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Original Paper

Predictors of Cardioembolic Stroke in Japanese Patients with Atrial Fibrillation in the Fushimi AF Registry

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Keywords
Atrial fibrillation · Cardioembolic stroke · Risk factors · Stroke subtype · Infarct volume · Cohort study

Abstract
Background: Large-scale clinical trials have analyzed risk factors for any ischemic stroke in patients with atrial fibrillation (AF). However, the risk factors for cardioembolic stroke (CES), specifically, have not been reported. To clarify the risk factors for CES and clinically significant cardioembolic infarction, we examined the incidence of CES and larger infarct volume (IV) (>30 mL) CES, employing the Fushimi AF Registry, a community-based prospective cohort of AF patients in the Fushimi ward, Kyoto, Japan. ***Methods:*** A total of 4,182 Fushimi AF patients were enrolled from March 2011 to December 2014. The risk factors for CES were evaluated using multivariate analysis. ***Results:*** Of 4,182 patients enrolled, 3,749 patients were observed for ≥1 year. During the follow-up period (mean duration, 979 ± 7.7 days), 91/3,749 patients experienced a CES (2.43%). Significant risk factors associated with CES were older age (odds ratio [OR], 1.31; 95% confidence interval [CI], 1.01–1.72; $p = 0.046$), low body weight (OR, 1.30; 95% CI, 1.03–1.65; $p = 0.033$), sustained AF (OR, 1.67; 95% CI, 1.05–2.71; $p = 0.034$), and previ-

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ous stroke or transient ischemic attack (TIA) (OR, 1.94; 95% CI, 1.22–3.06; $p = 0.004$). Predictors of a large IV were chronic kidney disease (CKD) (OR, 2.08; 95% CI, 1.09–4.05; $p = 0.027$) and previous stroke/TIA (OR, 2.27; 95% CI, 1.19–4.24; $p = 0.011$). ***Conclusions:*** In this population-based cohort of Japanese patients with AF, in addition to previous stroke/TIA and older age, sustained AF and low body weight emerged as risk factors for CES, as opposed to any stroke, which may have a different risk profile. Patients with CKD or previous stroke/TIA who developed cardioembolic infarction exhibited more advanced severity. There is a need for direct oral anticoagulants that can be used safely in patients with comorbid AF and CKD.

Introduction

Atrial fibrillation (AF), which is the most common type of arrhythmia, increases the risk of thromboembolic events [1], and in particular, cardioembolic stroke (CES), which is the severest ischemic stroke subtype. Stroke risk has been examined in patients with AF in several studies [2–6], wherein various risk score rubrics were advocated, such as the $CHADS_2$ scoring system [3] and, more recently, the CHA_2DS_2-VASc scoring system [4]. However, these scoring systems assess the risk for any stroke, including noncardioembolic ischemic stroke (i.e., lacunar or atherothrombotic infarction) and/or hemorrhagic stroke (i.e., cerebral, subarachnoid, or chronic subdural hemorrhage), without specificity for CES [5, 6]. This may be partly because diagnostic imaging examinations were not usually performed at the onset of stroke in these clinical studies. Thus, it is unclear what factors are closely associated with CES in AF patients. For the same reason, the risk factors associated with infarct volume (IV) have not been determined in most clinical studies either, although the clinical outcome, as indexed by clinical stroke scales, has been found to be correlated with the lesion volume [7].

The Fushimi ward is located in southern Kyoto, Japan. It is a densely populated region with a total population of 283,000 and can be considered representative of a typical urban community in Japan. The Fushimi AF Registry includes a community-based prospective cohort of Japanese patients with AF. Investigators have already developed several lines of evidence based on this resource [8–11].

The aims of this study were (1) to identify predictors specific to CES in Japanese AF patients and (2) to clarify risk factors associated with clinically meaningful large cardioembolic IV. Towards these aims, we used the Fushimi AF Registry to enroll all AF patients in the Fushimi ward in our analysis of stroke incidence and risk factors [8].

Materials and Methods

For further details, refer to online supplementary methods (for all online suppl. material, see www.karger.com/doi/10.1159/000488206).

