博士学位論文

心房細動患者における直接経口抗凝固薬を用いた抗凝固療法中の腎機能評価の推奨間隔

近畿大学大学院
医学研究科医学系専攻
永野兼也

Doctoral Dissertation

A proposed interval for evaluation of renal function during anticoagulation therapy using direct oral anticoagulants in patients with atrial fibrillation.

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論文題目

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Original article

A proposed interval for evaluation of renal function during anticoagulation therapy using direct oral anticoagulants in patients with atrial fibrillation

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ABSTRACT

Background: Direct oral anticoagulants (DOACs) have been used to prevent cardiogenic embolism in patients with atrial fibrillation (AF). No evidence has been established for the follow-up renal function evaluation intervals. We hypothesized that a proposed follow-up interval of renal function can be estimated by patient's baseline characteristics including creatinine clearance (CCr).

Methods: We conducted a single-center retrospective study at Kindai University Hospital from May 2011 to December 2017. Patients were screened and they were enrolled if baseline CCr of ≥50 mL/min. To provide a periodical synchronization for measurements of CCr in all patients, these were evaluated at four different time points (approximately at 3, 6, 9, and 12 months). Primary endpoint was defined as a CCr value of <50 mL/min during the follow-up period. We analyzed associations between the cumulative risk for renal endpoint and baseline characteristics by the Kaplan–Meier method and the Cox proportional hazards model.

Results: Renal endpoint was associated with age (95% CI: 0.07 to 0.21, p<0.01), body weight (95% CI: -0.09 to -0.01, p<0.01), CCr (95% CI: -0.18 to -0.07, p<0.01), and CHA2DS2-VASc score (95% CI: 0.14 to 0.63, p<0.01). Combining baseline CCr of <60 mL/min and other risk factors, acceptable intervals for 5% risk levels were 78 days (age ≥75 years old), 100 days (CHA2DS2-VASc score of> 4 points), and 90 days (body weight <60kg), respectively. Under conditions of baseline CCr of <60 mL/min, age ≥75 years old, CHA2DS2-VASc score of> 4 points, or body weight <60 kg, an increased risk of renal endpoints is 4.85, 3.29, 1.24, 2.44 fold, respectively.

Conclusions: We propose a risk-stratified follow-up interval for renal evaluation in patients with AF and DOACs therapy according to a combination of baseline CCr and other risk factors.

Introduction

Atrial fibrillation (AF) is recognized as a serious tachyarrhythmia because it increases the risk of severe systemic embolism (stroke), heart failure, and sudden cardiac death [1,2]. For several decades, warfarin has been used as an essential therapy to prevent cardiogenic embolism in patients with AF. However, many clinicians have been forced to challenge hemorrhagic complications during warfarin therapy [3]. Direct oral anticoagulants (DOACs) have been welcomed by many clinicians because they avoid several inferior aspects of warfarin therapy, such as their high incidence of bleeding and complicated dose control. In fact, several clinical studies have proven that DOACs provide more beneficial results compared with warfarin [4–8]. Although clinical use of DOACs is easier than that of warfarin because of the lack of a requirement for prothrombin time-international normalized ratio monitoring, an evaluation of renal function is recommended to determine the type and dose of DOACs. In general, a creatinine clearance (CCr) of 50 mL/min is recognized as an appropriate cut-off value to select standard or low doses of DOACs for patients with AF [9]. Several investigators have reported that AF increases the risk of developing chronic kidney disease (CKD), and CKD increases the risk of new-onset AF [10–15]. AF and CKD are closely associated, and one can be a cause but also a result of the other. Furthermore, CKD makes it difficult to manage anticoagulant therapy, because it increases the risk of both stroke and bleeding in patients with AF

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[16–18]. To provide appropriate DOACs therapy, sequential monitoring of renal function during DOACs therapy is essential. However, the adequate follow-up interval to assess renal function and optimize the DOACs dose (especially important to avoid overdose) has not been fully elucidated [19]. In this study, we aimed to evaluate our hypothesis that an adequate CCr measurement interval for DOACs can be estimated using several baseline parameters.

Methods

Study design and inclusion criteria

This was a single-center retrospective study conducted at Kindai University Hospital from May 2011 to December 2017. The inclusion criteria were as follows: (1) DOAC administration at our hospital to prevent systemic embolism due to AF; (2) baseline CCr of ≥50 mL/min; (3) age ≥20 years. Patients who were prescribed previous oral anticoagulant (OAC) therapy with DOACs at the first visit to our hospital were excluded. The study protocol was approved by the Research Review Board of our University and conducted in accordance with the Declaration of Helsinki (Clinical Research Registration Number: 31-127). Since this study is retrospective, we explain our study protocol on the website of Kindai University Faculty of Medicine Cardiovascular Medicine and give the patients concerned the chance of opt-out from our study.

