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Author(s)	Matsuoka, Yuki; Sakamoto, Daisuke; Sunaga, Akihiro et al.
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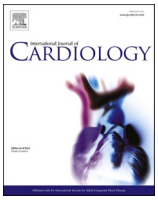

Clinical impact of kidney function in patients with atrial fibrillation receiving oral anticoagulants

Yuki Matsuoka [a], Daisuke Sakamoto [a], Akihiro Sunaga [a], Katsuki Okada [a,b], Daisaku Nakatani [a], Tetsuhisa Kitamura [c], Takashi Kanda [d], Hitoshi Minamiguchi [d], Ryuta Watanabe [e], Kouichi Nagashima [e], Yoshiharu Higuchi [d], Yasuo Okumura [e], Yohei Sotomi [a,*], Yasushi Sakata [a]

[a] Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[b] Department of Medical Informatics, Osaka University Graduate School of Medicine, Osaka, Japan
[c] Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[d] Cardiovascular Division, Osaka Keisatsu Hospital, Osaka, Japan
[e] Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

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ABSTRACT

Background: Renal function influences the pharmacokinetics of oral anticoagulants in atrial fibrillation (AF), potentially affecting both efficacy and bleeding risk. However, its differential impact across specific agents remains unclear. In this study, we aimed to evaluate the association between renal function and ischemic and bleeding risks in patients with AF, with analyses stratified by anticoagulant type.

Methods: We analyzed 7239 patients with non-valvular AF from the DIRECT-Extend registry, a pooled dataset of three large-scale registries. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula and categorized into ≥50, 30 to <50, and 15 to <30 mL/min. The primary ischemic endpoint was stroke or systemic embolism, and the primary bleeding endpoint was major bleeding. Cox proportional hazard models and restricted cubic spline analyses assessed associations between CrCl and outcomes, with subgroup analyses by anticoagulant type.

Results: Lower CrCl was associated with older age, female sex, and greater comorbidity burden. Impaired renal function was significantly associated with higher ischemic and bleeding risks. Spline analysis demonstrated a continuous increase in both risks with declining CrCl, with a nonlinear relationship for bleeding. Subgroup analyses revealed significant associations between reduced CrCl and ischemic risk in patients on dabigatran, rivaroxaban, edoxaban, and warfarin. Increased bleeding risk was evident for edoxaban and warfarin at lower CrCl levels. No significant association was observed between CrCl and either endpoint in patients receiving apixaban.

Conclusion: In this large real-world cohort, declining renal function was associated with increased ischemic and bleeding risks, highlighting the importance of renal function–based risk assessment in the management of anticoagulation therapy.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia. Direct oral anticoagulants (DOACs) and vitamin K antagonists are widely used to prevent stroke and systemic embolism. [1–4] Their plasma concentrations are influenced by renal function, as each drug is partially metabolized by the kidneys. [1,2] In clinical practice, dose adjustments based on renal function are necessary, making renal function a key consideration in the management of patients with AF. AF and chronic kidney disease (CKD) are closely related conditions that share common risk factors, such as hypertension and diabetes. [5] The prevalence of AF is consistently reported to be higher in patients with CKD than in those without. [6–8] Moreover, CKD itself is recognized as a risk factor for both ischemic and bleeding events. [9,10] Given these complexities, a thorough understanding of how renal function affects ischemic and bleeding events is crucial for optimizing anticoagulation therapy in AF

* Corresponding author at: 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.
E-mail address: sotomiyohei@gmail.com (Y. Sotomi).

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patients. Since each DOAC has distinct pharmacokinetics and dose reduction criteria, their impact on these events may vary depending on the specific DOAC used. However, this association has not been sufficiently investigated. Therefore, this study aims to examine the relationship between renal function and ischemic and bleeding events in AF patients receiving anticoagulation therapy, with a further analysis stratified by each DOAC.

2. Methods

2.1. Study design and study population

We conducted DIRECT-Extend registry (UMIN000050585), a pooled analysis combining three large-scale real-world datasets of non-valvular AF patients treated with anticoagulation [DIRECT registry ($N = 2543$), SAKURA-AF registry ($N = 3268$), and Osaka University Hospital registry ($N = 1742$)]. Patients who visited or were admitted to the study institutions (Osaka University Hospital, Osaka Keisatsu Hospital, and 63 facilities participating in SAKURA-AF) and who were newly prescribed oral anticoagulants for non-valvular AF were enrolled.

