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Difference in risk factors of silent brain infarction between paroxysmal and persistent atrial fibrillation

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ABSTRACT

Background: Although silent brain infarction is an independent risk factor for subsequent symptomatic stroke and dementia in patients with nonvalvular atrial fibrillation, little is known regarding differences in risk factors for silent brain infarction between patients with paroxysmal and persistent nonvalvular atrial fibrillation.

Methods: This study population consisted of 190 neurologically asymptomatic patients (mean age, 64 ± 11 years) with nonvalvular atrial fibrillation (119 paroxysmal, 71 persistent) who were scheduled for catheter ablation. All patients underwent brain magnetic resonance imaging to screen for silent brain infarction prior to ablation. Transthoracic and transesophageal echocardiography was performed to screen for left atrial abnormalities (left atrial enlargement, spontaneous echo contrast, or left atrial appendage emptying velocity) and complex plaques in the aortic arch.

Results: Silent brain infarction was detected in 50 patients (26%) [26 patients (22%) in paroxysmal vs. 24 patients (34%) in persistent, $p = 0.09$]. Multiple logistic regression analysis indicated that age and diabetes mellitus or chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) were associated with silent brain infarction in patients with paroxysmal nonvalvular atrial fibrillation ($p < 0.05$), whereas no modifiable risk factors of silent brain infarction were observed in patients with persistent nonvalvular atrial fibrillation.

Conclusions: These findings suggest that intensive intervention for diabetes mellitus and renal impairment from the paroxysmal stage or ablation therapy at the time of paroxysmal stage to prevent progression to persistent nonvalvular atrial fibrillation may prevent silent brain infarction and consequently reduce the risk of future symptomatic stroke.

1. Introduction

Nonvalvular atrial fibrillation (NVAF) is the most common arrhythmia increasing with age, and one in four individuals over 40 years of age will suffer from NVAF in their lifetime [1–3]. The prevalence and incidence of NVAF are gradually increasing worldwide, and are expected to triple by 2050 [1,2]. Since NVAF is associated with a three- to five-fold increased risk of ischemic stroke, which is linked to poor prognosis and higher healthcare costs [4–7], effective prevention is essential in daily patient care. Although uniform management with CHA_2DS_2-VASc scoring and anticoagulation therapy reduces the incidence of stroke and mortality, a substantial number of patients is still exposed to the risk of cerebral infarction [8,9]. Therefore, the identification of other preventive or therapeutic strategies is expected to improve long-term morbidity and mortality rates in patients with NVAF.

Silent brain infarction (SBI), a cerebral infarction (>3mm) that is evident on brain imaging but not associated with clinical symptoms [10] (since lacunar infarction is defined as a subcortical infarction, which typically ranges between 3 mm and 15 mm, caused by occlusion of penetrating artery with or without clinical

Abbreviations: NVAF, nonvalvular atrial fibrillation; SBI, Silent brain infarction; LA, left atrial; LAA, left atrial appendage; MRI, magnetic resonance imaging; eGFR, estimated glomerular filtration rate; FLAIR, fluid attenuated inversion recovery; OR, odds ratio; DOACs, direct oral anticoagulants.

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symptom [11], SBI includes asymptomatic lacunar infarction), is a subclinical abnormality that was traditionally considered a relatively benign degenerative change. However, this view has changed recently because SBI is reportedly associated with subsequent symptomatic stroke [12,13] and an increased risk of cognitive decline [14–16]. Moreover, NVAF is associated with more than a two-fold increase in the risk of SBI compared to sinus rhythm [17]. Therefore, the identification of risk factors associated with SBI would enable physicians to provide personalized treatment for each NVAF patient and further support for preventing future dementia or stroke and maintaining a better quality of life.