Clinical variables and echocardiographic data

We measured clinical parameters focusing on several risk factors for worsening renal function according to CKD practice guidelines [20]. The following baseline characteristics were evaluated: age, sex, height, body weight, body mass index (BMI), sustainability of AF (paroxysmal or persistent), baseline CCr, hypertension, diabetes mellitus (DM), CHA2DS2-VASc score, and underlying heart disease (non-valvular disease, valvular disease, cardiomyopathy). Because diuretics and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers can affect renal function, these were included in our analysis. Further, echocardiographic parameters [left atrial dimension and left ventricular ejection fraction (LVEF)] were evaluated by transthoracic echocardiography.

Estimation of renal function

To evaluate renal function, CCr was estimated using the following equation: CCr = [(140 −age) × body weight] / (72 × serum creatinine) × (0.85 if female). In the present study, body weight was measured at enrollment and was used to calculate CCr [19]. Although renal function has been generally assessed by estimated glomerular filtration rate (eGFR), we used the CCr for the criteria of renal endpoints, because CCr has been widely used to manage DOAC therapy.

Follow-up and primary endpoint of renal function

All patients were followed up for at least 12 months, and to provide a periodical synchronization for measurements of CCr in all patients, these were evaluated at four different time points (approximately at 3, 6, 9, and 12 months). We defined the primary outcome of this study as a CCr value of <50 mL/min during the follow-up period. We analyzed the time course of the renal endpoint (CCr < 50 mL/min) using the Kaplan–Meier method.

Detection of clinical factors associated with the renal endpoint

The flowchart used to identify the proposed follow-up interval is summarized in Fig. 1. A univariate logistic analysis was performed to detect clinical factors associated with the renal endpoint (Fig. 1, Step 1). When a detected factor was a continuous variable, a receiver operating characteristic (ROC) curve was constructed to identify the optimal cut-off value for the renal endpoint (Fig. 1, Step 2). A cut-off value (X) was modified to an approximated integer value (X') to provide convenience for clinical use (e.g. X = 64.4 modified to X' = 65).

Estimation of the proposed renal function follow-up intervals

We analyzed the number of days taken to reach the renal endpoint using the Kaplan–Meier method by dividing into two groups according to the optimal cut-off X' value (Fig. 1, Step 3). The proposed renal function follow-up intervals were defined as the number of days taken to reach three different risk levels (1%, 5%, and 10%) of the renal endpoint (decrease in CCr below 50 mL/min as a generally optimal cut-off value for low-dose DOAC therapy) in each group, and these were calculated for each continuous variable.

Construction of our recommendation for the proposed renal function follow-up intervals

Baseline renal function is suggested as the principal parameter to estimate the proposed renal function follow-up intervals; however, combined evaluation of several significant variables (including renal function) based on a scientific background can create a reliable recommendation. In addition, an acceptable incidence of risk (we selected 1% risk for the renal endpoint) may vary between clinicians and/or clinical situations. Therefore, we constructed our new proposal for renal function follow-up intervals by combining baseline CCr and other associated parameters at different acceptable risk levels of 1%, 5%, and 10%.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as numbers and percentages. Differences between groups were tested for statistical significance using Pearson's chi-squared test for categorical variables and the unpaired t-test or analysis of variance for continuous variables. A univariate logistic analysis was used, and odds ratios (ORs) and corresponding 95% confidence intervals (CIs) are presented to assess factors associated with OAC use. The Kaplan–Meier method was used to estimate the cumulative incidence of clinical events. The statistical analysis was performed using JMP software version 14.2.0 (SAS Institute Inc., Cary, NC, USA). The ROC curve analysis of the relationship between the renal endpoint and associated factors was performed to identify an optimal value to distinguish between patients with the renal endpoint and those without.

Results

Patient characteristics

Detailed clinical characteristics of 264 patients are summarized in Table 1. The mean age of patients was 68 ± 8.9 years, and 185 patients (70%) were male. A total of 125 patients (47%) had paroxysmal AF. The mean CCr was 78.1 ± 23.7 mL/min. Mean LVEF was 61.7% ± 12.8%, and 76 patients (29%) had a history of heart failure. CHA2DS2-VASc score was 2.9 ± 1.6. Administered DOACs were dabigatran (24%), apixaban (26%), rivaroxaban (33%), and edoxaban (17%). A total of 12% of patients replaced warfarin at baseline, there was no patient to take warfarin.