Fushimi AF Registry Data Sources

The detailed study design, patient enrollment, definition of the measurements, and Fushimi AF Registry subjects' baseline clinical characteristics have been described previously. All Fushimi AF Registry patients who had undergone 12-lead electrocardiography or Holter monitoring at any of the 80 participating institutions (all *Fushimi Ishi-Kai* [Fushimi Medical Association] members) since March 2011 were consecutively enrolled without exclusion. Patients without at least 1 year of follow-up were excluded. Most of the patients had undergone brain magnetic resonance imaging (MRI) examinations at stroke onset,

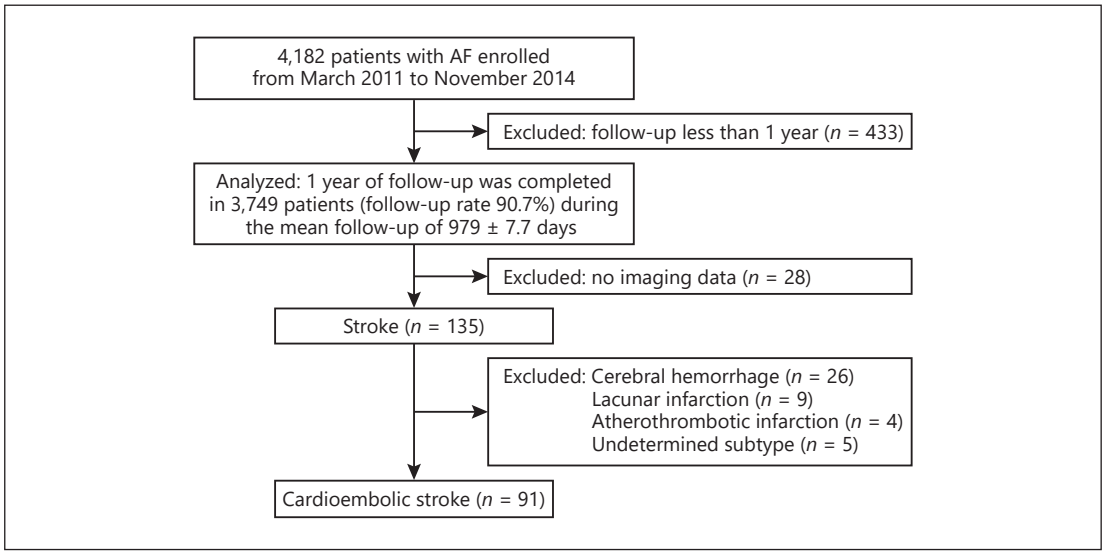

Fig. 1. Flowchart of this study.

enabling us to determine the ischemic stroke type and measure IV with diffusion-weighted imaging. Cases for which MRI or computed tomography (CT) data from stroke events were unavailable were excluded (Fig. 1).

The study protocol conformed to the ethical guidelines of the 2000 Declaration of Helsinki and was approved by the ethics committees of both the National Hospital Organization Kyoto Medical Center and Ijinkai Takeda General Hospital.

Stroke Ascertainment and Definitions

We identified stroke cases and determined stroke subtypes based on brain MRI or CT images obtained at stroke onset. Because all registry patients had cardiac-originated AF, we could not use a standard classification. Several independent neurologists reviewed each case and confirmed the stroke diagnoses, as informed by the literature [12]. The underlying stroke etiology was classified as CES, large-artery atherosclerosis, lacunar infarction, or undetermined etiology (see suppl. methods). Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

IV Measurement

IVs were measured manually in diffusion-weighted imaging or CT images, section by section, using the ITK-SNAP 2.2.0 software (http://www.itksnap.org/pmwiki/pmwiki.php?n=Main.Downloads). IV was classified as large (>30 mL) or small (≤30 mL), based on a study that showed that lesion volume is correlated with functional status [13]. Clinical background data were compared between the resulting large and small IV groups.

Statistical Analysis

Means are reported with standard deviations. We compared binary and categorical variables using the χ^2 test when appropriate; otherwise, the Fisher exact test was applied. We compared continuous variables using the Student *t* test or the Wilcoxon rank-sum test. We performed univariate and multivariate logistic regression for identified risk factors and calculated odds ratios (ORs) and 95% confidence intervals (CIs). A set of potential risk factors was chosen a priori based on biological plausibility and a priori knowledge [2–6]. A two-sided

Table 1. Comparison of baseline clinical characteristics between patients with and without CES

