 (51.3)	123 (59.4)	34 (64.2)	.05 [#]
Edoxaban (%)	91 (10.2)	67 (10.6)	19 (9.2)	5 (9.4)	.89 [#]
Inappropriate					
Under-dose (%)	138 (15.4)	88 (13.9)†	46 (22.2)	4 (7.5)	.005 [#]
Over-dose (%)	12 (1.3)	5 (0.8)†	7 (3.4)	0 (0.0)	.02 [#]

Note: Data are expressed as the median (25%-75%), or n (%).

Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; LVEF, left ventricular ejection fraction.

P values were determined by a [#]Fisher's exact test, or ^{##}Kruskal-Wallis test.

*P < .05 vs CrCl 15-29 mL/min.

†P < .05 vs CrCl 30-49 mL/min.

(Model 2), a history of CAD (Model 3), the HASBLED score (Model 4), and a history of cancer (Model 5).

3.3 | Primary efficacy outcome

During the follow-up period, TEs occurred in 10 patients (0.9/100 person-years). Of those, all had an ischemic stroke. Seven patients in the CrCl ≥ 50 mL/min group (0.9/100 person-years), two in the

CrCl 30-49 mL/min group (0.6/100 person-years), and one in the CrCl 15-29 mL/min group (1.5/100 person-years) experienced TEs. A Kaplan-Meier curve demonstrated that the incidence rate of TEs did not significantly differ among the three groups (log rank test, P = .71) (Figure 2). The incidence rate of TEs in each DOAC group based on the renal function is presented in Table 5. In all DOAC groups, there were no significant differences in the incidence rate of TEs among the three groups according to the renal function.

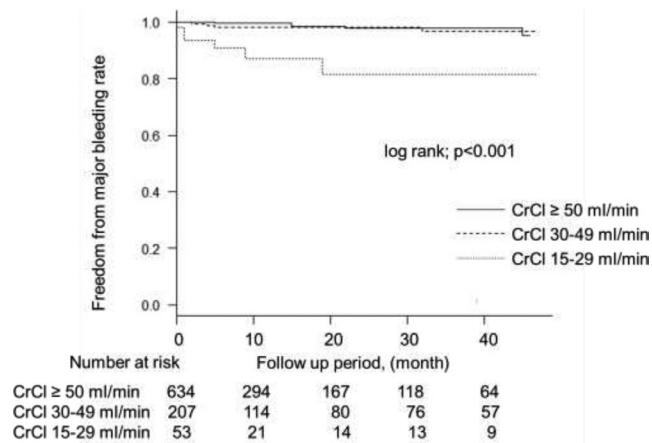


FIGURE 1 Kaplan-Meier curves regarding MB during the follow-up period. This figure shows the comparison of the event-free rate according to the renal function. The dotted line represents the CrCl 15-29 mL/min group. The fine dotted line represents the CrCl 30-49 mL/min group. The normal line represents the CrCl ≥ 50 mL/min group. The rate in the CrCl 15-29 mL/min group was significantly lower than that in the CrCl ≥ 50 mL/min group and CrCl 30-49 mL/min group (log rank test, $P < .001$). CrCl indicates creatinine clearance

4 | DISCUSSION

The main finding of the present study was that AF patients receiving DOACs with a CrCl of 15-29 mL/min had a significantly increasing risk for MB as compared to that in those with a CrCl of 30-49 and ≥50 mL/min. In the CrCl 15-29 mL/min group, the patients receiving apixaban tended to have a lower risk for MB than those receiving rivaroxaban or edoxaban. Of importance, the incidence rate of TEs among the three groups according to the renal function was comparable. To the best of our knowledge, this is the first study to demonstrate the safety and efficacy outcomes according to the type of DOAC among AF patients across the various renal function groups including patients with a CrCl of 15-29 mL/min.

