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ORIGINAL ARTICLE

Impact of renal function deterioration on adverse events during anticoagulation therapy using non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

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Abstract Renal function is crucial for patients with non-valvular atrial fibrillation (NVAF) using non-vitamin K antagonist oral anticoagulants (NOAC). The incidence of renal function deterioration during anticoagulation therapy and its impact of adverse events are unknown. In 807 consecutive NVAF patients treated with NOAC and with estimated creatinine clearance (eCCr) ≥ 50 ml/min (mean age 68 ± 11 years, mean $CHADS_2$ score = 1.8 ± 1.4, CHA_2DS_2-VASc score = 2.8 ± 1.8, HAS-BLED score = 1.7 ± 1.1), we analyzed the time course of renal function and clinical outcomes, and compared these with the data of general Japanese inhabitants from the Suita Study ($n = 2140$). Of the 807 patients, 751 (93 %) maintained eCCr ≥ 50 ml/min (group A) whereas the remaining 56 (7 %) fell into the eCCr < 50 ml/min (group B) during the 382 ± 288 days of follow-up. Multivariate logistic regression analysis revealed that advanced age, lower body weight, and congestive heart failure were independent predictors for renal function deterioration in patients with eCCr ≥ 50 ml/min at baseline. Major and/or minor bleedings were more commonly observed in group B than in group A (21 vs. 8 %; $P = 0.0004$). The $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were also significant predictors of renal function deterioration ($P < 0.0001$). The incidences of renal function deterioration were 1.4, 3.4, 10.5 and 11.7 % in patients with $CHADS_2$ score of 0, 1, 2 and ≥3, respectively. As to CHA_2DS_2-VASc score, renal function deterioration occurred in 0, 1.7, 9.8 and 15.0 % with a score of 0, 1–2, 3–4 and ≥5, respectively. In the Suita Study of the general population, on the other hand, 122 of 2140 participants with eCCr ≥ 50 ml/min at baseline (5.7 %) fell into the eCCr < 50 ml/min during about 2 years. The incidence of renal function deterioration increased with the $CHADS_2$ score in the general population as well as in our patients. Renal function deterioration was not uncommon and was associated with more frequent adverse events including major bleeding in NVAF patients with anticoagulation therapy. $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores may be useful as an index of predicting renal function deterioration.

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Keywords Atrial fibrillation · Non-vitamin K antagonist oral anticoagulants · Renal function · $CHADS_2$ score · CHA_2DS_2-VASc score

Abbreviations

NOAC	Non-vitamin K antagonist oral anticoagulants
NVAF	Non-valvular atrial fibrillation
AF	Atrial fibrillation
eCCr	Estimated creatinine clearance
CKD	Chronic kidney disease
CHF	Congestive heart failure
TIA	Transient ischemic attack
OR	Odds ratio
CI	Confidence interval

Introduction

Previous studies have reported the efficacy and safety of the non-vitamin K antagonist oral anticoagulants (NOAC) for anticoagulation in patients with non-valvular atrial fibrillation (NVAF) [1–6]. NOAC has many clinical advantages compared with warfarin. In particular, clinical studies on anticoagulation therapy using NOAC have consistently shown lower rates of major bleeding complications including intracranial bleeding, which is a devastating adverse event in patients receiving anticoagulation therapy [1–6].

Renal function is crucial in patients with NVAF who are to be treated with NOAC. It has been reported that atrial fibrillation (AF) patients with impaired renal function 'at baseline' (the start of anticoagulation therapy) are at higher risk of both thromboembolism and bleeding events compared with those with preserved renal function irrespective of whether patients are treated with warfarin or NOAC [7–12]. In contrast, the other suggested that renal impairment was not an independent predictor of ischemic stroke or thromboembolism in patients with AF [13]. However, the incidence of renal function deterioration during anticoagulation therapy and its impact of adverse events including major bleeding are unknown. The clinical practice guidelines for chronic kidney disease (CKD), which is a progressive deterioration of renal function, show that age, hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, and hematuria are the risk factors for renal function deterioration [14, 15]; some of these (age, hypertension, and diabetes mellitus) are identical to the factors used to calculate $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores [16–18]. The other $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED factors, such as congestive heart failure (CHF) and stroke history are also related to renal function deterioration [19, 20].