Incidence of the renal endpoint

Average timing of CCr evaluation was at 87±26 days (3 months), 179±25 days (6 months), 269±26 days (9 months), and

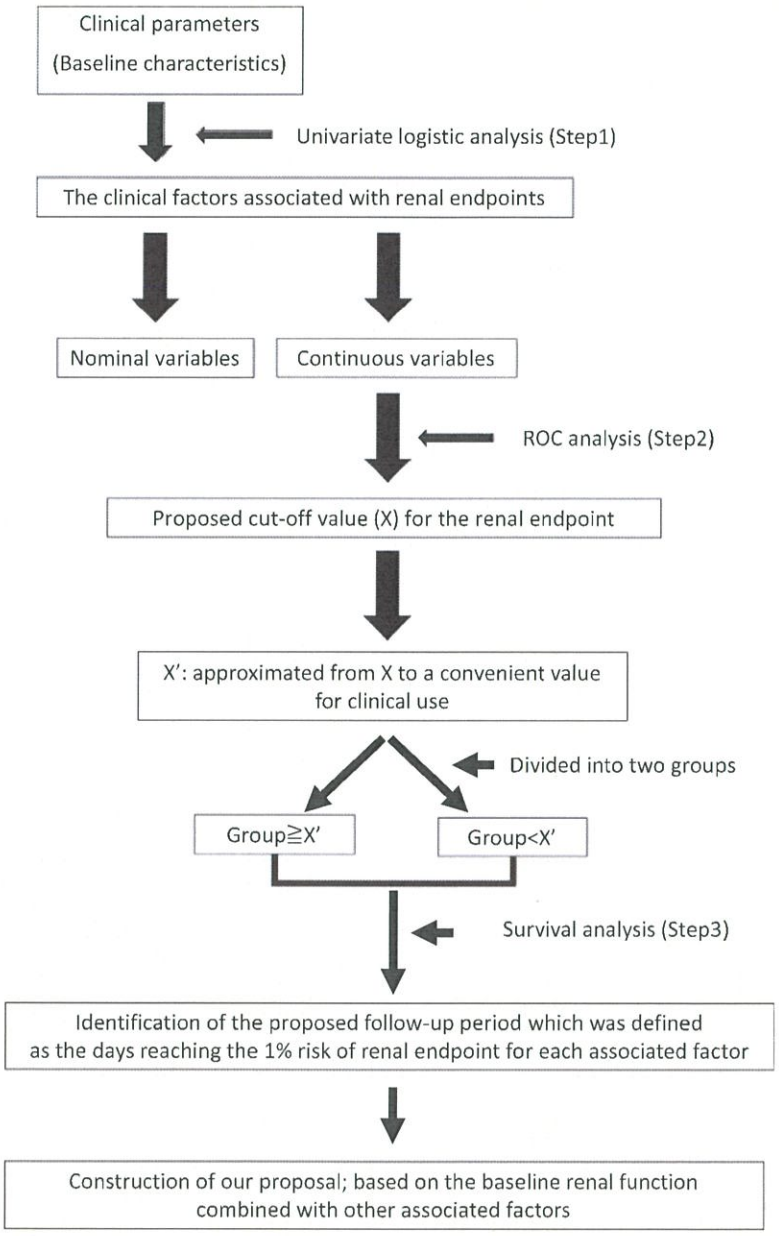

Fig. 1. Flowchart of the method to create our algorithm.
Step 1: Univariate logistic analysis.
A univariate logistic analysis was performed to detect clinical factors which were associated with the renal endpoint.
Step 2: Identification of the proposed cut-off value.
When a detected factor was a continuous variable, ROC curve was constructed to identify the proposed cut-off value to estimate the renal endpoint. A cut-off value (X) was modified to an approximated integer value (X') to provide convenience for clinical use.
Step 3: Identification of the proposed follow-up period
We analyzed the number of days taken to reach the renal endpoint using the Kaplan–Meier method by dividing into two groups according to the proposed cut-off X' value. Acceptable follow-up periods were defined as the number of days taken to reach 1% risk levels of the renal endpoint, and we constructed our proposed follow-up interval.
ROC, receiver operating characteristic.

368±31 days (12 months). Twenty-eight of 264 patients (10.6%) met the renal endpoint during the follow-up period. The mean interval from baseline to the endpoint was 221 ± 108 days (Fig. 2).