The pharmacokinetics of the DOACs are largely influenced by the renal function and thus require a dose adjustment in patients with renal dysfunction.¹⁶ Among the DOACs, the renal excretion rates are 80% for dabigatran, 66% for rivaroxaban, 50% for edoxaban, and

27% for apixaban.^{17,18} Based on these differences in the renal excretion rates among the individual DOACs, rivaroxaban, apixaban, and edoxaban are licensed for use in those with a CrCl level of up to as low as 15 mL/min and dabigatran a CrCl level as low as 30 mL/min in Japan and Europe.¹⁹ On the other hand, dabigatran in patients with a CrCl of 15-29 mL/min and apixaban in those with end-stage renal disease are approved in the United States.^{20,21} The present study revealed that patients receiving DOACs with a CrCl of 15-29 mL/min had an approximately 10.0-fold increased risk for MB than those with a CrCl ≥ 50 mL/min, while the majority of the patients with a CrCl of 15-29 mL/min were prescribed appropriate doses of DOACs. Of importance, all the patients that suffered from MB in the CrCl 15-29 mL/min group had received appropriate doses of DOACs. Our findings reflect that the appropriateness of the current dosing recommendations for patients with renal dysfunction has not been fully evidenced.²²⁻²⁴

Recently, the J-ELD AF registry sub-analysis was conducted to evaluate the efficacy and safety of apixaban in Japanese AF patients with renal dysfunction.²⁵ The analysis revealed that the incidence rate of bleeding events in the CrCl 15-29 mL/min group was similar to that in the CrCl 30-49 and ≥50 mL/min groups. The authors attributed this result to the minimal renal excretion rate of apixaban. Our results also showed that in the apixaban group the incidence rate of MB in the CrCl 15-29 mL/min group was comparable to that in the CrCl 30-49 and CrCl ≥ 50 mL/min groups. Unfortunately, we were not able to conduct a multivariate analysis to evaluate the prognostic values of renal dysfunction associated with MB in each DOAC group due to a small number of MB events. However, in the CrCl 15-29 mL/min group, the incidence rate of MB tended to be lower in the patients receiving apixaban than in those receiving rivaroxaban or edoxaban. Thus, we inferred that, in AF patients with a CrCl of 15-29 mL/min, the use of apixaban may be relatively safer than that of other DOACs. Taken together, we have to be more cautious when selecting the type of DOAC in patients with a CrCl of 15-29 mL/min, as the incidence rate of MB depends on the renal excretion rate of each DOAC even if patients with a CrCl of 15-29 mL/min adhere to the current dosing recommendation. Further larger studies are needed to reconsider the appropriate dose adjustment of each DOAC based on their renal excretion rate in these populations.

	CrCl ≥ 50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	P value
Rivaroxaban, n (per 100 person years)	0 (0.0)*	1 (0.8)	3 (14.3)	<.001
Apixaban, n (per 100 person years)	6 (1.4)	1 (0.5)	2 (4.6)	.19
Edoxaban, n (per 100 person years)	0 (0.0)*	2 (11.4)	1 (40.0)	.001

Note: P values were determined by a Fisher's exact test.

Abbreviations: CrCl, creatinine clearance; DOACs, direct oral anticoagulants; MB, major bleeding.

* $P < .05$ vs CrCl 15-29 mL/min.

TABLE 2 The incidence of MB in each DOAC group based on the renal function

TABLE 3 Comparison of the patients between with and without MB

	MB (n = 16)	Non-MB (n = 878)	P value
Age (y)	78.5 (73.0-82.5)	71.0 (62.0-78.0)	.006 ^{##}
Male (%)	8 (50.0)	590 (67.2)	.18 [#]
Body weight (kg)	52.6 (43.3-59.8)	60.0 (51.1-69.6)	.03 ^{##}
Body mass index (kg/m ²)	21.4 (19.0-23.6)	23.0 (20.3-25.5)	.16 ^{##}
Non-paroxysmal AF (%)	10 (62.5)	361 (41.1)	.18 [#]
Hypertension (%)	6 (37.5)	495 (56.4)	.20 [#]
Diabetes mellitus (%)	5 (31.2)	190 (21.6)	.36 [#]
History of heart failure (%)	6 (37.5)	177 (20.2)	.11 [#]
History of coronary artery disease (%)	5 (31.2)	96 (10.9)	.03 [#]
History of stroke (%)	1 (6.2)	95 (10.8)	.99 [#]
Cancer (%)	7 (43.8)	157 (17.9)	.02 [#]
CHADS ₂ score (mean)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	.40 ^{##}
CHA ₂ DS ₂ -VASc score (mean)	3.0 (3.0-4.0)	3.0 (2.0-4.0)	.15 ^{##}
HASBLED score (mean)	2.0 (1.0-2.5)	2.0 (1.0-2.0)	.80 ^{##}
Laboratory data			
Hemoglobin level (g/L)	13.5 (11.8-13.9)	13.4 (12.2-14.7)	.32 ^{##}
Creatinine level (μmol/L)	1.11 (0.8-1.2)	0.85 (0.7-1.0)	.02 ^{##}
CrCl value (mL/min)	41.7 (24.7-54.5)	63.6 (47.3-85.4)	<.001 ^{##}
Echocardiography findings			
LVEF (%)	62.4 (47.4-71.2)	65.0 (55.1-71.7)	.45 ^{##}
Left atrial distance (mm)	42.7 (35.0-49.2)	39.3 (35.1-45.0)	.41 ^{##}
Medication history			
Using anti-platelet agent (%)	6 (37.5)	159 (18.1)	.11 [#]
Previous catheter ablation (%)	2 (12.5)	239 (27.2)	.26 [#]
DOACs			
Rivaroxaban (%)	4 (25.0)	317 (36.1)	.44 [#]
Apixaban (%)	9 (56.2)	473 (53.9)	.99 [#]
Edoxaban (%)	3 (18.8)	88 (10.0)	.21 [#]
Inappropriate			
Under-dose (%)	2 (12.5)	136 (15.5)	.99 [#]
Over-dose (%)	0 (0.0)	12 (1.4)	.99 [#]