	CES	CES large IV	CES small IV	Non-CES	*p* value
Number	91	45	46	3,658	
Male	45 (49.5)	22 (24.2)	23 (25.3)	2,178 (59.5)	0.053
Age, years	78.9±8.4	79.6±1.63	78.1±1.61	73.5±11.0	<0.001
Height, cm	156.1±10.8	155.3±1.5	156.9±1.5	160.0±10.1	<0.001
Body weight, kg	53.5±12.7	52.3±2.0	54.8±2.0	59.3±13.2	<0.001
BMI	21.7±3.7	21.5±0.6	22.1±0.6	23.1±4.0	0.003
Systolic blood pressure, mm Hg	121.4±21.5	118.0±2.8	124.7±2.8	124.8±19.0	0.092
Diastolic blood pressure, mm Hg	67.5±15.3	64.0±1.9	70.9±1.9	70.7±12.8	0.018
Sustained AF	61 (67.3)	31 (34.0)	30 (33.3)	1,851 (50.6)	0.002
Paroxysmal AF	30 (33.0)	14 (15.3)	16 (17.7)	1,807 (49.4)	0.002
Comorbidities					
$CHADS_2$ score	2.69±1.30	2.76±0.20	2.63±0.20	2.01±1.33	<0.001
CHA_2DS_2-VASc score	4.28±1.60	4.31±0.25	4.26±0.25	3.34±1.70	<0.001
Congestive heart failure	35 (38.5)	18 (19.7)	17 (18.8)	973 (26.6)	0.012
Hypertension	59 (64.8)	30 (33.0)	29 (31.8)	2,270 (62.1)	0.589
Diabetes mellitus	19 (21.0)	5 (5.5)	14 (15.5)	841 (23.0)	0.636
Dyslipidemia	35 (38.5)	16 (17.6)	19 (20.9)	1,583 (43.3)	0.360
Chronic kidney disease	46 (50.6)	26 (28.6)	20 (22.0)	1,277 (34.9)	0.002
eGFR	46.2±17.5	44.9±3.1	47.3±3.0	51.2±20.7	0.022
Hemoglobin, g/dL	12.4±2.0	12.0±0.30	12.8±0.30	12.9±2.02	0.014
Previous stroke/TIA	33 (36.3)	18 (19.7)	15 (16.6)	707 (19.3)	<0.001
Dilated cardiomyopathy	0 (0)	0 (0)	0 (0)	51 (1.39)	
Hypertrophic cardiomyopathy	3 (3.3)	1 (1.1)	2 (2.2)	37 (1.01)	0.036
Ejection fraction	63.0±10.7	63.5±1.9	62.4±1.8	63.0±11.7	0.603
Left atrial dilation, mm	46.4±7.6	46.8±1.4	46.1±1.32	43.7±8.3	0.006
OAC prescription at baseline	54 (59.3)	29 (31.9)	25 (27.4)	1,944 (53.4)	0.262
Warfarin	50 (55.0)	26 (28.5)	24 (26.5)	1,678 (46.1)	0.095
Dabigatran	3 (3.3)	2 (2.2)	1 (1.1)	133 (3.64)	0.864
Rivaroxaban	1 (1.1)	1 (1.1)	0 (0)	84 (2.3)	0.449
Apixaban	0 (0)	0 (0)	0 (0)	49 (1.34)	
Antiplatelet drugs prescription at baseline	41 (45.1)	20 (22.0)	21 (23.1)	1,041 (27.7)	<0.001

Categorical data are presented as number (%) and continuous data as mean ± SD. We compared categorical variables using the χ^2 test when appropriate; otherwise, we used the Fisher exact test. Continuous variables were compared using the Student *t* test or Wilcoxon rank-sum test based on the distribution. *p* values were used for comparison between CES and non-CES. CKD was defined as eGFR <60 mL/min/1.73 m^2. Sustained AF referred to persistent and permanent AF. Infarct volume was classified as large (>30 mL) or small (≤30 mL). AF, atrial fibrillation; BMI, body mass index; CES, cardioembolic stroke; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IV, infarct volume; OAC; oral anticoagulant; TIA, transient ischemic attack.

p value <0.05 was considered statistically significant. The rationales for risk factor selection are described in the online supplementary methods. All analyses were performed with JMP, version 11 (SAS Institute, Cary, NC, USA).

Results

Of 4,182 patients that were enrolled from March 2011 to December 2014, 3,749 patients were observed for at least 1 year (follow-up rate, 90.7%). The mean follow-up period for these 3,749 patients was 979 ± 7.7 days (median, 1,099 days; range 553–1,470 days). CES occurred in 91/3,749 (2.43%) during follow-up. Twenty-eight cases for which we could not obtain MRI or CT data were excluded.