Factors associated with the renal endpoint

A univariate logistic analysis demonstrated that associated factors of the renal endpoint included age (95% CI: 0.07 to 0.21, $p < 0.01$), body weight (95% CI: -0.09 to -0.01, $p < 0.01$), CCr (95% CI: -0.18 to -0.07, $p < 0.01$), and CHA2DS2-VASc score (95% CI: 0.14 to 0.63, $p < 0.01$) (Table 1). The ROC curves of CCr level, age, CHA2DS2-VASc score, and body weight (listed in order of increasing area under the curve value) demonstrated that the optimal cut-off values to differentiate between patients with and without the renal endpoint were 61.8 mL/min, 73 years, 4.0 points, and 57.3 kg, respectively (Fig. 3A–D).

Table 1
Baseline patient characteristics.

	ALL	kidney endpoint (+)	kidney endpoint (-)	Univariate analysis	
Number of patients	264	28	236	95% CI	P value
Age, years	68±8.9	74.7±6.4	67.5±8.9	0.07 to 0.21	<0.001
Male - no. (%)	185(70)	16(57)	169(72)	-0.09 to 0.71	0.118
Height(cm)	163.7±9.0	159±8.4	164±8.9	-0.11 to -0.01	0.009
Body weight(kg)	65.2±12.5	59.3±10.3	65.9±12.6	-0.09 to -.0.01	<0.001
BMI(kg/m2)	24.2±3.9	23.3±3.4	24.2±3.9	-0.19 to 0.03	0.168
Type of atrial fibrillation – no. (%)					
paroxysmal	125(47)	14(50)	111(47)	-0.34 to 0.45	0.766
persistent	139(53)	14(50)	125(53)	-0.45 to 0.33	0.766
creatinine clearance(mL/min)	78.1±23.7	56.4±3.4	87.0±22.6	-0.18 to -0.07	<0.001
CHA2DS2-VASc score	2.9±1.6	3.8±1.7	2.8±1.5	0.14 to 0.63	0.002
Medical history – no. (%)					
Hypertension	173(66)	18(64)	155(66)	-0.43 to 0.40	0.884
Diabetes	73(28)	12(43)	61(26)	-0.03 to 0.78	0.062
Stroke or TIA	32(12)	2(7)	30(13)	-0.32 to 1.25	0.401
Heart failure	76(29)	13(46)	63(27)	-0.03 to 0.82	0.033
Cardiac Etiology – no. (%)					
none	169(64)	17(60)	152(64)	-0.34 to 0.48	0.701
Ischemic cardiac disease	43(16)	4(13)	39(17)	-0.42 to 0.72	0.762
Valvular disease	19(7)	3(10)	16(7)	-0.84 to 0.50	0.451
other	34(13)	5(17)	29(12)	-0.71 to 0.35	0.409
Echocardiography					
Left atrial diameter(mm)	43.6±7.2	44.5±(7.0)	43.5±7.2	-0.04 to 0.07	0.522
Left ventriclar Ejection Fraction(%)	61.7±12.8	61.0±13	61.7±13	-0.03 to 0.03	0.780
Administrated DOACs – no. (%)					
Dabigatran	64(24)	7(25)	57(24)	-0.45 to 0.46	0.921
Apixaban	68(26)	5(18)	63(27)	-0.21 to 0.81	0.316
Rivaroxaban	86(33)	10(36)	76(32)	-0.48 to 0.35	0.710
Edoxaban	46(17)	6(21)	40(17)	-0.60 to 0.38	0.556
Exchange from Warfarin– no. (%)	31(12)	1(3.6)	30(13)	-0.12 to 2.13	0.187
Diuretics– no. (%)	59(22)	9(32)	50(21)	-0.70 to 0.16	0.193
ACE-I/ARB– no. (%)	91(34)	12(43)	79(33)	-0.21 to 0.60	0.326

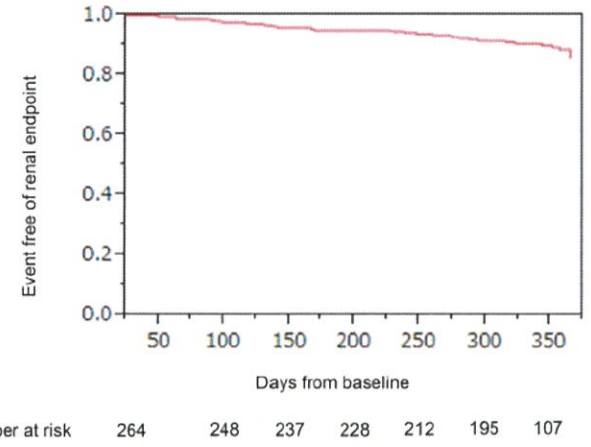

Fig. 2. Survival analysis for renal endpoint. Kaplan–Meier curve indicates the event-free rate against days from baseline. Twenty-eight of 264 patients (10.6%) met the renal endpoint during the follow-up period. The mean interval from baseline to the endpoint was 221 ± 108 days.