Note: Data are expressed as the median (25%-75%), or number (%).

P values were determined by a [#]Fisher's exact test or ^{##}Mann-Whitney U test.

Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance; DOACs, direct oral anticoagulants; LVEF, left ventricular ejection fraction; MB, major bleeding.

Whether the dose recommendations of DOACs are adhered to in clinical practice remains a major concern. As shown in previous studies, in which the majority of the patients on inappropriate doses of DOACs were found to be on a lower dose than recommended,^{26,27} we also found that the use of inappropriate under-doses of DOACs was more frequent than inappropriate over-doses of DOACs. In this study, approximately 30% of the patients in the CrCl 30-49 mL/min group received inappropriate doses of DOACs, which may have affected the study outcomes. However, the incidence rate of MB in the CrCl 30-49 min/min group did not differ among the appropriate dose of DOACs, inappropriate under-dose of DOACs, and

inappropriate over-dose of DOACs groups. These data are in line with the results of the previous studies, which showed that there were no significant differences in bleeding events in patients with inappropriate doses of DOACs and those with appropriate doses of DOACs.^{28,29} Taking that into consideration, we expect that the incidence rate of clinical events would not fluctuate even if all the patients in the CrCl 30-49 min/min group took appropriate doses of DOACs. While an appropriate dose prescription of DOACs is certainly mandatory, further study of the outcomes associated with inappropriate doses of DOACs in AF patients with renal dysfunction is needed.

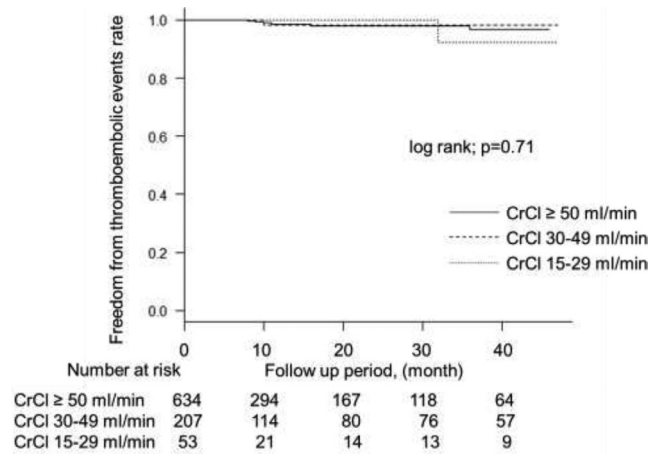
TABLE 4 Multivariate Cox-proportional hazard analysis for occurrence of MB