1) In the registry of Osaka University Hospital, we retrospectively collected data including patient demographics, comorbidities, medication history, laboratory and echocardiographic data, and outcome information from electronic medical records. This registry included patients prescribed DOACs between March 2011 and December 2021. 2) The DIRECT registry is a single-center registry of non-valvular AF patients on DOACs at Osaka Keisatsu Hospital from June 2011 to November 2017. In addition to the original dataset created in 2017, we further collected additional patient data and extended the follow-up period up to November 2023 for this pooled analysis. 3) The SAKURA-AF registry included 3268 patients with non-valvular AF treated with any anticoagulants including warfarin for stroke prevention in contrast to the former two registries. Patients were enrolled at any of 63 participating institutions (2 cardiovascular centers, 13 affiliated hospitals or community hospitals, and 48 private clinics) in the Tokyo area between September 2013 and December 2015 and followed up until December 2017.

We integrated these three registry datasets and unified the outcomes and variables to create a larger registry of AF patients on anticoagulants, the DIRECT-Extend registry. [11] The registry complies with all the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of each institution.

In this study, we investigated the impact of renal function evaluated by creatinine clearance (CrCl) on ischemic and bleeding events. CrCl was calculated using the Cockcroft-Gault formula, which estimates renal function based on age, body weight, and serum creatinine levels. [12] For male patients, CrCl is calculated by subtracting the patient's age from 140, multiplying by their weight in kilograms, and then dividing by 72 times the serum creatinine concentration in milligrams per deciliter. For female patients, the final result is multiplied by 0.85. Since CrCl of less than 15 mL/min is contraindicated for all anticoagulants except warfarin, these patients were excluded from the present analysis. Renal function and oral anticoagulant dosing were assessed using baseline data at the time of enrollment. DOAC dosing, including dose reduction, was determined at the discretion of the treating physician based on the criteria provided in the Japanese prescribing information and relevant guideline recommendations. [2] Additionally, we conducted a subgroup analysis to evaluate the relationship between CrCl and ischemic and bleeding events for each oral anticoagulant.

2.2. Study endpoints

The primary ischemic endpoint was a composite of any stroke and systemic embolism. The primary bleeding endpoint was major bleeding, according to the criteria of the International Society on Thrombosis and Hemostasis.

2.3. Statistical analysis

All statistical analyses were performed with R software (V.4.3.1; R Foundation for Statistical Computing, Vienna, Austria). *P* values less than 0.05 were considered statistically significant. Categorical variables were expressed as counts (percentages) and compared with the chi-squared test. Continuous variables were expressed as mean (SD) or median (IQR) and were compared using analysis of Student's *t*-test or Kruskal-Wallis test, as appropriate. The entire patient cohort was divided into three groups based on CrCl to evaluate baseline characteristics and clinical outcomes (Category 1, CrCl $\geq$50 mL/min; Category 2, CrCl 30 to <50 mL/min; Category 3, CrCl 15 to <30 mL/min). Survival analysis was performed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. Multivariable Cox proportional hazards models were constructed to estimate hazard ratios (HRs) for the primary ischemic and bleeding endpoints in relation to CrCl, adjusting for diabetes mellitus, hypertension, history of bleeding, vascular disease, and AF type (paroxysmal, persistent, long-standing persistent and unknown). In subgroup analyses, AF type was not included due to a limited number of events. Missing data for variables included in the multivariable analysis were imputed using a random forest algorithm with the missForest package in R. Restricted cubic splines were used to model the association between CrCl and the HR for the primary outcomes, with CrCl of 50 mL/min as the reference. Based on model fit evaluated by the Akaike Information Criterion (AIC), the number of knots was set at 3, which provided optimal or acceptable fit across outcomes. Knots were placed at the 10th, 50th, and 90th percentiles of the CrCl distribution. [13] Non-linear relationships were visualized regardless of the statistical significance for non-linearity. The spline curves were generated using the plotRCS package in R. The overall association (P for overall) and nonlinearity (P for nonlinear) were assessed using analysis of variance (ANOVA) based on the anova function from the rms package. These *p* values were extracted and displayed on the plot. As a sensitivity analysis, we repeated the cubic spline analyses limited to patients who received appropriately dosed oral anticoagulants, based on each agent's labeling criteria. [2]