Table 2. Predictors of CES during follow-up: multivariate analysis after adjustment for $CHADS_2$ score components, body weight loss (per 10 kg), prevalence of sustained AF, CKD, and OAC prescription at baseline

Variable (*n* = 3,343)	Odds ratio	95% CI	*p* value
Age (per 10 years)	1.31	1.01–1.72	0.046
Body weight loss (per 10 kg)	1.30	1.03–1.65	0.033
Previous stroke/TIA	1.94	1.22–3.06	0.004
Hypertension	1.00	0.64–1.60	0.969
Congestive heart failure	1.06	0.66–1.70	0.797
Diabetes mellitus	0.92	0.53–1.53	0.754
Sustained AF	1.67	1.05–2.71	0.034
OAC prescription at baseline	1.10	0.70–1.74	0.676
Chronic kidney disease	1.52	0.96–2.41	0.072
Male	1.04	0.63–1.76	0.857

AF, atrial fibrillation; CES, cardioembolic stroke; CI, confidence interval; CKD, chronic kidney disease; OAC, oral anticoagulant; TIA, transient ischemic attack.

Table 3. Predictors of large infarct volume CES (≥30 mL) during follow-up: multivariate analysis after adjustment for $CHADS_2$ score components, sex, body weight loss (per 10 kg), prevalence of sustained AF, CKD, and OAC prescription at baseline

Variable (*N* = 3,343)	CES large IV			CES small IV		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
Age (per 10 years)	1.34	0.92–1.99	0.141	1.29	0.91–1.88	0.166
Body weight loss (per 10 kg)	1.40	1.00–2.00	0.054	1.21	0.88–1.68	0.256
Previous stroke/TIA	2.27	1.19–4.24	0.011	1.65	0.83–3.12	0.138
Hypertension	1.15	0.61–2.26	0.662	0.88	0.47–1.69	0.700
Congestive heart failure	0.96	0.49–1.84	0.894	1.18	0.60–2.27	0.620
Diabetes mellitus	0.42	0.14–0.99	0.074	1.60	0.80–3.05	0.167
Sustained AF	1.86	0.96–3.81	0.074	1.50	0.79–2.93	0.220
OAC prescription at baseline	1.33	0.70–2.59	0.393	0.92	0.49–1.74	0.798
Chronic kidney disease	2.08	1.09–4.05	0.027	1.12	0.58–2.13	0.737
Male	1.16	0.56–2.42	0.691	0.96	0.47–1.96	0.903

AF, atrial fibrillation; CES, cardioembolic stroke; CI, confidence interval; CKD, chronic kidney disease; IV, infarct volume; OAC, oral anticoagulant; TIA, transient ischemic attack.

Baseline Clinical Characteristics

The baseline clinical characteristics of the 91 patients who experienced CES are summarized and are compared with the characteristics of non-CES patients (Table 1). Compared to those without CES, AF patients with CES tended to be older, shorter, and with a lower body weight, and were more likely to have a history of heart failure, prior stroke/transient ischemic attack (TIA), CKD, hypertrophic cardiomyopathy, and sustained AF. The average $CHADS_2$ and CHA_2DS_2-VASc scores were higher while average estimated glomerular filtration rate and hemoglobin levels were lower in CES than in non-CES patients. CES patients were less likely to be taking an oral anticoagulant (OAC) than non-CES patients, with the most common OAC being warfarin (alternative OACs were limited when the majority of patients were enrolled).

Table 4. CES case characteristics

Number of patients	91
mRS at discharge	3.27±2.05
ICA/M1 occlusion	28 (31)
rt-PA	8 (9.7)
Median infarct volume, mL	29.75 [4.47–88.2]
OAC prescription at onset	49 (54)
Warfarin prescription at onset	41 (45)
PT-INR under therapeutic range	25 (27)
PT-INR within optimal range	15 (16)
PT-INR over therapeutic range	2 (0.02)
DOAC prescription at onset	8 (9)
Apixaban	1
Dabigatran	4
Rivaroxaban	3
Without OAC at onset	36 (40)
Unknown OAC use at onset	6 (6)

Categorical data are presented as number (%) and continuous data as mean ± SD. ICA/M1 occlusion were disclosed on magnetic resonance imaging at the onset. CES, cardioembolic stroke; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; ICA, internal carotid artery; M1, M1 segment of middle cerebral artery; mRS, modified Rankin Scale; OAC, oral anticoagulant; PT-INR, prothrombin time-international normalized ratio; rt-PA, recombinant tissue plasminogen activator.

Compared to patients with a smaller IV (≤30 mL), patients with a larger IV (>30 mL) were, on average, older, of lower body weight, and more likely to have a history of heart failure, previous stroke/TIA, or CKD.