Several studies have consistently demonstrated that the prevalence of SBI was strongly associated with age and hypertension both in the general population and NVAF patients [17–20]. Moreover, left atrial (LA) abnormalities such as LA thrombus, spontaneous echo contrast, and low LA appendage (LAA) emptying velocity are associated with SBI in NVAF patients [21,22]. As transesophageal echocardiography, which provides information that is not obtained from conventional clinical assessments (i.e., CHA_2DS_2-VASc score), is semi-invasive, transthoracic echocardiography is an alternative non-invasive method that might be helpful for risk stratification. Mitral annular velocity during diastole (e′) and the ratio of early transmitral flow velocity (E) and e′ (E/e′), implying elevated filling pressure that facilitates blood stasis and thrombus formation in the LA, are associated with SBI [23,24]. However, as these studies included both paroxysmal and persistent NVAF patients, the differences in prevalence and risk factors of SBI between NVAF types have not yet been entirely elucidated.

Therefore, the aim of the present study was to assess the differences in prevalence and risk factors of SBI between patients with paroxysmal and those with persistent NVAF.

2. Methods

2.1. Study population

This cross-sectional study of prospectively collected data was conducted at Osaka City University Hospital. We initially included 278 consecutive 1) neurologically asymptomatic NVAF patients 2) who were scheduled for their first catheter ablation between October 2011 and April 2017. We excluded patients with contraindication to (n = 11) or refused (n = 77) brain magnetic resonance imaging (MRI). Thus, 190 patients (mean age, 64 ± 11 years) were eligible for inclusion in this study. All patients were taking anticoagulation therapy and underwent brain MRI to detect SBI. The patients were classified by duration into paroxysmal (that terminates within 7 days; n = 119) or persistent (that is sustained longer than 7 days; n = 71) [25]. Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, and/or treatment with an oral antihypertensive medication. Diabetes mellitus was defined as fasting blood glucose $\geq$ 7 mmol/L, glycated hemoglobin A1c $\geq$ 6.5%, and/or current use of insulin or oral hypoglycemic medication. Dyslipidemia was defined as a low-density lipoprotein cholesterol level $\geq$ 3.6 m mol/L and/or use of lipid-lowering medication. Patients were defined as non-smokers if they had never smoked. Chronic kidney disease was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 [26]. We calculated CHA_2DS_2-VASc scores using the above information [27]. Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Transthoracic echocardiographic analysis

Comprehensive transthoracic echocardiography was performed to evaluate LA enlargement or diastolic function using an iE33 (Philips Medical Systems, Andover, MA, USA), Vivid E9 (GE Healthcare, Milwaukee, WI, USA), or Aplio 500/Artida (Canon Medical Systems, Tochigi, Japan) machine equipped with a high-frequency transducer. Mitral peak E wave velocity and tissue Doppler-derived mitral annular e′ velocity were averaged from three nonconsecutive beats with cycle lengths within 10–20% of the average heart rate [28]. Bilateral carotid artery ultrasonography was performed to exclude carotid stenosis and ulcerated or mobile plaques using an iE33 (Philips Medical Systems, Andover, MA, USA) equipped with a 7.5-MHz linear transducer.

2.3. Transesophageal echocardiographic analysis

Comprehensive transesophageal echocardiography was performed to evaluate LA abnormalities such as thrombus, spontaneous echo contrast (Fig. 1a), and LAA emptying velocity (Fig. 1b) or complex plaques in the aortic arch defined as large ($\geq$4 mm), ulcerated, and mobile plaques (Fig. 1c) using an iE33 (Philips Medical Systems, Andover, MA, USA) equipped with a X7-2 t transducer providing a frequency range of 2.0–7.0 MHz. Spontaneous echo contrast was defined as smoke-like echoes curling up in a circular pattern, that were continuously present at standard gain after gain adjustment to distinguish background noise [29–31]. LAA emptying velocity was obtained at 10 mm below the orifice of the LAA over at least six cardiac cycles and averaged [30,31].

2.4. Brain MRI

We performed brain MRI using a superconducting magnet at a field strength of 1.5 T or 3.0 T on proton density, T1- and T2-weighted images, and fluid attenuated inversion recovery (FLAIR) images in axial planes with 5-mm-in-thickness slices and an interslice gap of 1.5 mm. SBI was defined as a lesion > 3 mm that was hypointense on T1-weighted images and hyperintense on T2-weighted images (Fig. 2). FLAIR images were used to distinguish dilated Virchow-Robin spaces from infarcts based on the absence or presence of a hyperintense rim around each of the suspected lesions [10].