Evaluation of the proposed renal function follow-up intervals by each associated factor

All cut-off values (X) were modified to convenient values (X') for clinicians, except for CHA2DS2-VASc score. For example, CCr was modified from 61.8 mL/min to 60 mL/min, age from 73 years to 75 years, and body weight from 57.3 kg to 60 kg. After modification, we calculated proposed renal function follow-up intervals by accepting a 1% risk of the renal endpoint for the two groups divided by the cut-off X' values. Fig. 4 shows Kaplan–Meier curves of the renal endpoint cumulative incidence for each significant parameter (small figures are displayed on a logarithmic scale in both vertical and horizontal axes to make it easy to identify 1% risk). Accordingly, the proposed renal function follow-up intervals for each parameter are as follows: 48 days and 134 days for patients with a baseline CCr of <60 mL/min and ≥60 mL/min, respectively (Fig. 4A); 36 days and 153 days for patients aged ≥75 years and <75 years, respectively (Fig. 4B); 52 days and 115 days for patients with a CHA2DS2-VASc score of ≥4 and <4, respectively (Fig. 4C); and 68 days and 96 days for patients with a body weight of <60 kg and ≥60 kg, respectively (Fig. 4D).

Construction of our recommendations for the proposed renal function follow-up intervals

To enhance our recommendations for the proposed renal function follow-up intervals, we combined a CCr of <60 mL/min, which is the greatest risk factor, with one of the other three risk factors (Combination 1: CCr level and age >75 years; Combination 2: CCr level and CHA2DS2-VASc score >4; Combination 3: CCr level and body weight <60 kg), because these factors overlapped in many cases. To verify the clinical significance of these combinations, we observed an increase in the hazard ratio of the renal endpoint using a stepwise comparison (i.e. patients with no risk factors, those with a single risk factor, and those with both risk factors). The hazard ratio (1.0) gradually increased as follows: Combination 1: 10.2 with an age >75 years, 15.2 with a CCr <60 mL/min, and 25.4 with both; Combination 2: 2.61 with a CHA2DS2-VASc score >4, 10.3 with a CCr <60 mL/min, and 15.6 with both; Comparison 3: 2.31 with a body weight <60 kg, 9.80 with a CCr <60 mL/min, and 14.6 with both. The proposed renal function follow-up intervals (round-off date to the nearest month) suggested by the combination was evaluated by three different acceptable risk levels (1%, 5%, and 10%; Table 2). Categories requiring a short-term interval (within 3 months) are indicated in red, an intermittent interval (over 3 months within 6 months) in orange, and a long-term in-

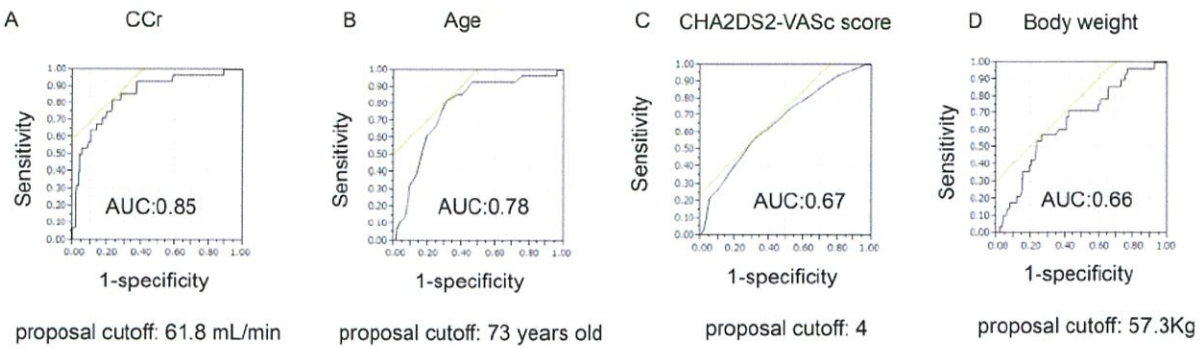

Fig. 3. ROC curves of factors associated with the renal endpoint. The ROC curves of CCr level, age, CHA2DS2-VASc score, and body weight demonstrated that the proposed cut-off values to differentiate between patients with and without the renal endpoint were 61.8 mL/min, 73 years, 4.0 points, and 57.3 kg, respectively.
AUC, area under the curve; CCr, creatinine clearance; ROC, receiver operating characteristic.