3. Results

3.1. Study patients

Figure 1 illustrates the patient flowchart. Of 7512 patients, 273 patients were excluded due to the lack of the data of CrCl ($N = 253$) or low CrCl (CrCl <15 mL/min, $N = 20$), leaving 7239 eligible patients. The number of patients with Category 1, 2 and 3 were 5331 (73.6 %), 1554 (21.5 %), and 354 (4.9 %), respectively. Patients' backgrounds are shown in Table 1. Patients with lower renal function were older, had a higher proportion of female, and tended to have lower body mass index. The prevalence of comorbidities such as hypertension, history of stroke or transient ischemic attack, and heart failure was higher in patients with lower CrCl. Regarding the prescribed anticoagulants, dabigatran and rivaroxaban were more frequently prescribed to patients with better renal function, whereas other anticoagulants were more commonly used in patients with impaired renal function. The median follow-up period was 856 [270, 1374] days.

3.2. The prognostic impact of kidney function

Kaplan-Meier curves are illustrated in Supplemental Fig. 1. Patients in Category 1 had a lower incidence of the primary ischemic endpoint (log-rank $p < 0.0001$). For the primary bleeding endpoint, patients in lower CrCl categories experienced a higher number of events (log-rank $p < 0.0001$). The association between renal function and the primary endpoints was further evaluated using cubic spline curves (Fig. 2), showing that poorer renal function was associated with higher risks of both ischemic ($p < 0.001$) and bleeding events ($p < 0.001$). A nonlinear

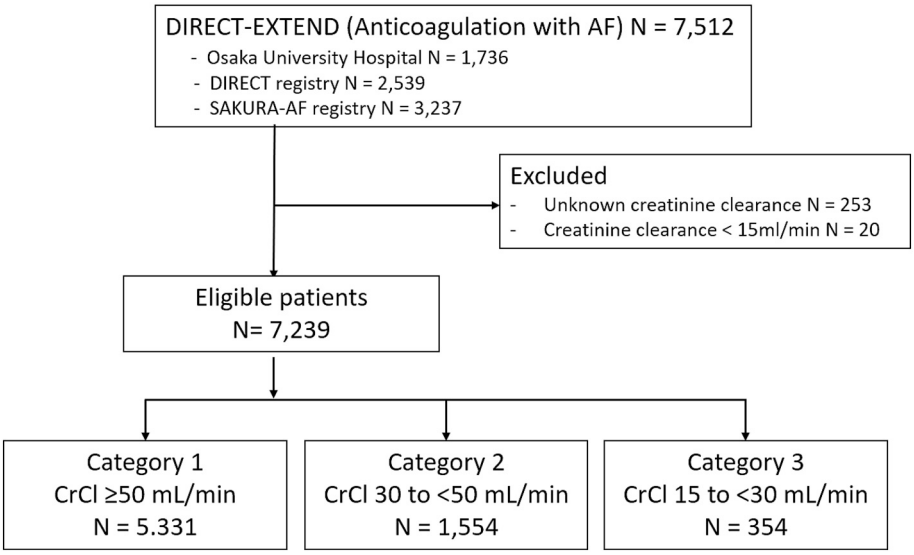

Fig. 1. Study flowchart.
A total of 7512 patients, 273 patients were excluded due to the lack of the data of Creatinine clearance (CrCl) ($N = 253$) or low CrCl (CrCl <15 mL/min), leaving 7239 eligible patients.
Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance.

relationship was observed for the bleeding endpoint (p for nonlinearity = 0.044). Multivariable Cox proportional hazards analysis demonstrated a general trend of increased risk of ischemic and bleeding events with declining CrCl categories, although not all comparisons reached statistical significance (Table 2). While variables such as hypertension and vascular disease were also associated with higher event risk, AF type itself was not significantly associated with the primary outcome (Supplemental Table 1).

