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Relation of Stroke and Major Bleeding to Creatinine Clearance in Patients With Atrial Fibrillation (From the Fushimi AF Registry)

Running Head: CrCl and outcomes in AF patients

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Abstract

Creatinine clearance (CrCl) has been widely used to adjust the dosage of non-vitamin K antagonist oral anticoagulants in atrial fibrillation (AF) patients and exclude contraindicated patients. However, there are few available real-world data on the relationship between CrCl and adverse clinical outcomes in AF patients. Therefore, we evaluated the clinical characteristics and adverse events in Japanese AF patients stratified by CrCl. We categorized patients in the Fushimi AF Registry, a large prospective community-based Japanese cohort of AF patients, into three groups as follows: (i) CrCl <30 mL/min, (ii) CrCl 30-49 mL/min, and (iii) CrCl ≥50 mL/min. We evaluated 3,080 patients after a median follow-up of 1,076 days. Comparing with patients with CrCl ≥50 mL/min, AF patients with CrCl <30 mL/min showed increased risks of stroke/systemic embolism (SE) (hazard ratio (HR), 1.68; 95% confidence interval (CI), 1.04 to 2.65; p = 0.04) and major bleeding (HR, 2.08; 95% CI, 1.23 to 3.39; p = 0.008) after adjustment for pre-specified factors. AF patients with CrCl <30 mL/min were also associated with higher risks of all-cause death, hospitalization for heart failure, myocardial infarction, or the composite of all-cause death and stroke/SE. However, no excess risk of stroke/SE (HR, 1.10; 95% CI, 0.76 to 1.58; p = 0.6) or major bleeding (HR, 0.98; 95% CI, 0.63 to 1.48; p = 0.9) was noted for patients with CrCl 30-49 mL/min. In conclusion, Japanese AF patients with CrCl <30 mL/min were closely associated with adverse clinical events including stroke/SE and major bleeding.

Key words: atrial fibrillation, creatinine clearance, stroke, major bleeding

Introduction

It is well known that atrial fibrillation (AF) patients with chronic kidney disease are at higher risks of stroke, systemic embolism (SE), bleeding, all-cause mortality, myocardial infarction, and heart failure.[1] A decreased estimated glomerular filtration rate was also reported to increase the risks of stroke, SE, and bleeding among patients with AF.[2-6] All four non-vitamin K antagonist oral anticoagulants (NOACs) are partially eliminated via the kidney, and the estimation of creatinine clearance (CrCl), not glomerular filtration rate, is recommended. The Cockcroft-Gault formula for CrCl includes the age, sex, and body weight, but the body weight is not included in equations for the estimated glomerular filtration rate. Therefore, CrCl was widely used to adjust the dosage of NOACs and exclude contraindicated patients in four large NOAC trials[7-10] and in the European Practical Guide.[11] Although CrCl was used in some limited subanalyses of randomized control trials,[3,4,12] there are few available real-world registry data on the relationship between CrCl and adverse clinical outcomes in patients with AF. To clarify that relationship, we evaluated the clinical characteristics and adverse clinical events including stroke/SE, major bleeding, death, hospitalization for heart failure, and myocardial infarction[13,14] in Japanese AF patients stratified by CrCl.

Methods

The Fushimi AF Registry is a community-based prospective all-comer cohort study of AF patients who visited the participating medical institution in the Fushimi district, Kyoto, Japan, which is a

densely populated urban area with a total population of 283,000. We enrolled AF patients defined by the documentation of AF on a 12-lead electrocardiogram or Holter monitoring at any time with no exclusion criteria from March 2011. The detailed study design, patient enrollment, definition of the measurements, and subjects' baseline clinical characteristics of the Fushimi AF Registry were previously described elsewhere (UMIN Clinical Trials Registry: UMIN000005834).[15-19] Oral anticoagulant (OAC) included warfarin, dabigatran, rivaroxaban, and apixaban, and the assignment to the OAC group was based on OAC usage at the time of enrollment. This study was conducted in accordance with the amended Declaration of Helsinki and the study protocol was approved by the ethical committees of the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

We excluded the patients on hemodialysis and without baseline CrCl data. The CrCl was calculated with the Cockcroft-Gault formula,[20] and patients were categorized into three groups as follows: (i) CrCl <30 mL/min, (ii) CrCl 30-49 mL/min, and (iii) CrCl ≥50 mL/min.

Clinical outcomes evaluated in this study were stroke/SE, major bleeding, all-cause death, hospitalization for heart failure, myocardial infarction, and the composite of all-cause death and stroke/SE. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery, and the diagnosis was confirmed by computed tomography or magnetic resonance imaging. SE was defined as an acute vascular occlusion of an extremity or organ other than the brain. Major bleeding was defined as a reduction in the hemoglobin

level by at least 2 g/dL, transfusion of at least 2 units of blood, or clinically overt bleeding in a critical area or an organ, according to the definition by the International Society on Thrombosis and Haemostasis.[16,21] Hospitalization for heart failure was defined as an admission to the hospital and the final diagnosis at discharge was heart failure by each attending physician. The diagnosis of myocardial infarction was made by the charged physician who was recommended to follow the third universal definition of myocardial infarction.[22]