	HR (95% CI)	P value
Model 1. Age \geq 75 y + CrCl		
Age \geq 75	1.36 (0.43-4.29)	.60
CrCl \geq 50 mL/min	1 (REF)	—
CrCl 30-49 mL/min	1.39 (0.36-5.45)	.64
CrCl 15-29 mL/min	9.76 (2.69-35.5)	<.001
Model 2. Body weight \leq 60 kg + CrCl		
Body weight \leq 60	1.00 (0.33-3.00)	.99
CrCl \geq 50 mL/min	1 (REF)	—
CrCl 30-49 mL/min	1.57 (0.43-5.80)	.50
CrCl 15-29 mL/min	11.5 (3.44-38.1)	<.001
Model 3. History of coronary artery disease + CrCl		
History of coronary artery disease	2.78 (0.81-9.57)	.11
CrCl \geq 50 mL/min	1 (REF)	—
CrCl 30-49 mL/min	1.36 (0.37-5.00)	.72
CrCl 15-29 mL/min	11.0 (3.50-34.8)	<.001
Model 4. HASBLED score (mean) $>$ 3 + CrCl		
HASBLED score (mean) $>$ 3	0.66 (0.18-2.41)	.53
CrCl \geq 50 mL/min	1 (REF)	—
CrCl 30-49 mL/min	1.62 (0.45-5.91)	.46
CrCl 15-29 mL/min	12.4 (3.86-39.8)	<.001
Model 5. Cancer + CrCl		
Cancer	2.55 (0.93-6.99)	.07
CrCl \geq 50 mL/min	1 (REF)	—
CrCl 30-49 mL/min	1.44 (0.40-5.23)	.58
CrCl 15-29 mL/min	9.48 (2.95-30.5)	<.001

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; MB, major bleeding; REF, reference.

4.1 | Limitations

The present study had several limitations. First, the analysis was performed in a single center, and the number of patients with a

**FIGURE 2** Kaplan-Meier curves regarding TEs during the follow-up period. This figure shows the comparison of the event-free rate according to the renal function. The dotted line represents the CrCl 15-29 mL/min group. The fine dotted line represents the CrCl 30-49 mL/min group. The normal line represents the CrCl \geq 50 mL/min group. The rate was comparable among the three groups (log rank test, $P = .71$). CrCl indicates creatinine clearance

CrCl of 15-29 mL/min and the clinical events were small. Thus, it should be noted that the prognostic value of renal dysfunction for the clinical outcomes might not be fully evaluated. Especially, we enrolled only five patients receiving edoxaban in the CrCl 15-29 mL/min group when our survey was conducted, because of the limited spread within the market during that early period after it obtained approval in Japan. We need to be careful in interpreting the results regarding the safety and efficacy of edoxaban in the CrCl 15-29 mL/min group. However, the proportion of patients receiving edoxaban in the CrCl 15-29 mL/min group in our study was comparable to that in the ETNA-AF-Japan study, which examined the efficacy and safety of edoxaban in Japanese AF patients (5.5% vs 4.8%).³⁰ Taking that into consideration, the amount of the AF patients treated with edoxaban in the CrCl 15-29 mL/min group might be appropriate for a single-center study. Second, this was a retrospective and observational study, and therefore the first selection of the DOAC was decided for each patient by the physician and was nonrandomized. In addition, because of the retrospective characteristic of this study, the prognostic value

	CrCl \geq 50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	P value
Rivaroxaban, n (1/100 person years)	1 (0.4)	1 (0.8)	0 (0.0)	.43
Apixaban, n (1/100 person years)	5 (1.2)	1 (0.5)	1 (2.3)	.52
Edoxaban, n (1/100 person years)	1 (1.9)	0 (0.0)	0 (0.0)	.99

Note: P values were determined by a Fisher's exact test.

Abbreviations: CrCl, creatinine clearance; DOACs, direct oral anticoagulants; TEs, thromboembolic events.

TABLE 5 The incidence of TEs in each DOAC group based on the renal function

of renal dysfunction for the clinical outcomes was not directly evaluated. Even though there were significant differences in the clinical characteristics among the three groups based on the CrCl value, a multivariate Cox regression analysis showed the statistically significant association between the CrCl 15–29 mL/min group and an increased risk for MB. Therefore, we inferred that the CrCl 15–29 mL/min group may be indeed a significant predictor of MB. Future prospective studies with large populations are needed to more accurately confirm the prognostic values of renal dysfunction in AF patients receiving DOACs and to compare them according to the DOAC type. Finally, we had a serum creatinine level drawn only at the time of the DOAC initiation. We therefore did not investigate the changes in the renal function over time. A significant proportion of AF patients have experienced fluctuations in the renal function while on a DOAC treatment.^{31,32} Thus, it is strictly unknown whether patients with renal dysfunction at baseline are still in a state of renal dysfunction when they experience their clinical events.

5 | CONCLUSIONS

In the current study of patients with comorbid AF and renal dysfunction, a severely impaired renal function was significantly associated with an increased risk of MB. The use of apixaban might be effective and relatively safe in AF patients with a severely impaired renal function because of its minimal renal excretion rate.

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CONFLICT OF INTEREST

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