3.3. Clinical impact of kidney function in patients with each oral anticoagulant

The patients' backgrounds stratified by the type of anticoagulants are shown in Supplemental Table 2. The number of patients prescribed dabigatran ($N = 1304$), rivaroxaban ($N = 1847$), apixaban ($N = 1645$), edoxaban ($N = 905$), and warfarin ($N = 1538$) were relatively balanced across the different anticoagulants. Patients receiving apixaban or edoxaban were older, had a higher proportion of females, and exhibited a greater burden of comorbidities, including a history of stroke, compared to those receiving other anticoagulants. Moreover, they had higher CHA_2DS_2-VASc scores, and the proportion of patients classified in CrCl category 1 was lower in these groups.

The impact of renal function on the primary endpoints was evaluated using cubic spline curves for each anticoagulant (Fig. 2). Declining CrCl was significantly associated with an increased risk of ischemic events in patients receiving dabigatran ($p = 0.026$), rivaroxaban ($p = 0.003$), and warfarin ($p = 0.015$). For the bleeding endpoint, a significant association was observed in patients receiving edoxaban ($p < 0.001$), and a similar trend was noted for warfarin ($p = 0.058$). In contrast, no significant association between CrCl and event risk was observed for apixaban in either endpoint (ischemic endpoint, $p = 0.190$; bleeding endpoint, $p = 0.431$). These findings remained consistent in a sensitivity analysis limited to patients who received appropriately dosed anticoagulants, based on each agent's labeling criteria (Supplemental Fig. 2).

Further details of clinical outcomes based on CrCl categories are summarized in Table 2. Among patients receiving dabigatran, a significantly increased risk of ischemic events was observed in Category 2 (HR 2.07, 95 % CI 1.06–4.04; $p = 0.033$). In the rivaroxaban group, ischemic risk (HR 2.23, 95 % CI 1.38–3.59; $p = 0.001$) and bleeding risk (HR 1.69, 95 % CI 1.16–2.45; $p = 0.006$) were significantly higher in Category 2. In patients receiving edoxaban, ischemic risk was significantly elevated in Category 2 (HR 2.06, 95 % CI 1.05–4.03; $p = 0.035$), and bleeding risk was significantly higher in Category 3 (HR 4.28, 95 % CI 2.32–7.88; $p < 0.001$). For warfarin, bleeding risk was significantly higher in Category 3 (HR 2.66, 95 % CI 1.23–5.75; $p = 0.013$), while trends toward increased ischemic risk were observed in Categories 2 and 3 (HR 1.76, 95 % CI 0.98–3.17; $p = 0.060$ and HR 2.34, 95 % CI 0.97–5.63; $p = 0.057$, respectively). No significant associations between CrCl categories and event risk were detected in the apixaban group.

4. Discussion

The main findings of the present study, based on a large-scale real-world dataset, are summarized as follows: (1) Among patients receiving anticoagulation therapy, those with higher CrCl had a lower risk of both ischemic and bleeding events. (2) In the analysis of individual anticoagulants, a decline in CrCl was generally associated with an increased risk of ischemic events, bleeding events, or both. However, for apixaban, no significant association was observed between CrCl and either ischemic or bleeding events.

AF and CKD have an interactive relationship, in which CKD increases the risk of incident of AF while AF contributes to the development and progression of CKD. [14,15] AF promotes systemic inflammation, [16] which has been associated with progression of CKD. [17] AF also contributes to decline of left ventricular systolic and diastolic function over time, which may promote progression of CKD through altered hemodynamics, [18,19] venous congestion, and activation of the renin-angiotensin-aldosterone system. [14,20] These mechanisms may be particularly relevant in patients with persistent or long-standing persistent AF, who are chronically exposed to such pathophysiological stressors. In our study, the distribution of AF types varied across renal function categories (Table 1), suggesting a possible link between AF type and kidney dysfunction. However, multivariable analysis did not show the significant associations in ischemic or bleeding outcomes and AF types in this cohort (Supplemental Table 1). This discrepancy between pathophysiological plausibility and clinical outcomes may be partly explained by the fact that all patients were receiving oral anticoagulation therapy and were regularly monitored in clinical practice, which might have mitigated outcome differences across AF types.

In patients with AF, impaired renal function was a significant risk

Table 1
Patient background stratified by creatinine clearance.