The risk of stroke was assessed by the $CHADS_2$ score[23] or the CHA_2DS_2-VASc score,[24] and the bleeding risk was estimated by the HAS-BLED score.[25] In this analysis, "V" in the CHA_2DS_2-VASc score was defined by prior myocardial infarction or peripheral vascular disease. In the HAS-BLED score, "L" was not assessed because international normalized ratio data were unavailable in the present study and drugs of "D" were replaced by the concomitant use of antiplatelets based on a modified HAS-BLED score.[26]

Categorical variables are expressed as numbers and percentages and compared using the chi-square test. Continuous variables of each group are presented with the mean ± standard deviation and compared using Student's *t*-test or the Wilcoxon rank-sum test based on their distributions. The cumulative incidence of stroke/SE, major bleeding, all-cause death, hospitalization for heart failure, myocardial infarction, and the composite of all-cause death/stroke/SE were estimated by the Kaplan-Meier method, and differences were assessed with the log-rank test. The adjusted relationships between CrCl and the adverse clinical events were evaluated using Cox proportional

hazard models.

To adjust the baseline characteristics for the assessment of stroke/SE, we adopted 8 components of the CHA_2DS_2-VASc stroke risk score, such as congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior cerebral ischemia, vascular disease, age 65-74 years old, and a female sex, and added one factor on the status of OAC consumption. Therefore, nine factors were finally adjusted. We also adopted 7 components of the HAS-BLED bleeding risk score: hypertension, abnormal liver function, prior stroke, history of major bleeding, age 65 years or older, drug usage, and alcohol abuse, and added the status of OAC treatment. Therefore, eight factors were entered into a multivariate Cox proportional hazard model to adjust and evaluate the risk of bleeding. For the multivariate model, we excluded abnormal renal function as a HAS-BLED risk factor in order to avoid the confounding effects to evaluate the relationship between CrCl, which was mainly dependent on the renal function, and adverse clinical outcomes. The results of analyses are shown as the hazard ratio (HR) with 95% confidence intervals (CIs) and p values. Results were considered significant with a p value of <0.05. We used JMP 12.0 (SAS Institute Inc., Cary, NC, USA) for all analyses. The authors had full access to the data and take responsibility for its integrity.

Results

Of the 4,115 patients enrolled in the Fushimi AF Registry by the end of July 2014, 3,080 patients who were categorized by CrCl were finally analyzed (Fig 1). The numbers of patients categorized

into CrCl <30, CrCl 30-49, and CrCl ≥50 mL/min group were 322 (10%), 814 (26%), and 1,944 (63%), respectively. The median follow-up was 1,076 days (interquartile range, 448 to 1,315).

Baseline characteristics were significantly different among patients categorized by CrCl (Table 1). Amongst the 3,080 patients analyzed, 1,671 patients (54%) were treated with OAC. Baseline characteristics of patients with or without OAC are given in Table 2, and those of patients with or without OAC in each CrCl category are given in Table 3.

The incidences of stroke/SE in patients stratified by CrCl were significantly different (p = 0.0002) (Fig 2A). Kaplan-Meier curves for the incidences of stroke/SE in patients with and without OAC are shown in Figure 2B and 2C, respectively.

After adjustment for pre-specified factors, patients with CrCl <30 mL/min had a significantly higher risk of stroke/SE compared with patients with CrCl ≥50 mL/min (HR, 1.68; 95% CI, 1.04 to 2.65; p = 0.04), but no significant difference was seen in patients with CrCl 30-49 mL/min (HR, 1.10; 95% CI, 0.76 to 1.58; p = 0.6) (Table 4). Besides CrCl categories, elderly (≥75 years old) (HR, 1.97; 95% CI, 1.19 to 3.44; p = 0.008) and prior stroke/TIA/SE (HR, 1.79; 95% CI, 1.30 to 2.45; p = 0.0005) were significantly correlated with stroke/SE. After adjustment for factors including the renal function, OAC use was not associated with stroke (HR, 1.06; 95% CI, 0.78 to 1.44; p = 0.7).

Kaplan-Meier curves for the incidences of major bleeding among patients stratified by CrCl are shown in Figure 3A, and those of patients treated with or without OAC are shown in Figure 3B and 3C, respectively. The highest rates of major bleeding in the CrCl <30 mL/min group were observed

in the entire cohort and cohort without OAC, but not in those taking OAC.

After adjustment for factors composed of the HAS–BLED score and status of OAC prescription, patients with CrCl <30 mL/min had a significantly higher risk of major bleeding (HR, 2.08; 95% CI, 1.23 to 3.39; p = 0.008), compared with patients with CrCl ≥50 mL/min (Table 5). However, patients with CrCl 30-49 mL/min showed no significant difference (HR, 0.98; 95% CI, 0.63 to 1.48; p = 0.9). Only a history of major bleeding (HR, 3.69; 95% CI, 1.95 to 6.48; p = 0.0002) and an elderly age (>65 years old) (HR, 1.82; 95% CI, 1.07 to 3.29, p = 0.03) were significantly correlated with major bleeding. After adjustment for pre-specified factors including CrCl, OAC use was not significantly correlated with major bleeding (HR, 1.41; 95% CI, 0.99 to 2.03, p = 0.06).