In this study, we hypothesized that renal function deterioration during anticoagulation therapy was associated with increased risk for bleeding complications compared with preserved renal function, even in patients with preserved renal function 'at baseline' and that higher $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores were associated with renal function deterioration in the AF patients receiving anticoagulation therapy. Furthermore, we investigated the relationship between the $CHADS_2$ score and renal function deterioration in the general population using data from the Suita Study.

Methods

Study populations: NVAF patients receiving NOAC

This retrospective study consisted of 807 NVAF patients with estimated creatinine clearance (eCCr) ≥ 50 ml/min, who received NOAC between April 2011 and December 2013 at the National Cerebral and Cardiovascular Center

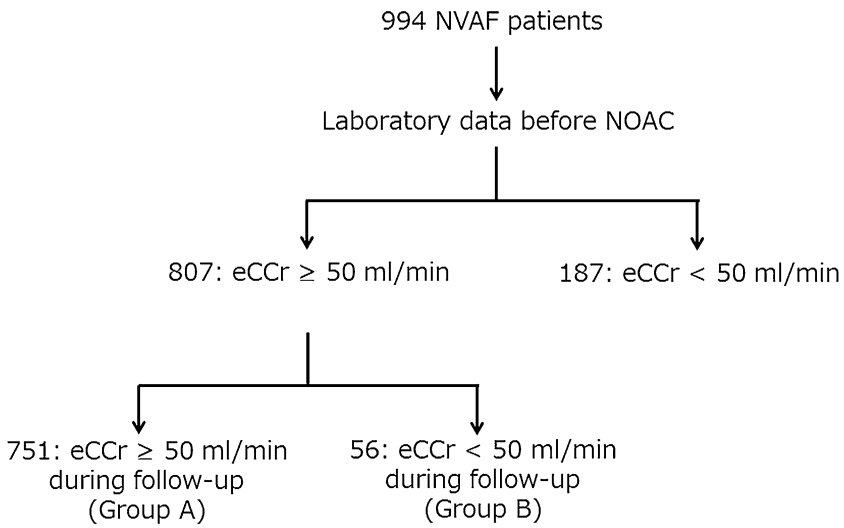

Fig. 1 Schema of the study design. *NVAF* non-valvular atrial fibrillation, *NOAC* non-vitamin K antagonist oral anticoagulants, *eCCr* estimated creatinine clearance

(68 ± 11 years old, 486 paroxysmal and 321 persistent AF, mean $CHADS_2$ score = 1.8 ± 1.4, CHA_2DS_2-VASc score = 2.8 ± 1.8, HAS-BLED score = 1.7 ± 1.1) (Fig. 1). Dabigatran was prescribed in 512 patients (300 mg/day: 200, 220 mg/day: 312), rivaroxaban in 265 patients (15 mg/day: 165, 10 mg/day: 100), and apixaban in 30 patients (10 mg/day: 18, 5 mg/day: 12). The type and dosage of NOAC were determined by the patient's primary physician based mainly on patient's age, body weight and renal function. The dosage of rivaroxaban was set at 15 mg for patients with estimated creatinine clearance (eCCr) ≥ 50 ml/min, and at 10 mg for patients with eCCr < 50 ml/min base on Japanese pharmacokinetic modeling data [4]. We retrospectively analyzed the clinical characteristics and relationship between the time course of renal function and the efficacy and safety of the NOAC therapy. We also investigated the relationship between the $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores and renal function deterioration. Patients with impaired renal function (eCCr < 50 ml/min) at baseline (the start of anticoagulation therapy) were excluded from this study.

All patients were divided into two groups according to whether their renal function was preserved eCCr ≥ 50 ml/min during follow-up (group A) or fell into < 50 ml/min (group B) during follow-up (Fig. 1). We investigated the clinical characteristics of patients in each group, and whether or not the renal function deterioration was associated with adverse events during anticoagulation therapy in patients with AF. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by the ethics committee of the National Cerebral and Cardiovascular Center (M26-87 and M19-5).

Study population: the Suita Study

We also examined the relationship between the $CHADS_2$ score and renal function deterioration in the general population, using data from the Suita Study, an ongoing epidemiologic study of cerebrovascular and cardiovascular diseases in Suita City, Japan [21, 22]. The Suita Study was based on a random sampling from the Suita City stratified into groups by sex and age in 10-year increments, and underwent regular health checkups. Each participant's health status was checked at clinical visits to the National Cerebral and Cardiovascular Center every 2 years. The participants who were selected in 2007 or 2008 were included in this study. Participants less than 40 or more than 90 years of age were excluded from this study. Participants with follow-up periods of <180 days ($n = 12$), those with AF and/or atrial flutter ($n = 60$), and those with eCCr < 50 ml/min at baseline ($n = 269$) were also excluded from the study. Data on the remaining 2140 participants' characteristics, including $CHADS_2$ score and renal function, were collected.