	Category 1 (CrCl ≥50 mL/min)	Category 2 (CrCl 30 to <50 mL/min)	Category 3 (CrCl 15 to <30 mL/min)	*P* value	Missing, %
Number	5331	1554	354		
Registry				0.025	0
SAKURA-AF	2416 (45.3)	644 (41.4)	143 (40.4)		
DIRECT registry	1748 (32.8)	532 (34.2)	119 (33.6)		
Osaka university hospital	1167 (21.9)	378 (24.3)	92 (26.0)		
Type of oral anticoagulant				<0.001	0
Dabigatran	1064 (20.0)	223 (14.4)	17 (4.8)		
Rivaroxaban	1432 (26.9)	364 (23.4)	51 (14.4)		
Apixaban	1105 (20.7)	411 (26.4)	129 (36.4)		
Edoxaban	615 (11.5)	232 (14.9)	58 (16.4)		
Warfarin	1115 (20.9)	324 (20.8)	99 (28.0)		
Age	70.0 [63.5, 76.0]	79.0 [74.0, 84.0]	83.0 [78.0, 88.0]	<0.001	0
Female	1392 (26.1)	632 (40.7)	210 (59.3)	<0.001	0
Body mass index, kg/m2	24.2 [21.8, 26.9]	21.7 [19.1, 24.1]	20.9 [18.0, 23.4]	<0.001	1.1
Body weight, kg	65.0 [58.0, 73.6]	54.0 [46.7, 61.0]	48.1 [41.0, 56.0]	<0.001	0
Type of AF				<0.001	0
Paroxysmal	2678 (50.2)	748 (48.1)	151 (42.7)		
Persistent	1008 (18.9)	236 (15.2)	58 (16.4)		
Long-standing persistent	1465 (27.5)	478 (30.8)	125 (35.3)		
Unknown	180 (3.4)	92 (5.9)	20 (5.6)		
History of stroke or transient ischemic attack	880 (16.5)	350 (22.5)	89 (25.1)	<0.001	0
Hypertension	3605 (67.6)	1135 (73.0)	278 (78.5)	<0.001	0
Diabetes	1303 (24.4)	399 (25.7)	93 (26.3)	0.493	0
Dyslipidemia	2539 (47.6)	728 (46.8)	158 (44.6)	0.499	0
History of heart failure	1223 (22.9)	582 (37.5)	213 (60.2)	<0.001	0
Vascular disease	874 (16.4)	378 (24.3)	98 (27.7)	<0.001	0
History of CAD	523 (9.8)	232 (14.9)	57 (16.1)	<0.001	0
History of bleeding	425 (8.0)	185 (11.9)	46 (13.0)	<0.001	0.1
CHA_2DS_2-VASc score				<0.001	0.1
0	297 (5.6)	4 (0.3)	0 (0.0)		
1	809 (15.2)	39 (2.5)	2 (0.6)		
2	1207 (22.7)	165 (10.6)	12 (3.4)		
3	1223 (23.0)	344 (22.2)	44 (12.4)		
4	884 (16.6)	423 (27.2)	99 (28.0)		
5	500 (9.4)	267 (17.2)	87 (24.6)		
6	261 (4.9)	183 (11.8)	56 (15.8)		
7	116 (2.2)	94 (6.1)	33 (9.3)		
8	25 (0.5)	25 (1.6)	17 (4.8)		
9	6 (0.1)	9 (0.6)	4 (1.1)		
Antiplatelet therapy	904 (17.0)	393 (25.3)	94 (26.6)	<0.001	
Beta blocker	2454 (46.0)	792 (51.0)	180 (50.8)	0.001	0
Calcium channel blocker	1382 (25.9)	443 (28.5)	105 (29.7)	0.054	0
Hemoglobin, g/dL	14.0 [12.8, 15.1]	12.7 [11.5, 13.9]	11.6 [10.5, 12.8]	<0.001	1.3
Platelet, $10^3/\mu L$	196.0 [165.0, 232.0]	183.0 [150.0, 221.0]	186.0 [151.5, 225.0]	<0.001	1.6
Creatinine, mg/dL	0.82 [0.70,0.95]	1.03 [0.85,1.23]	1.39 [1.13,1.73]	<0.001	0
B-type natriuretic peptide, pg/mL	95.4 [43.8, 184.7]	169.8 [90.8, 323.4]	254.1 [139.3, 448.9]	<0.001	60.6
N-terminal pro-B-type natriuretic peptide, pg/mL	524.0 [178.0, 1051.0]	1168.0 [486.4, 2334.5]	1839.0 [986.0, 4312.0]	<0.001	58.5
Albumin, g/dL	4.0 [3.7, 4.3]	3.8 [3.4, 4.1]	3.6 [3.2, 3.9]	<0.001	65.4
Low-density lipoprotein cholesterol, mg/dL	103.0 [84.6, 123.0]	98.0 [79.8, 116.8]	98.0 [75.0, 118.5]	<0.001	16.4