Kaplan-Meier curves for other adverse clinical events, such as all-cause death, hospitalization for heart failure, myocardial infarction, and the composite of all-cause death and stroke/SE are shown in Supplementary Data. The incidences of all these adverse events were the highest in patients with CrCl <30 mL/min.

Discussion

In the present study, we evaluated the relationship between CrCl and adverse clinical outcomes in patients with AF. Patients with CrCl <30 mL/min were excluded in three large NOAC trials,[7,8,10] and three NOACs were recommended for dosage reduction in patients with CrCl <50 mL/min and the other NOAC was recommended for reduction in patients with CrCl <30 mL/min in the European

Practical Guide.[11] Therefore, we categorized patients into three groups as follows: (i) CrCl <30 mL/min, (ii) CrCl 30-49 mL/min, and (iii) CrCl ≥50 mL/min. Our results revealed novel findings that patients with CrCl <30 mL/min had the greatest risks of stroke/SE, major bleeding, all-cause death, hospitalization for heart failure, myocardial infarction, and the composite of all-cause death and stroke/SE. Although the sub-analyses of ARSITOTLE[3] and ROCKET-AF[12] trials both showed that CrCl <60 mL/min was a strong predictor of stroke/SE or major bleeding, no additional risk was observed in AF patients with CrCl 30-49 mL/min compared with patients in the CrCl ≥50 mL/min category in our cohort. The reasons for this discrepancy might be as follows: (1) There was a racial difference; (2) The median body weight was about 80 kg in previous reports, whereas it was about 60 kg in our report. This is the first real-world registry data on the relationship between CrCl and adverse clinical outcomes in patients with AF. The results of this study may help physicians to adjust the dosage of the treatment for AF patients with NOACs in daily clinical practice and exclude contraindicated patients.

In our analysis, the crude incidence of stroke/SE in patients with CrCl <30 mL/min treated with OAC was paradoxically higher than in patients not treated with OAC. This might be partially explained by the patients prescribed OAC exhibiting higher incidences of comorbidities, although the CHA_2DS_2-VASc score was comparable between with and without OAC treatment in patients with CrCl <30 mL/min. In a multicenter registry enrolling patients undergoing first percutaneous coronary intervention in Japan, Goto et al. reported similar results showing that the cumulative

5-year incidence of stroke in patients treated with OAC was not different from that in patients without OAC (13.8 vs. 11.8%, respectively, p = 0.49) in 1,057 AF patients.[27] The crude incidence of major bleeding in patients with CrCl <30 mL/min treated with OAC in the current study was also paradoxically lower than in patients not treated with OAC. The initiation of OAC treatment was left to the discretion of the charged physician, which undoubtedly resulted in selection bias, although the HAS-BLED score and history of major bleeding were comparable between with and without OAC treatment in patients with CrCl <30 mL/min. However, the factor closely related to stroke and major bleeding is the quality of anticoagulation control,[28] as reflected by the average time in the therapeutic range, which was not available in our cohort.

Apart from CrCl <30 mL/min, an elderly age (≥75 years old) and prior stroke/TIA/SE were significantly correlated with stroke/SE. Patients with a history of major bleeding and an elderly age (>65 years old) also had an increased risk of major bleeding after adjustment for the HAS-BLED risk factors and status of OAC prescription. Importantly, after adjusting for factors including CrCl, OAC use was not independently associated with an excess of stroke or major bleeding. This study was not a randomized trial and there were a number of confounders for choosing each drug. Therefore, we did not examine the event rates based on each type of OAC.

Some limitations merit emphasis. First, this was a prospective observational study; therefore, it only shows associations, and not causality. Second, about 10% of patients were lost during follow-up, which could undoubtedly result in a selection bias. Third, this study involved AF patients recruited

from a small region of Japan, and so the study results may not be applicable to other Asian (or non-Asian) populations. Fourth, the statistical analysis was based only on OAC usage at the time of enrollment. This did not take into account the initiation, adherence, and switching of OACs, or the quality of the adjustment such as the time in therapeutic range for patients taking warfarin through the follow-up period.

Disclosures

Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, and Bayer Healthcare. Dr. Lip has served as a consultant or advisory board member for Bayer/Janssen, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo, and has been on the speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. The other authors have no conflicts of interest to disclose.

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FIGURE LEGENDS

Figure 1

Patient flowchart for the present analysis.

AF = atrial fibrillation; CrCl = creatinine clearance.

Figure 2

Unadjusted Kaplan-Meier curves for the incidences of stroke/SE in the entire cohort (A) and in patients treated with (B) or without (C) OAC.

CrCl = creatinine clearance; OAC = oral anticoagulant; SE = systemic embolism.

Figure 3

Unadjusted Kaplan-Meier curves for the incidences of major bleeding in the entire cohort (A) and in patients treated with (B) or without (C) OAC.

CrCl = creatinine clearance; OAC = oral anticoagulant.