Definition of ischemic stroke, hemorrhage, and renal function

Ischemic stroke was defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a cerebral artery. Asymptomatic stroke at a new location in patients with prior history of stroke was also defined as stroke if the patient's physician considered it significant. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented by imaging, surgery, or autopsy.

Major bleeding was defined as a decrease in hemoglobin of 2 g/dl or more, a transfusion of two or more units of whole blood or packed red blood cells, or symptomatic bleeding in a critical area or organ. Intracranial hemorrhage included intracerebral, subdural, and subarachnoid hemorrhage [1–6]. Minor bleeding was defined as a clinically overt bleeding that did not meet the criteria for major bleeding [1–6].

The eCCr was calculated using the Cockcroft–Gault equation [23].

$$\text{eCCr} = \frac{(140\text{-age}) \times \text{Body weight (kg)} \times [0.85 \text{ if female}]}{72 \times \text{Serum creatinine (Cr) (mg/dl)}}$$

It is recommended that the dosage of the NOAC should be decreased when CCr is <50 ml/min in patients receiving dabigatran, rivaroxaban [1, 2, 4, 5]. Therefore, renal function deterioration was defined as a decrease in eCCr to a level <50 ml/min during the follow-up period in patients with eCCr ≥ 50 ml/min at baseline.

$CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores

We assessed stroke risk using the $CHADS_2$ and CHA_2DS_2-VASc scores [16, 17]. The $CHADS_2$ score assigns 1 point each for CHF, hypertension, age 75 years or older, and diabetes mellitus and 2 points for history of stroke or transient ischemic attack (TIA) [16]. The CHA_2DS_2-VASc score assigns 1 point each for CHF, hypertension, age 65–74 years, diabetes mellitus, vascular disease, and female sex, and 2 points for age 75 years or older and history of stroke or TIA [17]. The HAS-BLED score, used to assess risk for cerebral and systemic bleeding, is calculated using hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (≥75 years), and drug/alcohol use (1 point each) [18].

Follow-up

After prescription of the NOAC, patients visited for the first time within 2–4 weeks at our institute, another hospital or the patient's family doctor for outpatients. After

that patients were followed up every few months. Three of the authors (K.M., K.I., and S.K.) independently reviewed the medical records at our institute and extracted data on patient characteristics, concomitant medication, continuation of the NOAC, thromboembolic events, and adverse events. We investigated the relationship between the $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores and renal function deterioration in our patients receiving NOAC and the $CHADS_2$ score in the general population surveyed in the Suita Study.

Statistical analysis

Data are expressed as means ± standard deviations for the continuous variables and as numbers and percentages for categorical variables. Data were analyzed by the unpaired *t* test if they were normally distributed, or Wilcoxon rank sum test if they were not normally distributed. The χ^2-test was used to analyze the independence of the two classification criteria in the qualitative data. Univariate and multivariate logistic regression analyses were used to identify predictive factors for renal function deterioration during the follow-up periods. Odds ratios (OR) are presented with 95 % confidence intervals (CI). *P* values <0.05 were considered statistically significant. Major bleeding free survival curves were plotted using Kaplan–Meier method and analyzed by log-rank test.

Results

Patient characteristics

Table 1 shows the patient characteristics in this study. Mean age was 68 ± 11 years old, and 599 of the 807 patients were male. The mean eCCr was 78 ± 22 ml/min; 229 patients (28 %) had a prior stroke or TIA; the mean (median) $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores were 1.8 (2.0), 2.8 (3.0), and 1.7 (2.0), respectively.

Of the 807 patients with eCCr ≥ 50 ml/min at baseline (the start of anticoagulation therapy), 751 (93 %) maintained eCCr ≥ 50 ml/min (group A) whereas the remaining 56 (7 %) fell into the eCCr < 50 ml/min (group B) during 382 ± 288 days of follow-up. Patients in group B were older and had lower body weights than those in group A. Female gender, previous history of stroke or TIA, and CHF were more frequently observed in group B than in group A. Accordingly, the $CHADS_2$, CHA_2DS_2-VASc, and HAD-BLED scores were higher in group B than in group A. In particular, patients with CHA_2DS_2-VASc score 0 for male and score 0–1 for female were completely no risk, whereas those with score ≥2 were higher risk for renal function deterioration during follow-up. Interestingly, although the eCCr at baseline was lower in group B than in group A, there was no significant difference in serum Cr at baseline between the 2 groups.