Data are expressed as median [IQR] or number (percentage).
Abbreviations: CrCl, creatinine clearance.

factor for left atrial thrombus formation, leading to an increased incidence of thromboembolism and ischemic stroke. [21,22] At the same time, CKD also amplifies the risk of hemorrhagic events through multiple mechanisms, including uremia-related platelet dysfunction, impaired platelet adhesion and aggregation, altered glycoprotein IIb/IIIa receptor activation, and disturbances in von Willebrand factor and nitric oxide metabolism. [23] As a result, the presence of CKD in patients with AF is associated not only with a higher risk of ischemic complications but also with an elevated risk of bleeding. [24,25] Given these dual risks, understanding the impact of renal function on both ischemic and hemorrhagic events is crucial for optimizing anticoagulation therapy in AF patients.

Currently, four DOACs and vitamin K antagonists are available in Japan. [2] The dose reduction criteria differ for each DOAC, based on factors such as serum creatinine levels, body weight, and age. Renal excretion rates play a crucial role, with reported values of 80 % for dabigatran, 35 % for rivaroxaban, 27 % for apixaban, and 50 % for edoxaban. [1] Additionally, while dabigatran is contraindicated in patients with a CrCl below 30 mL/min, the other DOACs are contraindicated in those with a CrCl below 15 mL/min. [2] In the present study, patients receiving apixaban and edoxaban tended to have poorer renal function. Given its relatively low renal excretion rate, apixaban may not have been associated with an increased bleeding risk even in patients with reduced CrCl. This theoretical hypothesis is supported by a previous study demonstrating the consistent superiority of apixaban over warfarin in both efficacy and safety among patients with impaired renal function. [26] Notably, apixaban is the only DOAC evaluated in patients on dialysis or those with end-stage CKD (CrCl <15 mL/min). [4,27] Furthermore, a previous study has suggested that anticoagulants administered twice daily are associated with a lower risk of gastrointestinal bleeding compared to once-daily regimens. [28] In a large-scale real-world population-based cohort study in the United Kingdom (n = 47,242), apixaban provided similar thromboembolism prevention as edoxaban, but was associated with a lower risk of major bleeding in elderly patients with AF. [29] The stable plasma concentration achieved with twice-daily dosing may have contributed to the absence of an