Table 1: Baseline Characteristics of Patients Categorized by CrCl

Variable	CrCl <30 (n = 322)	30≤ CrCl <50 (n = 814)	50≤ CrCl (n = 1,944)	p Value
Age (years)	84.0 ± 8.1	80.5 ± 7.1	69.8 ± 9.8	<0.0001
≥75	283 (88%)	662 (81%)	689 (35%)	<0.0001
65-74 years old	33 (10%)	135 (17%)	776 (40%)	<0.0001
Female	203 (63%)	430 (53%)	623 (31%)	<0.0001
Body weight (kg)	47.8 ± 10.5	52.7 ± 10.6	63.8 ± 12.5	<0.0001
Body mass index (kg/m^2)	20.5 ± 3.4	21.8 ± 3.5	24.0 ± 3.9	<0.0001
Systolic BP (mmHg)	121.2 ± 22.1	124.0 ± 19.4	125.1 ± 17.2	0.002
Diastolic BP (mmHg)	65.4 ± 14.3	68.3 ± 12.5	71.8 ± 12.0	<0.0001
Heart rate (beats/min)	78.4 ± 19.3	77.9 ± 16.2	77.9 ± 15.1	0.9
Symptomatic	139 (43%)	378 (46%)	945 (49%)	0.2
Palpitation	72 (22%)	229 (28%)	697 (36%)	<0.0001
Hemoglobin (g/dL)	10.7 ± 1.7	12.2 ± 1.8	13.6 ± 1.7	<0.0001
Platelet count (×10^9/L)	188 ± 69	196 ± 74	202 ± 66	0.001
Baseline renal function				
Serum creatinine (mg/dL)	1.8 ± 1.2	1.0 ± 0.3	0.8 ± 0.2	<0.0001
Estimated glomerular filtration rate (mL/min/1.73 m^2)	29.6 ± 11.1	50.8 ± 12.9	71.9 ± 19.3	<0.0001
Calculated creatinine clearance (mL/min)	21.5 ± 5.9	41.0 ± 5.6	78.0 ± 25.2	N/A
Comorbidities				
Heart failure	187 (58%)	316 (39%)	407 (21%)	<0.0001
Hypertension	214 (66%)	548 (67%)	1,190 (61%)	0.005
Diabetes mellitus	72 (22%)	194 (24%)	485 (25%)	0.5
Receiving insulin therapy	17 (5.3%)	30 (3.7%)	60 (3.1%)	0.2
Prior stroke	84 (26%)	169 (21%)	307 (16%)	<0.0001
Prior stroke/TIA	86 (27%)	183 (22%)	337 (17%)	<0.0001
History of major bleeding	19 (5.9%)	32 (3.9%)	71 (3.7%)	0.2
Dyslipidemia	126 (39%)	353 (43%)	909 (47%)	0.02
Coronary artery disease	78 (24%)	147 (18%)	251 (13%)	<0.0001
Prior myocardial infarction	47 (15%)	53 (6.5%)	96 (4.9%)	<0.0001
Peripheral vascular disease	9 (2.8%)	53 (6.5%)	446 (12%)	<0.0001
COPD	21 (6.5%)	65 (8.0%)	69 (3.6%)	0.001
Abnormal liver function	9 (2.8%)	10 (1.2%)	31 (1.6%)	0.2

History of catheter ablation	8 (2.5%)	28 (3.4%)	133 (6.8%)	<0.0001
History of defibrillation	12 (3.7%)	25 (3.1%)	76 (3.9%)	0.6
$CHADS_2$ score	2.9 ± 1.3	2.6 ± 1.2	1.8 ± 1.3	<0.0001
CHA_2DS_2-VASc score	4.7 ± 1.4	4.2 ± 1.4	2.9 ± 1.6	<0.0001
HAS-BLED score	2.0 ± 1.0	1.7 ± 0.8	1.5 ± 0.9	<0.0001
Basal medications				
OAC prescription	146 (45%)	481 (59%)	1,044 (54%)	0.0001
Warfarin	136 (42%)	433 (53%)	863 (44%)	<0.0001
PT-INR value	1.9 ± 0.5	1.9 ± 0.5	1.8 ± 0.5	0.08
Dabigatran	6 (1.9%)	20 (2.5%)	97 (5.0%)	0.0005
Rivaroxaban	2 (0.6%)	19 (2.3%)	54 (2.8%)	0.03
Apixaban	2 (0.6%)	9 (1.1%)	30 (1.5%)	0.3
Antiplatelet prescription	119 (37%)	270 (33%)	498 (26%)	<0.0001
Number of antiplatelets	0.5 ± 0.6	0.4 ± 0.6	0.3 ± 0.5	<0.0001

BP = blood pressure; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; OAC = oral anticoagulant; PT-INR = prothrombin time-international normalized ratio; TIA = transient ischemic attack.

Values are mean ± SD or n (%).