Table 1 Baseline patient characteristics

	Total	Group A	Group B
Patient number, *n* (%)	807	751 (93)	56 (7)
NOAC, dabigatran:rivaroxaban:apixaban	512:265:30	479:245:27	33:20:3
Age, years	68 ± 11	67 ± 11	76 ± 8*
Sex, *n* (m/f)	599/208	566/185	33/23†
Weight (kg)	65 ± 11	65 ± 11	58 ± 8*
Serum Cr (mg/dl)	0.83 ± 0.17	0.83 ± 0.17	0.87 ± 0.19
eCCr (ml/min)	78 ± 22	80 ± 22	56 ± 5*
AF, *n*: (paroxysmal/persistent)	486/321	451/300	35/21
Previous stroke or TIA, *n* (%)	229 (28)	203 (27)	26 (46)†
LA diameter (mm)	42 ± 7	42 ± 7	42 ± 5
Congestive heart failure, *n* (%)	158 (20)	140 (19)	18 (32)†
Hypertension, *n* (%)	486 (60)	450 (60)	36 (64)
Diabetes mellitus, *n* (%)	132 (16)	123 (16)	9 (16)
$CHADS_2$ score, mean	1.8 ± 1.4	1.7 ± 1.4	2.7 ± 1.4*
Score 0, *n* (%)	140 (17)	138 (18)	2 (4)†
Score 1, *n* (%)	264 (33)	255 (34)	9 (16)†
Score ≥2, *n* (%)	403 (50)	358 (48)	45 (80)*
CHA_2DS_2-VASc score, mean	2.8 ± 1.8	2.7 ± 1.8	4.3 ± 1.7*
Score 0, *n* (%)	67 (8)	67 (9)	0 (0)†
Score 1, *n* (%)	145 (18)	142 (19)	3 (5)†
Score 0 for males and 1 for females, *n* (%)	84 (10)	84 (11)	0 (0)†
Score 1 for males, *n* (%)	128 (16)	125 (17)	3 (5)
Score ≥2, *n* (%)	595 (74)	542 (72)	53 (95)†
HAS-BLED score, mean	1.7 ± 1.1	1.7 ± 1.1	2.3 ± 1.0†
Concomitant use of antiplatelet agent, *n* (%)	69 (9)	62 (8)	7 (13)
Follow-up period, days	382 ± 288	376 ± 281	431 ± 365

NOAC non-vitamin K antagonist oral anticoagulants, *Cr* creatinine, *eCCr* estimated creatinine clearance, *AF* atrial fibrillation, *TIA* transient ischemic attack, *LA* left atrium

* $P < 0.0001$, † $P < 0.05$

Univariate analysis for predictors of deteriorating renal function

Univariate logistic regression analysis revealed that age, female gender, lower body weight, eCCr, previous stroke/TIA, CHF, $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were predictive factors for renal function deterioration in patients with eCCr ≥ 50 ml/min at baseline (Table 2). Among these, we excluded eCCr,

Table 2 Univariate analysis for predictors of renal function deterioration

	Odds ratio	95 % confidence interval	*P* value
Age	1.15	1.10–1.20	<0.0001
Female gender	2.13	1.21–3.71	0.01
Lower body weight	1.08	1.05–1.11	<0.0001
Serum Cr (per 0.1 mg/dl)	1.14	0.98–1.33	0.10
eCCr (per 1 ml/min)	0.80	0.75–0.84	<0.0001
Persistent AF	1.11	0.64–1.97	0.72
Previous stroke or TIA	2.34	1.34–4.05	0.003
LA diameter	1.01	0.97–1.05	0.72
Congestive heart failure	2.07	1.12–3.68	0.02
Hypertension	1.20	0.69–2.16	0.52
Diabetes mellitus	0.98	0.44–1.96	0.95
$CHADS_2$ score	1.60	1.33–1.93	<0.0001
CHA_2DS_2-VASc score	1.59	1.37–1.86	<0.0001
HAS-BLED score	1.71	1.32–2.29	<0.0001
Concomitant use of antiplatelet agent	1.59	0.63–3.44	0.28