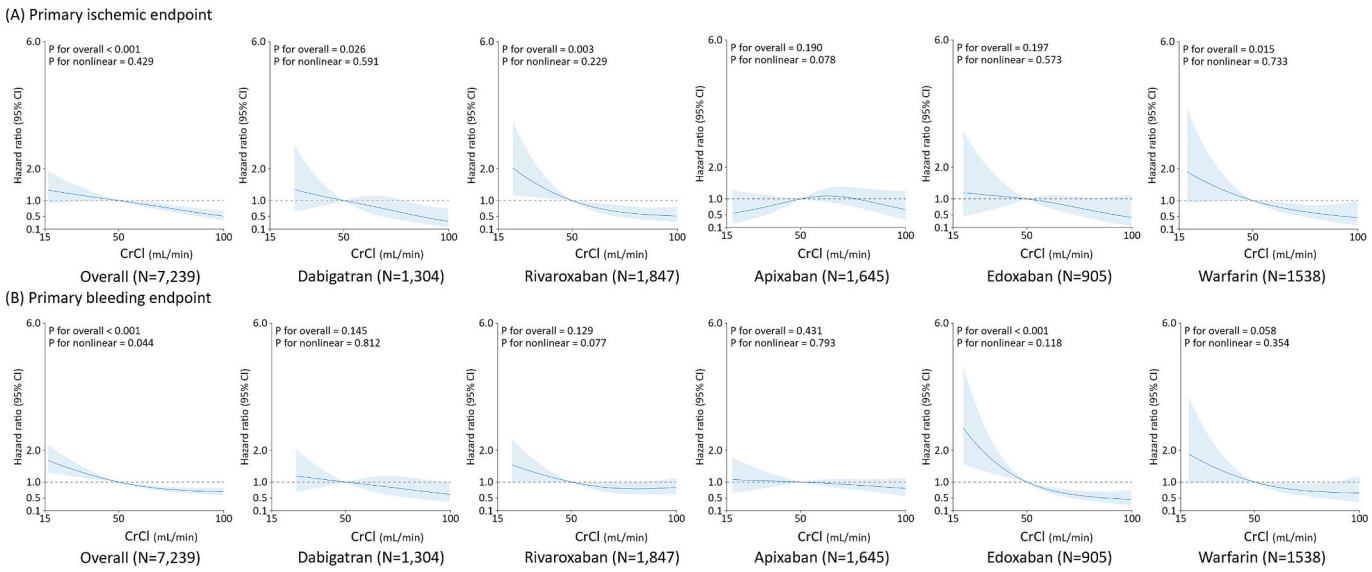

Fig. 2. Cubic spline curves of hazard ratios for ischemic and bleeding outcomes by creatinine clearance in the overall population and each anticoagulant subgroup. Cubic spline curves showing hazard ratios for (A) the primary ischemic and (B) the primary bleeding endpoints by creatinine clearance (mL/min), with a reference value of 50 in overall population and in each oral anticoagulant subgroup. Vertical axis represents hazard ratio, and horizontal axis represents creatinine clearance. Abbreviations: CrCl, creatinine clearance.

Table 2
Event rates of primary endpoints in the overall population and subgroups stratified by the type of anticoagulation therapy.

		Primary ischemic endpoint				Primary bleeding endpoint			
	CrCl category	Event rate (/100 person-year)	$_{adj}$HR	95 % CI	P value	Event rate (/100 person-year)	$_{adj}$HR	95 % CI	P value
Overall	Category 1 (CrCl ≥50)	1.24	1.00	Reference		2.40	1.00	Reference	
	Category 2 (CrCl 30 to <50)	2.28	1.70	(1.32–2.19)	<0.001	<0.001	1.39	(1.15–1.70)	<0.001
	Category 3 (CrCl 15 to <30)	2.10	1.48	(0.89–2.48)	0.132	0.132	2.15	(1.56–2.96)	<0.001
Dabigatran	Category 1 (CrCl ≥50)	1.02	1.00	Reference		1.86	1.00	Reference	
	Category 2 (CrCl 30 to <50)	2.15	2.07	(1.06–4.04)	0.033	2.64	1.35	(0.76–2.38)	0.308
	Category 3 (CrCl 15 to <30)	2.51	2.44	(0.32–18.51)	0.389	2.60	1.18	(0.16–8.59)	0.872
Rivaroxaban	Category 1 (CrCl ≥50)	1.20	1.00	Reference		2.51	1.00	Reference	
	Category 2 (CrCl 30 to <50)	2.89	2.23	(1.38–3.59)	0.001	4.40	1.69	(1.16–2.45)	0.006
	Category 3 (CrCl 15 to <30)	3.18	2.65	(0.95–7.38)	0.062	3.21	1.28	(0.47–3.49)	0.629
Apixaban	Category 1 (CrCl ≥50)	1.73	1.00	Reference		3.63	1.00	Reference	
	Category 2 (CrCl 30 to <50)	1.77	1.00	(0.59–1.70)	0.992	3.93	1.01	(0.70–1.45)	0.958
	Category 3 (CrCl 15 to <30)	1.14	0.60	(0.19–1.93)	0.389	6.73	1.53	(0.90–2.61)	0.119
Edoxaban	Category 1 (CrCl ≥50)	1.55	1.00	Reference		4.14	1.00	Reference	
	Category 2 (CrCl 30 to <50)	3.42	2.06	(1.05–4.03)	0.035	6.94	1.58	(1.00–2.50)	0.052
	Category 3 (CrCl 15 to <30)	2.68	1.31	(0.30–5.70)	0.722	21.16	4.28	(2.32–7.88)	<0.001
Warfarin	Category 1 (CrCl ≥50)	0.98	1.00	Reference		1.12	1.00	Reference	
	Category 2 (CrCl 30 to <50)	1.80	1.76	(0.98–3.17)	0.060	1.80	1.54	(0.87–2.73)	0.143
	Category 3 (CrCl 15 to <30)	2.31	2.34	(0.97–5.63)	0.057	3.15	2.66	(1.23–5.75)	0.013