Table 2: Baseline Characteristics of Patients With or Without Oral Anticoagulant Prescription

Variable	OAC prescription		p Value
	Yes (n = 1,671)	No (n = 1,409)	
Age (years)	74.2 ± 9.3	74.0 ± 12.1	0.7
≥75	893 (54%)	736 (52%)	0.4
65-74 years old	542 (32%)	402 (29%)	0.02
Female	648 (39%)	608 (43%)	0.01
Body weight (kg)	60.0 ± 13.3	58.2 ± 13.3	0.0002
Body mass index (kg/m^2)	23.3 ± 4.0	22.8 ± 3.9	<0.0001
Systolic BP (mmHg)	123.3 ± 18.0	125.7 ± 18.8	0.0005
Diastolic BP (mmHg)	70.1 ± 12.5	70.3 ± 12.7	0.7
Heart rate (beats/min)	77.6 ± 15.7	78.4 ± 16.1	0.2
Symptomatic	778 (47%)	684 (49%)	0.3
Palpitation	491 (29%)	507 (36%)	<0.0001
Hemoglobin (g/dL)	13.0 ± 1.9	12.8 ± 2.1	0.0007
Platelet count (×10^9/L)	197 ± 69	201 ± 69	0.12
Baseline renal function			
Serum creatinine (mg/dL)	1.0 ± 0.6	0.9 ± 0.5	0.01
Estimated glomerular filtration rate (mL/min/1.73 m^2)	60.1 ± 20.5	64.0 ± 24.1	<0.0001
Calculated creatinine clearance (mL/min)	60.9 ± 26.4	63.9 ± 32.5	0.005
Comorbidities			
Heart failure	607 (36%)	303 (22%)	<0.0001
Hypertension	1,100 (66%)	852 (60%)	0.002
Diabetes mellitus	434 (26%)	317 (23%)	0.03
Receiving insulin therapy	53 (3.2%)	54 (3.8%)	0.3
Prior stroke	369 (22%)	191 (14%)	<0.0001
Prior stroke/TIA	405 (24%)	201 (14%)	<0.0001
History of major bleeding	61 (3.7%)	61 (4.3%)	0.3
Dyslipidemia	772 (46%)	616 (44%)	0.2
Coronary artery disease	248 (15%)	228 (16%)	0.3
Prior myocardial infarction	102 (6.1%)	94 (6.7%)	0.5
Peripheral vascular disease	79 (4.7%)	52 (3.7%)	0.2

COPD	105 (6.3%)	71 (5.0%)	0.1
Abnormal liver function	27 (1.6%)	23 (1.6%)	1.0
History of catheter ablation	91 (5.5%)	78 (5.5%)	0.9
History of defibrillation	67 (4.0%)	46 (3.3%)	0.3
$CHADS_2$ score	2.3 ± 1.3	1.9 ± 1.3	<0.0001
CHA_2DS_2-VASc score	3.7 ± 1.6	3.2 ± 1.7	<0.0001
HAS-BLED score	1.6 ± 0.9	1.6 ± 0.9	0.3
Basal medications			
Antiplatelet prescription	393 (24%)	494 (35%)	<0.0001
Number of antiplatelets	0.3 ± 0.5	0.4 ± 0.6	<0.0001

BP = blood pressure; COPD = chronic obstructive pulmonary disease; OAC = oral anticoagulant; TIA = transient ischemic attack.

Values are mean ± SD or n (%).

Table 3: Baseline Characteristics of Patients Categorized by CrCl and OAC

Variables	CrCl <30		p Value	CrCl 30-49		p Value
	OAC+ (n = 146)	OAC- (n = 176)		p Value	OAC- (n = 333)	
Age (years)	82.0 ± 7.3	85.6 ± 8.3	<0.0001	79.6 ± 6.7	81.8 ± 7.3	<0.0001
Prior stroke	43 (29%)	41 (23%)	0.2	104 (22%)	65 (20%)	0.5
History of major bleeding	6 (4.1%)	5 (2.8%)	0.6	15 (3.1%)	15 (4.5%)	0.3
$CHADS_2$ score	2.9 ± 1.3	2.9 ± 1.3	0.8	2.7 ± 1.2	2.4 ± 1.3	0.004
CHA_2DS_2-VASc score	4.7 ± 1.5	4.6 ± 1.4	0.6	4.3 ± 1.4	4.1 ± 1.4	0.1
HAS-BLED score	2.0 ± 1.0	2.0 ± 0.9	0.7	1.7 ± 0.8	1.8 ± 0.9	0.03

Variables	CrCl ≥50		p Value
	OAC+ (n = 1,044)	OAC- (n = 900)	
Age (years)	70.6 ± 8.7	68.9 ± 11.0	<0.0001
Prior stroke	222 (21%)	85 (9.4%)	<0.0001
History of major bleeding	20 (1.9%)	24 (2.7%)	0.3
$CHADS_2$ score	2.1 ± 1.3	1.4 ± 1.2	<0.0001
CHA_2DS_2-VASc score	3.3 ± 1.6	2.6 ± 1.5	<0.0001
HAS-BLED score	1.5 ± 0.9	1.4 ± 0.9	0.009

CrCl = creatinine clearance; OAC = oral anticoagulant.

Values are mean ± SD or n (%).