Cr creatinine, *eCCr* estimated creatinine clearance, *AF* atrial fibrillation, *TIA* transient ischemic attack, *LA* left atrium

Table 3 Multivariate analysis for predictors of renal function deterioration

	Odds ratio	95 % confidence interval	*P* value
Age	1.13	1.09–1.19	<0.0001
Female gender	1.19	0.58–2.48	0.64
Lower body weight	1.07	1.03–1.16	0.0002
Previous stroke or TIA	1.52	0.82–2.78	0.18
Congestive heart failure	2.35	1.21–4.44	0.01

TIA transient ischemic attack

$CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores from multivariate analysis because these factors were related to others, including age, gender, serum Cr, previous stroke/TIA, and CHF. Multivariate logistic regression analysis revealed that advanced age (OR 1.13; 95 % CI 1.09–1.19; $P < 0.0001$), lower body weight (OR 1.07; 95 % CI 1.03–1.16; $P < 0.0001$), and congestive heart failure (OR 2.35; 95 % CI 1.21–4.44; $P = 0.01$) were independent predictors for renal function deterioration (Table 3).

Receiver operating characteristic curve analysis was performed on continuous variables including age and body weight to define an optimal cut-off for prediction of a decrease in eCCr to <50 ml/min during the follow-up period in patients with eCCr ≥ 50 ml/min at baseline. The optimal cut-offs for this prediction were 72 years of age (sensitivity of 84 % and specificity of 62 %) and 66 kg of body weight (sensitivity of 93 % and specificity of 43 %).

Thromboembolic and adverse events according to renal function deterioration

Table 4 shows the relationship between renal function deterioration and adverse events. There was no significant difference in the frequency of thromboembolic events between group A and group B during the follow-up period of 382 ± 288 days. The frequency of adverse events was significantly higher in group B than in group A (36 vs. 24 %; $P = 0.04$), and drug discontinuation due to adverse events was more common in group B than in group A (27 vs. 13 %; $P = 0.004$). Major and/or minor bleeding events were more commonly observed in group B than in group A (21 vs. 8 %; $P = 0.0004$). The frequency of major bleeding events in group A was lower than 1.0 %; in group B, in contrast, it was 7 % ($n = 4$ patients, $P < 0.0001$). Kaplan–Meier analysis for major bleeding events shows that group B has a significantly higher bleeding risk compared to group A ($P < 0.0001$, Fig. 2).

$CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores and renal function deterioration

Figure 3 shows the frequency of renal function deterioration according to $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores in NVAF patients receiving NOAC with preserved renal function at baseline. The incidence of renal function deterioration during follow-up (mean 382 ± 288 days) was 1.4, 3.4, 10.5 and 11.7 % in patients with $CHADS_2$ score of 0, 1, 2, and ≥3, respectively (Fig. 3a). Renal function deterioration became more frequent depending on the increased $CHADS_2$ score, and higher $CHADS_2$ score was a significant predictor for renal function deterioration ($P < 0.0001$). Similar to the $CHADS_2$ score, CHA_2DS_2-VASc and HAS-BLED scores are associated with renal function deterioration, which occurred in 0, 1.7, 9.8 and 15.0 % of patients with the CHA_2DS_2-VASc score of 0, 1–2, 3–4, and ≥5, respectively (Fig. 3b), and 0, 6.5, 6.7 and 12.2 % of patients in the HAS-BLED score of 0, 1, 2 and ≥3, respectively (Fig. 3c).

We also analyzed the frequency of renal function deterioration in general population with eCCr ≥ 50 ml/min at baseline, using the data from the Suita Study ($n = 2140$, 1026 men, 67 ± 9 years old, eCCr: 81 ± 21 ml/min). The mean $CHADS_2$ score was 0.9 ± 1.0 (score 0: $n = 933$, 1:

Table 4 Thromboembolic, adverse events and discontinuation of NOAC

	Group A ($n = 751$)	Group B ($n = 56$)	*P* value
Thromboembolic event, *n*	12 (2)	2 (4)	ns
Adverse event, *n* (%)	177 (24)	20 (36)	0.04
Major and/or minor bleeding, *n* (%)	58 (8)	12 (21)	0.0004
Major bleeding, *n* (%)	5 (0.7)	4 (7)	<0.0001
Discontinuation, *n* (%)	235 (31)	20 (36)	ns
Due to adverse event, *n* (%)	97 (13)	15 (27)	0.004
Death from any cause, *n* (%)	2 (0.3)	2 (4)	0.0007
Follow-up periods, days	376 ± 281	431 ± 365	ns