Abbreviations: CrCl, CrCl: creatinine clearance, expressed in mL/min (Cockcroft–Gault formula); $_{adj}$HR, adjusted hazard ratio; CI, confidence interval.

increased bleeding risk in apixaban users even with renal dysfunction. [30] Rather than comparing different anticoagulants, our analysis focused on assessing the association between renal function and outcomes within each OAC group under a unified dataset and standardized methodology. This within-agent approach reflects real-world prescribing patterns and may support individualized risk assessment and anticoagulation strategies based on patients' renal profiles.

4.1. Clinical implications

In patients with impaired renal function, the risks of both ischemic and bleeding events increased. In the subgroup analysis of each anticoagulant, apixaban did not show a significant increase in event risk with declining CrCl. This finding suggests that the dose reduction criteria for apixaban may be more effective compared to other anticoagulants. These results provide valuable insights for optimizing anticoagulation therapy based on individual patient characteristics.

4.2. Limitation

This study has several limitations. First, information on medication changes, including any modifications to anticoagulation therapy during the follow-up period, was not available. Second, we did not perform head-to-head comparisons between different anticoagulants due to confounding by indication and differences in baseline characteristics. Notably, warfarin-treated patients were exclusively derived from the SAKURA-AF registry, whereas the other two registries included only patients receiving DOAC therapy. Third, the number of patients in Category 3 (CrCl 15 to <30 mL/min) was relatively small, limiting the statistical power to detect associations within this subgroup. Finally, as this study was based solely on Japanese registries, the generalizability of the findings to other populations or healthcare settings may be limited.

5. Conclusion

In this large real-world cohort, declining renal function was associated with increased ischemic and bleeding risks, highlighting the importance of renal function–based risk assessment in the management of anticoagulation therapy.

CRediT authorship contribution statement

Yuki Matsuoka: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daisuke Sakamoto:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Akihiro Sunaga:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Katsuki Okada:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Daisaku Nakatani:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Tetsuhisa Kitamura:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Takashi Kanda:** Writing – review & editing, Supervision. **Hitoshi Minamiguchi:** Writing – review & editing, Supervision. **Ryuta Watanabe:** Writing – review & editing, Supervision, Conceptualization. **Kouichi Nagashima:** Writing – review & editing, Supervision. **Yoshiharu Higuchi:** Writing – review & editing, Supervision. **Yasuo Okumura:** Writing – review & editing, Supervision. **Yohei Sotomi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Funding acquisition. **Yasushi Sakata:** Writing – review & editing, Supervision.

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Declaration of competing interest

Akihiro Sunaga has received personal fees from Daiichi Sankyo. Hidetaka Kioka has received personal fees from Bayer and Daiichi Sankyo. Takashi Kanda has received personal fees from Boehringer Ingelheim, Daiichi Sankyo. Hitoshi Minamiguchi has received personal fees from Bayer, Boehringer Ingelheim, Bristole-Myers Squibb, Daiichi Sankyo, Pfizer Pharmaceuticals. Yasuo Okumura received research grants unrelated to this study from Nippon Boehringer Ingelheim, remuneration from Daiichi-Sankyo, Bayer Healthcare, Bristol-Myers Squibb. Yohei Sotomi has received grants from Bristol-Myers Squibb, and personal fees from Bayer, Boehringer Ingelheim, Bristole-Myers Squibb, Daiichi Sankyo, and Pfizer Pharmaceuticals. Yasushi Sakata has received grants from Bristol-Myers Squibb Company, Bayer AG, and Boehringer Ingelheim, and personal fees from Bristol-Myers Squibb Company, Pfizer Inc., Bayer AG, Daiichi Sankyo Company, and Boehringer Ingelheim. The other authors have nothing to disclose.

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Appendix A. Supplementary data

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