2.5. Statistical analysis

The statistical analysis was performed using EZR graphical user interface (Saitama Medical Center, Jichi Medical University, Saitama, Japan) for R programming language (The R Foundation for Statistical Computing, Vienna, Austria). The distribution of echocardiographic variables and potential covariates was evaluated among patients with versus without SBI and paroxysmal or persistent NVAF. The intergroup comparison was performed using an unpaired Student's *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. P values < 0.05 were used to select variables for multiple logistic regression analysis; however, since CHA_2DS_2-VASc score includes age, hypertension, and diabetes mellitus, we entered only CHA_2DS_2-VASc score when putting it into the multivariate analysis to avoid the issue of multicollinearity. Multiple logistic regression analyses were performed to identify the variables associated with the presence of SBI in all patients and patients with paroxysmal or persistent NVAF. At first, we performed multivariate analysis to identify the variables other than CHA_2DS_2-VASc score associated with the presence of SBI (Model 1). Second, since anticoagulation therapy is recommended to prevent cerebral infarction for NVAF patients with CHA_2DS_2-VASc score $\geq$ 2, we performed multivariate analysis

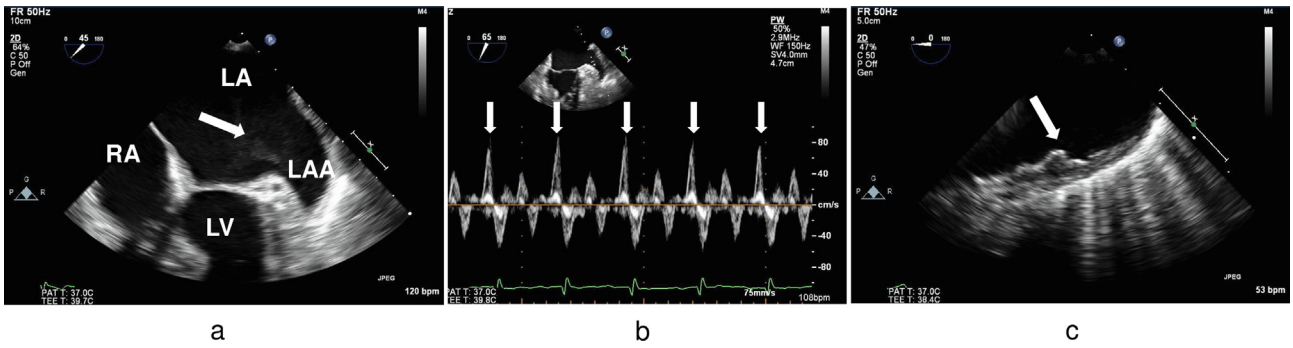

Fig 1. Example images of transesophageal echocardiography. a spontaneous echo contrast in the left atrium (arrow). b pulsed-wave Doppler recording showed left atrial appendage emptying velocity of 79 cm/s (arrow). c a large atherosclerotic plaque (arrow) in the aortic arch. LA, left atrium; LAA, left atrial appendage; LV, left ventricle; RA, right atrium; SEC, spontaneous echo contrast.