NOAC non-vitamin K antagonist oral anticoagulants

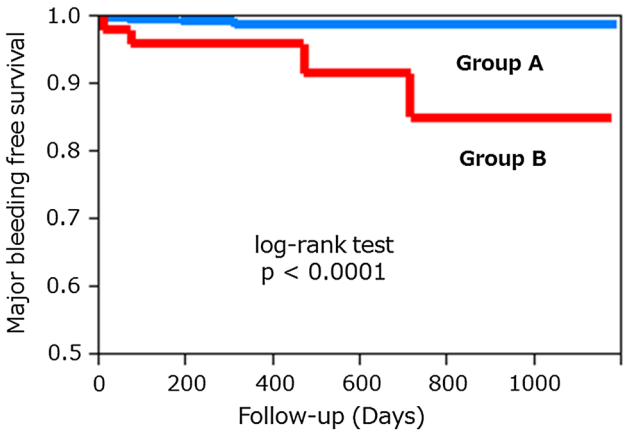

Fig. 2 Kaplan–Meier analysis of major bleeding. The frequency of major bleeding was significantly higher in group A than group B ($P < 0.0001$)

$n = 715$, 2: $n = 378$, 3: $n = 74$, 4: $n = 34$, 5: $n = 7$, and 6: $n = 0$). Of the 2140 participants, 122 (5.7 %) of them fell into eCCr < 50 ml/min during about 2 years. Figure 4 shows the incidence renal function deterioration among participants from the Suita Study according to $CHADS_2$ score (score 0 = 1.4 %, 1 = 5.9 %, 2 = 13.2 %, and ≥3 = 15.7 %). Although many factors such as age, gender and follow-up periods were not completely matched to the NVAF patients, renal function deterioration occurred more frequent depending on the increased $CHADS_2$ score in the general population as well as in the NVAF patients.

Discussion

Main findings

Several novel findings were uncovered in this study. First, 7 % of patients experienced renal function deterioration (eCCr fall <50 ml/min) annually during anticoagulation therapy even among patients who previously had eCCr ≥ 50 ml/min (at the start of anticoagulation therapy). Second, advanced age, lower body weight, and CHF were the independent predictors for renal function deterioration in patients receiving anticoagulation therapy; higher $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores were, therefore, a significant predictor for renal function deterioration. In contrast, patients with CHA_2DS_2-VASc score 0 for male and score 0–1 for female were lower risk for renal function deterioration. Third, renal function deterioration during anticoagulation therapy exposed patients to higher risk for major and/or minor bleeding compared to patients with preserved renal function.

Bleeding risk during anticoagulation and impaired renal function

Previous studies have reported that the rate of intracranial bleeding is lower in patients receiving NOAC for anticoagulation therapy compared with warfarin [7–10]. This may be due to the fact that NOAC medications affect a single target in the hemostatic system (inhibition of factor Xa or thrombin), whereas warfarin has multiple targets. On the other hand, AF patients with impaired renal function are at higher risk for bleeding as well as thromboembolism compared with those with preserved renal function [7–12]. Eikelboom et al. reported that patients with CCr < 50 ml/min have a twofold higher risk of major bleeding during anticoagulation therapy compared with patients with CCr ≥ 80 ml/min [7]. Several mechanisms have been identified for the higher bleeding risk in patients with impaired renal function, including enhanced coagulability, endothelial dysfunction, hypertension, increased levels of inflammatory factors, increased arterial calcification, arterial stiffness, anemia, concomitant medications, and comorbidities [24–28]. This study showed that patients with preserved renal function (eCCr ≥ 50 ml/min) at baseline, but renal function deterioration (decrease in eCCr to <50 ml/min) during NOAC therapy were also at higher risk for bleeding complications.