Table 2.
The proposed renal function follow-up intervals by accepting 1%, 5%, and 10% risk levels of the renal endpoint.

Other factors		patients with CCr<60mL/min			patients with CCr≧60mL/min		
		Proposal renal function follow-up period at 1% risk	Proposal renal function follow-up period at 5% risk	Proposal renal function follow-up period at 10% risk	Proposal renal function follow-up period at 1% risk	Proposal renal function follow-up period at 5% risk	Proposal renal function follow-up period at 10% risk
Age	≧75yo	1 month	3 month	4 month	2 month	5 month	8 month
	<75 yo	4 month	6 month	8 month	7 month	>12 month	>12 month
CHA2DS2VASc	≧4points	1 month	3 month	5 month	2 month	8 month	>12 month
Score	<4points	2 month	5 month	6 month	6 month	>12 month	>12 month
Body weight	<60Kg	1 month	3 month	5 month	6 month	10 month	>12 month
	≧60Kg	3 month	5 month	7 month	4 month	>12 month	>12 month

terval (over 6 months) in green. As shown in Table 2, even in patients with a baseline CCr of >60 mL/min, if the patient's age is ≥75 years or CHA2DS2-VASc score is ≥4, a follow-up interval of <3 months is proposed.

Multivariate analysis with the Cox proportional hazards model

A multivariate analysis with the Cox proportional hazards model for risk factors associated with the renal endpoint. A baseline CCr of <60 mL/min, an age ≥75 years, a CHA2DS2-VASc score of ≥4, and a body weight of <60 kg carried a 4.85-, 3.29-, 1.24-, and 2.44-fold risk of the renal endpoint, respectively.

Discussion

To the best of our knowledge, this is the first study to elucidate proposed follow-up intervals to evaluate renal function using the sequential change in CCr after the beginning of DOAC therapy combined with other associated risk factors in patients with AF. The major findings of the present study are as follows: (1) the proposed renal function follow-up intervals should be determined not only using baseline CCr, but also using associated parameters, such as age, CHA2DS2-VASc score, and body weight, even in patients with a baseline CCr of >60 mL/min; (2) we proposed the renal function follow-up intervals individualized by three different levels of risk (1%, 5%, and 10%) in combination with associated clinical parameters (Table 2). It is generally accepted that aging is a major risk factor for a deterioration in eGFR because substantial loss of nephrons is physiological. It has been suggested that the annual decrease in eGFR ranges from 0.4 to 1.0 mL/min/1.7m^2 in the general population [20]. On the contrary, the annual decrease in eGFR in patients with AF is thought to be approximately 2.0 mL/min/1.7m^2 [21]. In the present study, the optimal cut-off value for age to estimate the renal endpoint was 73 years (approximate value of 75 years). Our data support the recommendations of previous guidelines, which suggest a relatively short follow-up interval (6 months) for patients aged ≥75 years. CHA2DS2-VASc score includes multiple clinical parameters (heart failure, hypertension, age, and DM), which may affect renal function. The relationship between heart failure and renal dysfunction is well known as the "heart–kidney interaction" or "cardiorenal syndrome." A low cardiac output, excessive diuretic use, and increased renin–angiotensin system activation are suggested as causes of renal dysfunction. Hypertension induces arteriolar vasoconstriction to regulate excessive blood flow to the nephrons, and it causes nephrosclerosis by inducing focal ischemic glomerular obsolescence and nephron loss. DM is associated with glomerular hypertrophy, glomerulosclerosis, and tubulointerstitial inflammation and fibrosis, and it is the biggest cause of hemodialysis. Accordingly, CHA2DS2-VASc score considers many reno-toxic factors; therefore, it is reasonable that the scoring system was detected as an independent factor related to the renal endpoint in the present study.