Univariate and Multivariate Analysis

The univariate analysis results for CES and IV are reported in online supplementary Tables 1 and 2. Subsequent multivariate analysis after adjustment indicated that age (per decade; OR, 1.31; 95% CI, 1.10–1.72), low body weight (LBW; i.e., body mass ≤50 kg) (OR, 1.30; 95% CI, 1.03–1.65), sustained AF (OR, 1.67; 95% CI, 1.05–2.71), and previous stroke/TIA (OR, 1.94; 95% CI, 1.22–3.06) were risk factors for CES (Table 2). CKD (OR, 2.08; 95% CI, 1.09–4.05) and previous stroke/TIA (OR, 2.27; 95% CI, 1.19–4.24) were found to be associated with a larger IV (Table 3).

CES Cases

Of the 91 patients who experienced CES during the follow-up period (Table 4), 8 (9.7%) received recombinant tissue plasminogen activator (rt-PA); the mean modified Rankin Scale score of these patients was 3.27 ± 2.05. Notably, 41 of the 91 CES patients (45%) received warfarin at the time of stroke onset, although only 34 (37%) had a follow-up prothrombin time-international normalized ratio (PT-INR) value maintained within the warfarin therapeutic target range as established in the Japanese guidelines (PT-INR of 1.6–2.6 for patients ≥70 years old and PT-INR of 2.0–3.0 for patients <70 years old) [14]. Most of the remaining patients (61%) had a PT-INR under the therapeutic range, indicating OAC underdosage. Sixteen (39%) of the patients were not administered an OAC at the time of CES onset.

Discussion

Predictors of CES

Predictors of CES identified in this study were of an older age, had an LBW, sustained AF, and prior stroke/TIA.

Sustained AF

Several studies have reported that patients with paroxysmal AF have a risk of thromboembolic events similar to those with sustained (persistent and permanent) AF [6]. However, a recent meta-analysis reported that patients with sustained AF had a higher rate of stroke/systemic embolism than patients with paroxysmal AF [15]. AF events lasting longer than 1 day have been shown to be independently associated with embolism, and AF burden (i.e., time spent in AF) has been shown to be associated with an increased risk of stroke [16]. AF presence, duration, and burden status data may be integrated to obtain improved clinical risk stratification with continuous arrhythmia burden monitoring [17]. A previous study based on a Fushimi AF Registry cohort showed that sustained AF was independently associated with a higher incidence of stroke/systemic embolism than paroxysmal AF [9]. The present findings suggest that patients with sustained AF are also at a greater risk than patients with paroxysmal AF for CES, in particular.

Low Body Weight

In the Fushimi AF Registry, patients with LBW (body mass ≤50 kg) had high-risk profiles and showed a higher incidence of any stroke and systemic embolism [10]. The inverse relationship between obesity and prognosis in AF patients has been termed an "obesity paradox." Several large studies have found that AF patients who were overweight (body mass index, 25–30) or obese (body mass index, ≥30) tended to have a better prognosis in terms of cardiovascular hospitalizations, global mortality risk, and cardiovascular mortality risk [18]. We also found that LBW was a risk factor for CES in Japanese AF patients. Hence, there may be an inverse relationship between body weight and prognosis in AF patients, which extends beyond the normal weight versus obesity range into the LBW versus normal body weight range of comparison.

Asian AF patients are generally leaner and smaller than European and North American AF patients; relative to Europeans and North Americans in the RE-LY [19], ROCKET-AF [20], and ARISTOTLE [21] studies, Asian patients were, on average, 20, 16 and 17 kg lighter, respectively. The proportions of Fushimi AF Registry enlistees with a body weight <50 and <60 kg have been reported to be 25.7 and 55.0%, respectively [8]. According to the National Health and Nutrition Survey, the mean body weights of Japanese men and women over 70 years old in 2014 were 50.7 and 50.1 kg, respectively (http://www.mhlw.go.jp/).

There are several possible explanations for the association of LBW with a higher risk of stroke [22]. First, LBW may be due to poor nutritional status or illness-related weight loss (e.g., malignancy, chronic obstructive pulmonary disease, and gastrointestinal disease). Second, underweight patients may have advanced atrial fibrosis and remodeling involving the activation of the renin-angiotensin system.