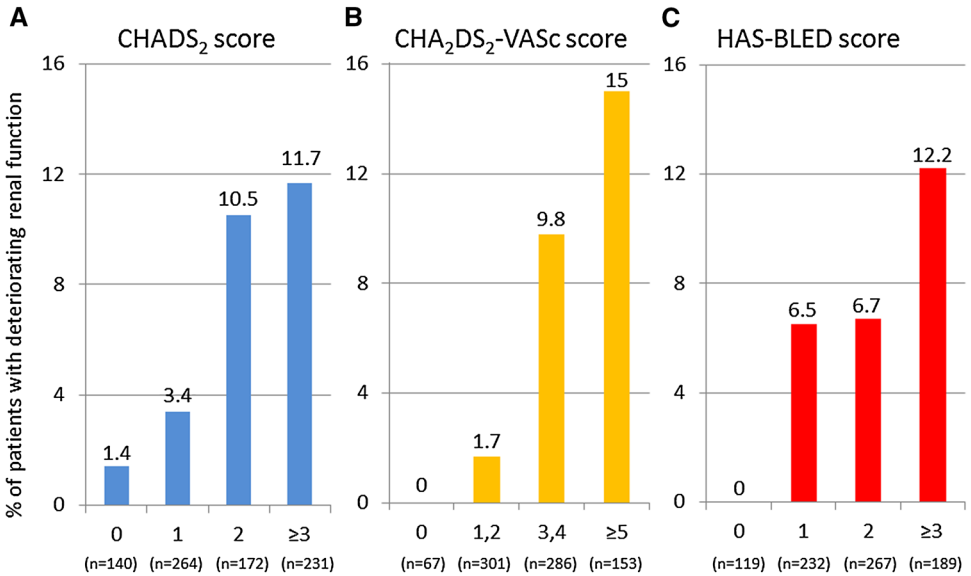

Fig. 3 The frequency of renal function deterioration according to $CHADS_2$ score (**a**), CHA_2DS_2-VASc score (**b**), and HAS-BLED score (**c**) in NVAF patients receiving NOAC with preserved renal function (eCCr ≥ 50 ml/min) at baseline. The incidence of renal function deterioration after NOAC therapy increased dramatically as these scores increased. Abbreviations are shown in Fig. 1

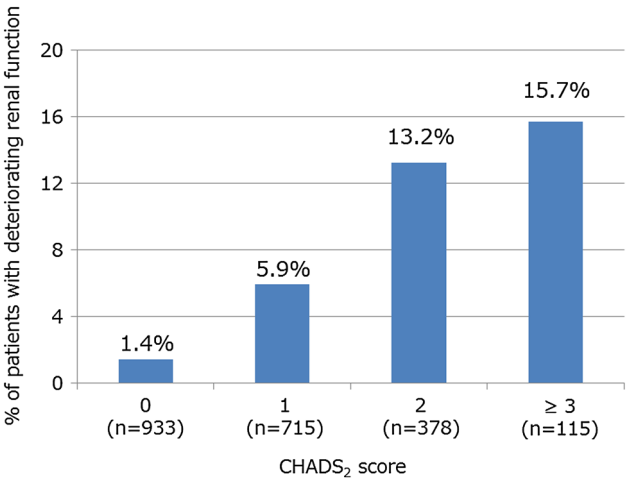

Fig. 4 The frequency of renal function deterioration according to $CHADS_2$ score in the general population surveyed in the Suita Study. The incidence of renal function deterioration increased dramatically as the $CHADS_2$ score increased

$CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores as index for renal function deterioration

In this study, advanced age, lower body weight, and CHF were independent predictors for renal function deterioration. A lot of patients with AF are aged, and advanced age itself is a risk factor for renal dysfunction [29]. Poggio et al. investigated the relationship between kidney donors' glomerular filtration rate and age, and reported a significant increase in the rate of glomerular filtration rate decline as subjects got older [30]. In addition, elderly people often have comorbidities such as diabetes mellitus, which are important risk factors for renal function deterioration [31].

It has been reported that patients with CHF were at high risk for developing CKD [19]. The prevalence of renal dysfunction in CHF has been reported to be approximately 25 %. The "cardio-renal syndrome" is a dysfunction of the heart and kidneys, in which a disorder of one of these two organs results in dysfunction or injury to the other [32]. Renal function deterioration in patients with CHF may be attributed to several factors such as reduced renal perfusion, impaired endothelial function, inflammation, diuresis-associated hypovolemia, early introduction of renin–angiotensin–aldosterone system blockade, and drug-induced hypotension [19, 32].