Deciding the next CCr follow-up examination in patients administered DOACs

According to the CKD-JAC study [22], annual rates of decline in eGFR were reported as −1.925 ± 5.681 mL/min/1.73 m^2 (Stage G3a); −2.056 ± 5.924 mL/min/1.73 m^2 (Stage G3b); and −3.182 ± 14.189 mL/min/1.73 m^2 (Stage G4). They also demonstrated that hypertension and increased urinary albumin-to-creatinine ratio are risk factors significantly associated with CKD progression toward the end stages in Japanese patients. Although approximately 20% of patients had a history of cardiovascular disease in their cohort, the proportion of patients with AF was not described. The RE-LY trial was a large-scale clinical trial conducted on patients with AF with mostly normal renal function (Stage G1) and mild CKD (Stages G2–3), and a sub-analysis of the RY-LY study indicated that eGFR decreases annually by 1–2 mL/min/1.73 m^2 in patients with AF [21]. However, these data have not been utilized to determine appropriate hospital visit intervals to optimize the DOAC dose.

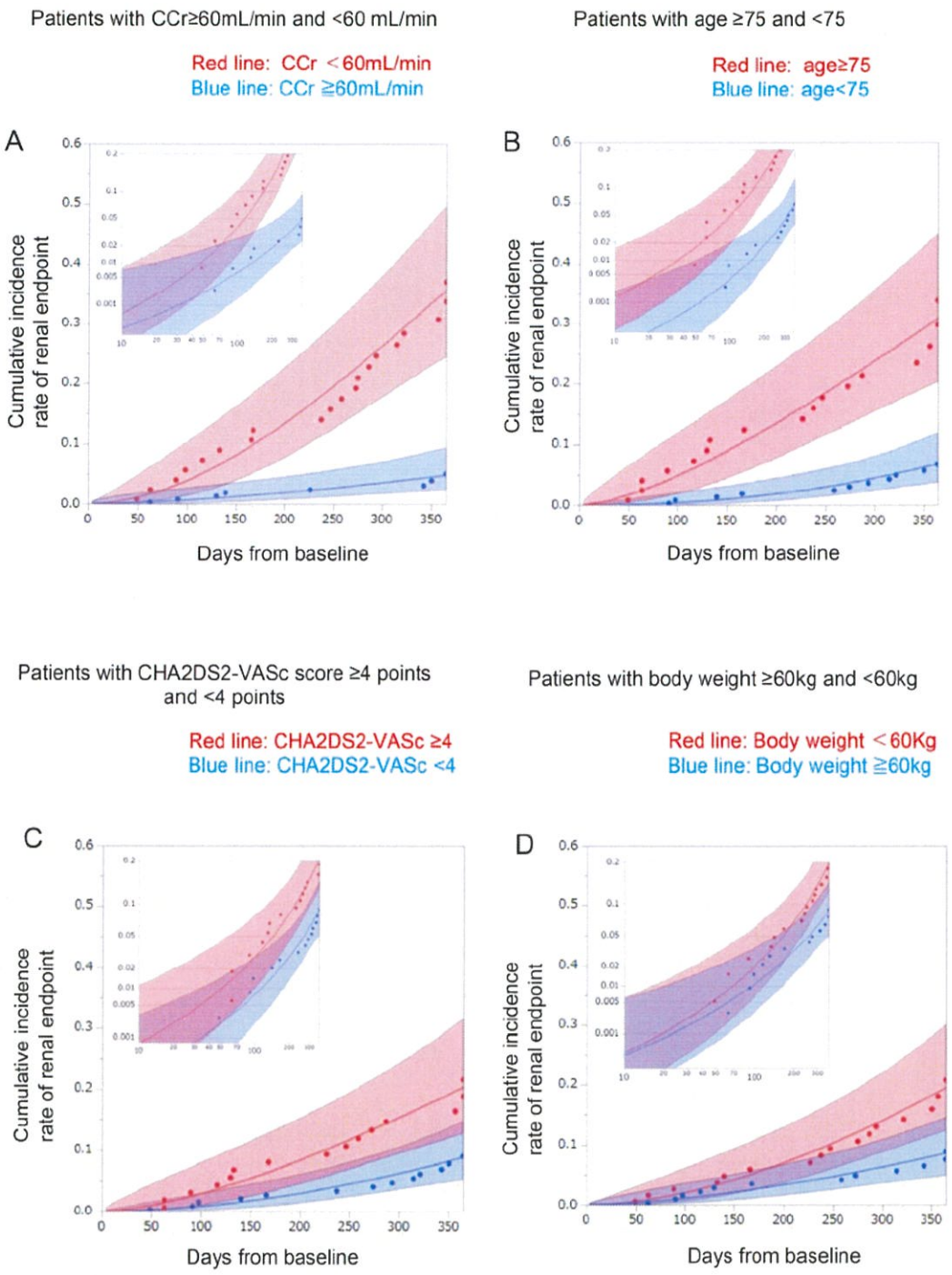

Fig. 4. Cumulative incidences of the renal endpoint by the factors. Kaplan–Meier curves indicate that the cumulative incidence rate for the renal endpoint against days from baseline by the four factors (A) baseline CCr, (B) age, (C) CHA2DS2-VASc score, (D) baseline body weight. Each factor is color coded by the red and blue according to the cut-off. Red indicates having higher risk for renal endpoint than blue. The small figure in the upper left corner shows both the vertical and horizontal axes on a logarithmic scale to focus on 1% risk for renal endpoint. Color coded zone indicates the 95%CI.
CCr, creatinine clearance.