Other Risk Factors

Advanced age and previous stroke/TIA are widely recognized as risk factors for stroke in patients with AF, including in the $CHADS_2$ rubric [3] and $CHADS_2$-VASc rubric [4]. The present study confirmed these two factors as independent risk factors for CES. In contrast, diabetes mellitus, hypertension, or congestive heart failure, which are commonly listed as risk factors for any ischemic stroke in AF patients, were not found to be significant risk factors for CES.

In a previous study, diabetes mellitus was associated with a significantly increased risk of AF (+26%) among women, but not among men [23]. It is still controversial whether diabetes mellitus is [2] or is not [23] a risk factor even for any ischemic stroke in patients with AF. The present study supports the view that diabetes mellitus is not a risk factor for CES.

Hypertension was not identified as an independent predictor of CES in the present study despite its common description as an important risk factor for any stroke. It may be that hypertension is associated with atherothrombotic cerebral infarction, lacunar infarction, hypertensive cerebral hemorrhage, and subarachnoid hemorrhage, but not with CES. Another possibility is that blood pressure (BP) was well controlled in the Fushimi AF Registry cohort (systolic BP 124.7 ± 19.1 mm Hg, diastolic BP 70.6 ± 12.8 mm Hg, n = 3,719). Future investigations are needed to clarify the possible role of hypertension in CES.

Predictors of IV

IV has been proposed as an alternative criterion (surrogate endpoint) to classical disability scales [24]. However, IV has not been associated with predictors of disability. The present study, to our knowledge, is the first to demonstrate that CKD and previous stroke/TIA are significant predictors of a larger IV. Notably, LBW, sustained AF, hypertension, and diabetes mellitus were not identified as significant risk factors for a larger IV.

CKD is characterized by endothelial dysfunction and increased coagulation in association with factor VIII activity [25]. The abnormal hemostatic profiles of patients with CKD may be related to an elevated risk of thrombotic events. Thus, CKD has been associated with an increased risk of stroke or systemic thromboembolism among patients with AF [5]. The mechanism of this increased risk may be related to anemia, oxidative stress, elevated plasma asymmetrical dimethylarginine (an inhibitor of nitric oxide synthesis), inflammation, and coagulation-promoting conditions [26].

Therefore, anticoagulation therapy should be sufficiently performed for AF patients with CKD. However, there are concerns regarding OAC prescriptions in these patients because of the increased risk of bleeding associated with CKD [27], which may lead to OAC underuse or underdosage. In addition, the metabolism of direct OAC drugs is largely dependent on the kidneys for elimination and little is known regarding the safety and efficacy of these drugs in patients with a creatinine clearance rate <25 mL/min because they were excluded from all pivotal phase-3 direct OAC trials [27]. Because direct OAC use is often restricted in patients with advanced CKD, it has not been shown which direct OACs, if any, are safe for CKD patients at risk of large infarction [27].

CES Cases

Kim et al. [12] found that 81.2% of ischemic stroke patients had AF-related stroke. Similarly, in the present study, CES patients accounted for 67.4% of all stroke patients and 83.5% of all ischemic stroke patients. The proportion of patients receiving rt-PA was larger in the present study than in other studies [28, 29], perhaps because Japan has a relatively high MRI delivery capacity (http://www.oecd.org/), with a large portion of hospitals capable of supporting rt-PA therapy, particularly in the Fushimi ward, where these capacities exceed the national average. Accordingly, it might be that education for stroke in the Fushimi ward has been widely dispersed among our patients.

In the present study, the absence of an OAC prescription was not a significant risk factor. This negative finding may be related to inappropriate OAC use in the study region. The Fushimi AF Registry has been demonstrated to encompass inappropriate OAC use in AF management, including OAC overuse among low-risk patients, OAC underuse among at-risk patients, and underdosing of warfarin [30]. Such inappropriate OAC use may be related to the narrow therapeutic range of OACs, drug and food interactions, the need for better monitoring,

and/or concerns regarding bleeding risk [8]. Regardless, there is discordance between recommended guidelines and real-world clinical practice.

Limitations

This study has several limitations. First, there were a limited number of stroke patients in the study population during the observation period. Second, antithrombotic drugs and doses were determined at the discretion of the attending physician. These limitations are intrinsic to most large multicenter registry studies.

Conclusions

In this population-based cohort of Japanese patients with AF, older age, sustained AF, previous stroke/TIA, and LBW were independently associated with the incidence of CES, as opposed to any stroke, which may have a different risk profile. Patients with CKD or previous stroke/TIA who developed cardioembolic infarction exhibited more advanced severity. There is a need for direct OACs that can be used safely in patients with comorbid AF and CKD.

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Disclosure Statement

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