Table 4: Univariate and Multivariate Analysis of the Risk Factors for Stroke/SE

Variables	Univariate	Multivariate	
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	p Value
CrCl <30 (vs. CrCl ≥50)	2.05 (1.34 to 3.02)	1.68 (1.04 to 2.65)	0.04
30≤ CrCl <50 (vs. CrCl ≥50)	1.29 (0.93 to 1.76)	1.10 (0.76 to 1.58)	0.6
OAC prescription	1.17 (0.87 to 1.58)	1.06 (0.78 to 1.44)	0.7
Congestive heart failure	1.27 (0.92 to 1.72)	1.06 (0.76 to 1.47)	0.7
Hypertension	1.12 (0.83 to 1.53)	1.06 (0.78 to 1.45)	0.7
Age, ≥75 years old	2.12 (1.56 to 2.92)	1.97 (1.19 to 3.44)	0.008
Age, 65-74 years old	0.59 (0.41 to 0.82)	1.09 (0.64 to 1.96)	0.8
Diabetes mellitus	1.10 (0.79 to 1.51)	1.08 (0.77 to 1.50)	0.6
Prior stroke/TIA/SE	2.00 (1.46 to 2.71)	1.79 (1.30 to 2.45)	0.0005
Vascular disease	1.22 (0.75 to 1.88)	1.00 (0.61 to 1.55)	1.0
Female sex	1.03 (0.76 to 1.38)	0.88 (0.64 to 1.20)	0.4

CI = confidence interval; CrCl = creatinine clearance; OAC = oral anticoagulant; SE = systemic embolism; TIA = transient ischemic attack.

Table 5: Univariate and Multivariate Analysis of the Risk Factors for Major Bleeding

Variables	Univariate	Multivariate	
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	p Value
CrCl <30 (vs. CrCl ≥50)	2.14 (1.31 to 3.34)	2.08 (1.23 to 3.39)	0.008
30≤ CrCl <50 (vs. CrCl ≥50)	0.98 (0.65 to 1.44)	0.98 (0.63 to 1.48)	0.9
OAC prescription	1.33 (0.94 to 1.90)	1.41 (0.99 to 2.03)	0.06
Hypertension, SBP >160mmHg	1.32 (0.41 to 3.14)	1.40 (0.43 to 3.33)	0.5
Abnormal liver function	1.36 (0.22 to 4.27)	1.48 (0.24 to 4.68)	0.6
Prior stroke	1.31 (0.86 to 1.95)	0.87 (0.55 to 1.35)	0.5
History of major bleeding	3.44 (1.89 to 5.77)	3.69 (1.95 to 6.48)	0.0002
Age, >65 years old	1.97 (1.19 to 3.51)	1.82 (1.07 to 3.29)	0.03
Antiplatelet prescription	1.40 (0.98 to 1.98)	1.41 (0.98 to 2.01)	0.07
Alcohol abuse	1.30 (0.87 to 1.90)	1.48 (0.98 to 2.19)	0.06

CI = confidence interval; CrCl = creatinine clearance; OAC = oral anticoagulant; SBP = systolic blood pressure.

Figure 1

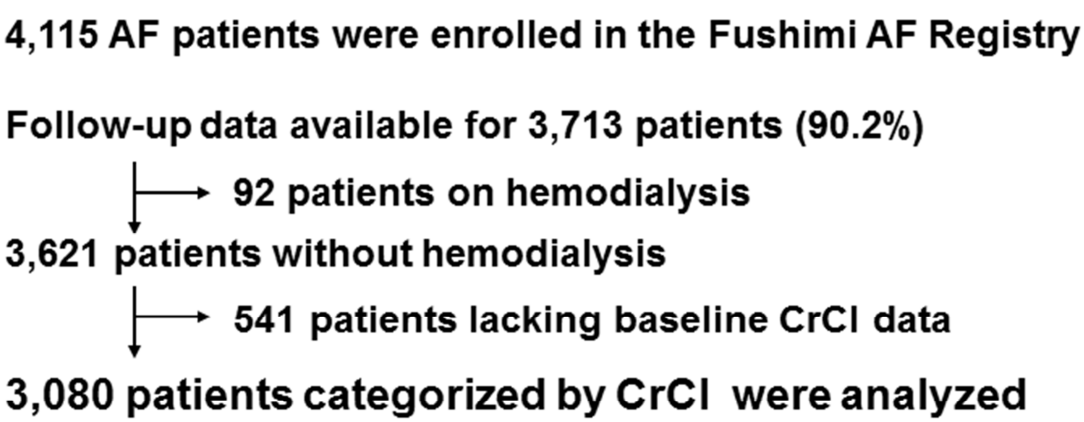

4,115 AF patients were enrolled in the Fushimi AF Registry
Follow-up data available for 3,713 patients (90.2%)
92 patients on hemodialysis
3,621 patients without hemodialysis
541 patients lacking baseline CrCl data
3,080 patients categorized by CrCl were analyzed