Comparison of the present results with guideline recommendations for follow-up period

European Society of Cardiology guidelines recommend the appropriate follow-up interval as follows: (1) if CCr is ≤60 mL/min, recheck CCr at an interval of x months (x = CCr ÷ 10); (2) if patient age is ≥75 years, recheck CCr at an interval of 6 months; and (3) if other than those specified, recheck CCr at an interval of 12 months [18]. However, no definitive evidence exists to verify these recommendations. The present study is the first clinical trial to estimate the proposed interval for the next CCr examination for safe DOAC use. On the basis of our results, such as a case with a baseline CCr of 50 mL/min and 77 years of age, the next visit to the outpatient clinic should be scheduled 1 or 2 months later (<5 months, as recommended by current guidelines) to avoid DOAC overdose at an acceptable risk of 1% or 5%, respectively. On the contrary, in a

case with a baseline CCr of >60 mL/min and with no other risk factors, the proposed renal function follow-up intervals can be extended beyond the guideline recommendation (7 or 12 months at an acceptable risk of 1% or 5%, respectively) [20].

Clinical implications

In the present study, the proposed follow-up interval was estimated using baseline CCr and/or presence of risk factors (old age, high CHA2DS2-VASc score, and low body weight). Our study may help to reduce medical fees by avoiding unnecessary or excessive blood tests, because the visit-to-visit interval can be extended to ≥12 months in patients without any risk factors for the renal endpoint. Conversely, in patients with any of the risk factors for the renal endpoint, our study proposes a shorter interval of examination compared with current guidelines, but it provides safe management of DOAC therapy by estimating the timing of DOAC dose reduction.

Limitations

The present study has some limitations. First, we did not investigate sequential changes in body weight during the study period. Therefore, we estimated subsequent changes in CCr using baseline body weight. To validate the results of this study, evaluation of CCr by tracking the changes in body weight is required. However, according to a Japanese study, patients aged >65 years have a weight variation of <500 g per year [23]. Therefore, utilizing baseline body weight to estimate subsequent CCr is not expected to significantly influence the results of this study. Second, our study included patients (n = 31) in whom anticoagulant therapy had been switched from warfarin to DOACs, and we did not evaluate renal function in these patients during warfarin therapy. The sub-study of RE-LY compared sequential changes in eGFR between patients receiving warfarin therapy and those receiving dabigatran therapy. They demonstrated that warfarin may facilitate renal dysfunction [21]. However, the absolute difference in the change in eGFR between the two groups was only 4 mL/min during a 30-month follow-up period [24]. Therefore, we believe that warfarin administration before the start of DOAC therapy did not largely affect the results of the present study. Third, the thresholds based on renal function to select a low dose of DOACs are not common; a low dose of dabigatran, rivaroxaban, and edoxaban was recommended when CCr reduces to 50 or less, while a low dose of apixaban was recommended when a serum creatinine level reaches to 1.5 or more. In the present study, CCr (50 mL/min or less) was used for the definition of renal event, because this criterion is the most common for majority of DOACs to reduce the doses. Actually, in the present study, to set a different renal endpoint according to particular type of DOACs was impossible because of a limited number of our patients. Furthermore, the main purpose of this study was to evaluate the transition of renal function of AF patients during DOAC therapy by covering all the types of DOACs. To remove AF patients with apixaban therapy may rather provide selection bias in this study. Fourth, proteinuria and hematuria are known risk factors for a deterioration in renal function [25,26]. Particularly, albuminuria is the first sign of early-phase diabetic nephropathy. Therefore, evaluating proteinuria and hematuria plays an important role in predicting CKD [27]. Because data on proteinuria and hematuria were lacking in the present study, we only evaluated renal function using CCr, but we did not address kidney damage.

Conclusion

We demonstrated a proposed interval for renal evaluation in patients with AF receiving DOAC therapy according to a combination of baseline CCr and other risk factors. These observations provide scientific support for previous guidelines.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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