Clinical guidelines for CKD identify the risk factors for renal function deterioration [14, 15]. Yamagata et al. investigated the risk factors for renal function deterioration in the Japanese general population and reported that advanced age, hypertension, diabetes mellitus, dyslipidemia, smoking, proteinuria, and hematuria were risk factors for CKD [33]. Clearly, some factors associated with increased risk of renal function deterioration are also associated with the risk of stroke as predicted by the $CHADS_2$ score and/or the CHA_2DS_2-VASc score. In this study, we showed that patients with higher $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were more likely to experience renal function deterioration after starting NOAC, and confirmed that the usefulness of the $CHADS_2$ score as a predictive index for renal function deterioration in the general population.

It should be borne in mind that most patients with AF who are receiving anticoagulation therapy have higher than normal risk not only for stroke events but also for renal function deterioration. NOAC medications do not require the patients to undergo routine laboratory monitoring, due to their predictable pharmacokinetics. However, fixed-dose unmonitored NOAC administration may lead to have

risk of higher blood concentrations of the NOAC by renal function deterioration. If physicians are unaware of this phenomenon, it may lead to increased risk of major and/or minor bleeding events [34]. From these findings, we recommend the regular monitoring of laboratory data including renal function and hematological values during anticoagulation therapy. We believe that such regular monitoring of NOAC raises the possibility to avoid bleeding events by the dose adjustment or the change of medication for anticoagulation therapy.

Because renal function, age, and body weight are important factors that influence the efficacy and safety of anticoagulation therapy in patients with AF, physicians evaluate these factors at the start of anticoagulation therapy [7–12]. It is also important, however, for physicians to pay special attention to any changes in renal function during anticoagulation therapy, because renal function deterioration is often observed during the follow-up period. Roldán et al. reported that 20 % of anticoagulated patients with AF had significant impairment in renal function during follow-up period (median 875 days) [35]. They also suggested that normal or mild renal dysfunction at baseline did not exclude the subsequent development of severe renal dysfunction during the follow-up period, thus renal function should be carefully monitored in patients with AF, independently of the type of oral anticoagulation chosen. In this study, although eCCr at baseline was lower in B group than in A group, there was no significant difference in serum Cr level between these 2 groups. Therefore, the renal function should be evaluated during follow-up not only by serum Cr level but also the eCCr using Cockcroft–Gault equations.

Study limitations

There were several limitations of this study. First, this study was a retrospective and nonrandomized one with a relatively small sample size at a single institute, and the antithrombotic drugs and dosage were selected by the patient's primary physicians. Second, the course of renal function was not compared with that of patients receiving any form of control (i.e., warfarin, aspirin, or placebo), and we could not exclude the possibility of the influence of acute ischemic stroke on renal function. Third, the follow-up period was relatively short, so that further investigations with large populations and long-term follow-up periods are necessary to evaluate the time course of renal function and its impact on thromboembolic and adverse events in patients receiving NOAC. Finally, the data on patient characteristics, continuation of NOAC, thromboembolic events, and adverse events were extracted from medical records at our institute, allowing some potential for biased data acquisition and outcome ascertainment. We also calculated $CHADS_2$ scores in general population, most of them had not been diagnosed AF, although the clinical implications of such calculations are still unclear.

Conclusions

Renal function deterioration is not uncommon in AF patients receiving anticoagulation therapy event if the renal function is preserved when anticoagulation therapy starts. Renal function deterioration is associated with increased incidence of adverse events including major bleeding. Regular monitoring of laboratory data during NOAC administration is important to avoid such adverse events. The $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores could be useful as an index predicting renal function deterioration in both patients receiving anticoagulation therapy and the general population.

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Compliance with ethical standards

Conflict of interest Dr. Koji Miyamoto received lecture fees/honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers, Pfizer, and Daiichi-Sankyo. Dr. Aiba received lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers, and Pfizer. Dr. Ishibashi received lecture fees/honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers, and Pfizer. Dr. Yasuda received lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers, Pfizer, and Daiichi-Sankyo. Dr. Shimizu received lecture fees/honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers, Pfizer, and Daiichi-Sankyo. Dr. Ogawa received lecture fees/honoraria from Boehringer Ingelheim. Dr. Toyoda received lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers, and Pfizer. Dr. Kusano received lecture fees from Bayer, Boehringer Ingelheim, and Bristol-Myers. Dr. Kamakura received research funds from Boehringer Ingelheim and Daiichi-Sankyo. Dr. Ogawa received research funds from Bayer, Bristol-Myers, Daiichi-Sankyo, and Pfizer. Dr. Shimizu received scholarship funds from Bayer, Boehringer Ingelheim, Bristol-Myers, Pfizer, and Daiichi-Sankyo.

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