Figure 2

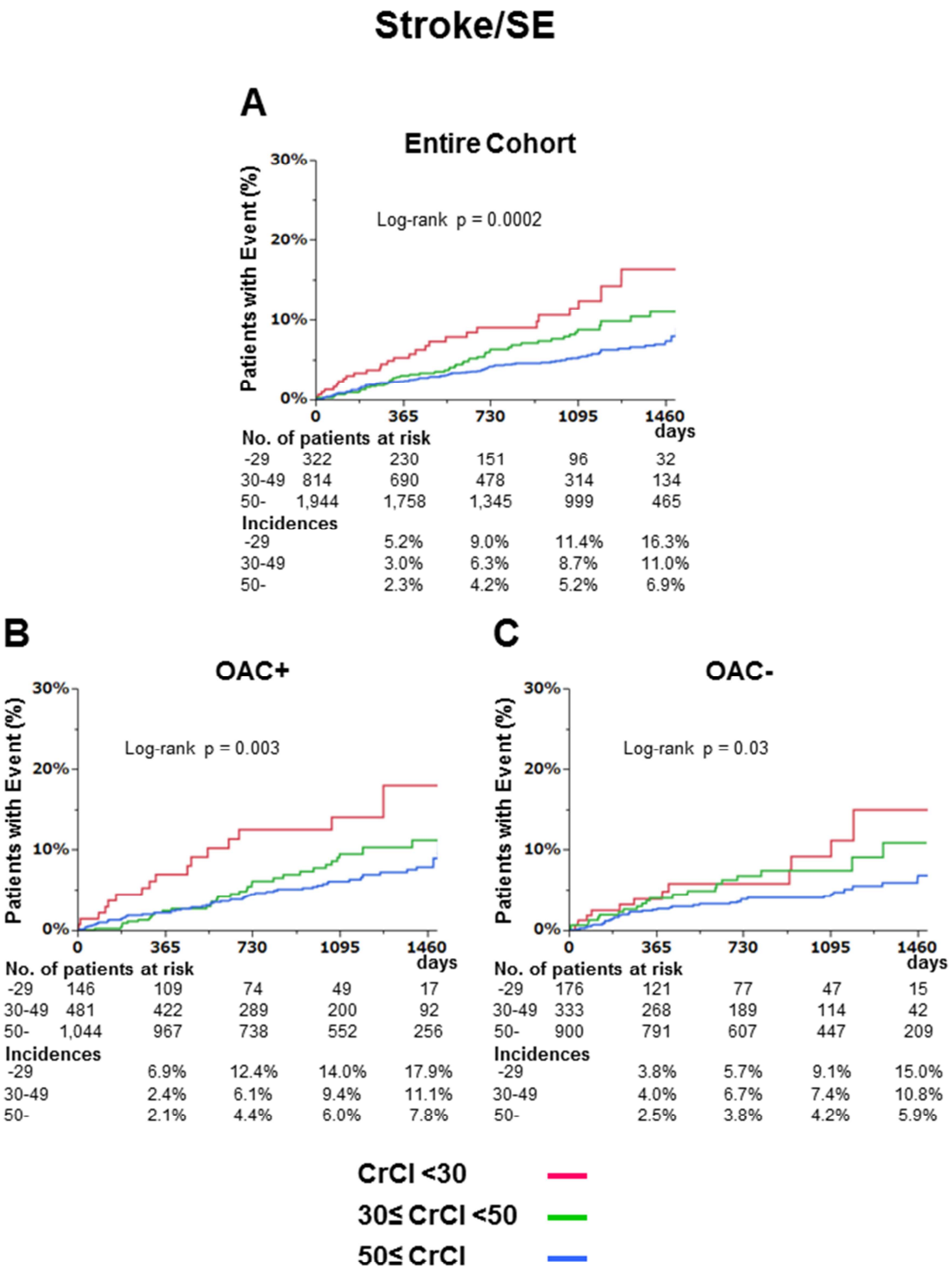
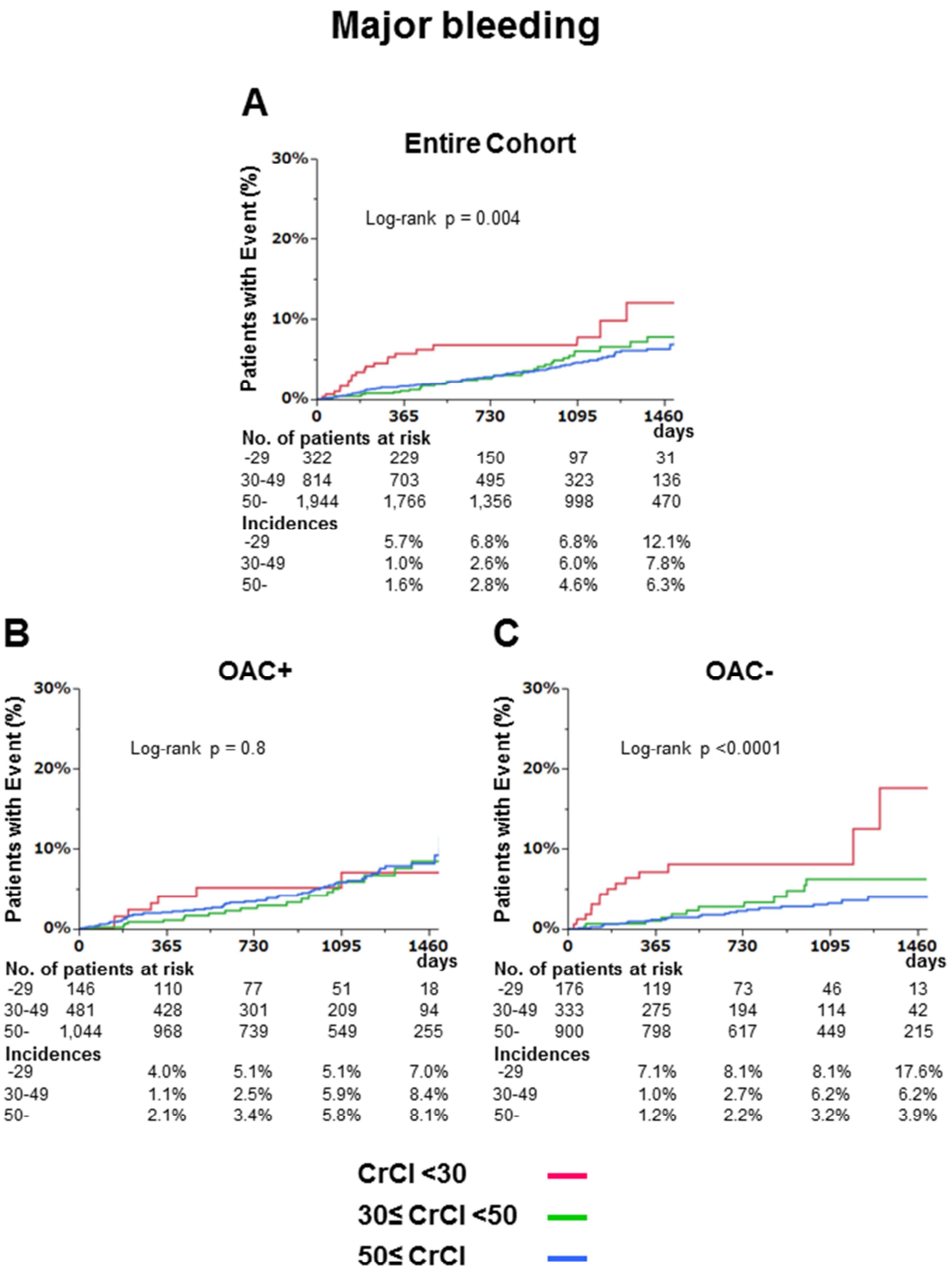

Stroke/SE
A
Entire Cohort
Log-rank p = 0.0002
Patients with Event (%)
30%
20%
10%
0%
0
365
730
1095
1460
days
No. of patients at risk
-29 322 230 151 96 32
30-49 814 690 478 314 134
50- 1,944 1,758 1,345 999 465
Incidences
-29 5.2% 9.0% 11.4% 16.3%
30-49 3.0% 6.3% 8.7% 11.0%
50- 2.3% 4.2% 5.2% 6.9%
B
OAC+
Log-rank p = 0.003
Patients with Event (%)
30%
20%
10%
0%
0
365
730
1095
1460
days
No. of patients at risk
-29 146 109 74 49 17
30-49 481 422 289 200 92
50- 1,044 967 738 552 256
Incidences
-29 6.9% 12.4% 14.0% 17.9%
30-49 2.4% 6.1% 9.4% 11.1%
50- 2.1% 4.4% 6.0% 7.8%
C
OAC-
Log-rank p = 0.03
Patients with Event (%)
30%
20%
10%
0%
0
365
730
1095
1460
days
No. of patients at risk
-29 176 121 77 47 15
30-49 333 268 189 114 42
50- 900 791 607 447 209
Incidences
-29 3.8% 5.7% 9.1% 15.0%
30-49 4.0% 6.7% 7.4% 10.8%
50- 2.5% 3.8% 4.2% 5.9%
CrCl <30
30≤ CrCl <50
50≤ CrCl

Figure 3


Major bleeding
A
Entire Cohort
Log-rank p = 0.004
Patients with Event (%)
30%
20%
10%
0%
0
365
730
1095
1460
days
No. of patients at risk
-29 322 229 150 97 31
30-49 814 703 495 323 136
50- 1,944 1,766 1,356 998 470
Incidences
-29 5.7% 6.8% 6.8% 12.1%
30-49 1.0% 2.6% 6.0% 7.8%
50- 1.6% 2.8% 4.6% 6.3%
B
OAC+
Log-rank p = 0.8
Patients with Event (%)
30%
20%
10%
0%
0
365
730
1095
1460
days
No. of patients at risk
-29 146 110 77 51 18
30-49 481 428 301 209 94
50- 1,044 968 739 549 255
Incidences
-29 4.0% 5.1% 5.1% 7.0%
30-49 1.1% 2.5% 5.9% 8.4%
50- 2.1% 3.4% 5.8% 8.1%
C
OAC-
Log-rank p <0.0001
Patients with Event (%)
30%
20%
10%
0%
0
365
730
1095
1460
days
No. of patients at risk
-29 176 119 73 46 13
30-49 333 275 194 114 42
50- 900 798 617 449 215
Incidences
-29 7.1% 8.1% 8.1% 17.6%
30-49 1.0% 2.7% 6.2% 6.2%
50- 1.2% 2.2% 3.2% 3.9%
CrCl <30
30≤ CrCl <50
50≤ CrCl