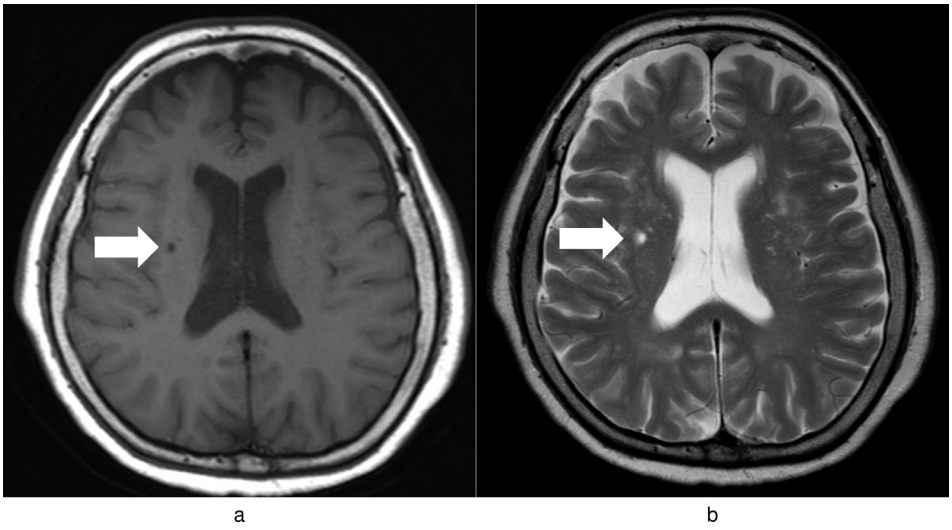

Fig 2. Example images of silent brain infarction on brain magnetic resonance imaging. A small (5 mm) silent brain infarct in the basal ganglia (arrow) is visible as a hypointense on T1-weighted image (a) and as a hyperintense on T2-weighted image (b).

with CHA_2DS_2-VASc score as a binary variable (i.e., CHA_2DS_2-VASc score ≥ 2) to investigate whether CHA_2DS_2-VASc score ≥ 2 is also associated with SBI (Model 2). Third, since CHA_2DS_2-VASc score is useful for risk stratification of cerebral infarction in NVAF patients, we performed multivariate analysis with CHA_2DS_2-VASc score as a continuous variable to investigate whether CHA_2DS_2-VASc score is also useful for risk stratification of SBI (Model 3). P values < 0.05 were considered statistically significant.

3. Results

3.1. Study population

Among the 190 neurologically asymptomatic NVAF patients (mean age, 64 ± 11 years), 119 (63%) had paroxysmal and 71 (37%) had persistent NVAF. The patients' clinical and echocardiographic characteristics are listed in Table 1. The study population predominantly consisted of men (74%) who had a preserved ejection fraction (58 ± 5%), and who had a low CHA_2DS_2-VASc score (1.8 ± 1.2). The prevalence of SBI was 26% and there were no significant differences between NVAF types (p = 0.09). LA diameter (39 ± 6 mm vs. 44 ± 6 mm, p < 0.001), E wave (68 ± 19 cm/s vs. 83 ± 17 cm/s, p < 0.001), e′ (6.6 ± 2.0 cm/s vs. 7.7 ± 1.9 cm/s, p = 0.001), and the prevalence of spontaneous echo contrast (3% vs. 21%, p < 0.001) were significantly higher in patients with persistent NVAF. On the other hand, left ventricular ejection fraction (59 ± 5% vs. 55 ± 6%, p < 0.001) and LAA emptying velocity (58 ± 18 cm/s vs. 37 ± 17 cm/s, p < 0.001) were significantly higher in patients with paroxysmal NVAF. LA/LAA thrombus was not detected in both NVAF groups.

3.2. Clinical and echocardiographic variables associated with SBI in all patients

Clinical and echocardiographic characteristics by SBI status in all patients are shown in Table 2. Age, hypertension, diabetes mellitus, CHA_2DS_2-VASc score, LA diameter, E wave, and E/e′ were positively associated with SBI. On the other hand, eGFR, e′, and LAA emptying velocity were negatively associated with SBI. Table 3 shows the clinical and echocardiographic variables associated with the presence of SBI and their odds ratios (ORs) obtained on multiple logistic regression analysis. Age (OR, 1.06; 95% confidence interval, 1.01–1.10; p = 0.02), diabetes mellitus (OR, 3.00; 95% confidence interval, 1.21–7.44; p = 0.02), and LAA emptying velocity (OR, 0.98; 95% confidence interval, 0.96–0.998; p = 0.03) remained independently associated with the presence of SBI (Model 1). When putting CHA_2DS_2-VASc score instead of age, hypertension, and diabetes mellitus into multivariate analysis, only CHA_2DS_2-VASc score ≥ 2 (a binary variable) remained independently associated with the presence of SBI (OR, 2.24; 95% confidence interval,

Table 1
Clinical and echocardiographic characteristics according to NVAF types.

	All patients (n = 190)	Paroxysmal AF (n = 119)	Persistent AF (n = 71)	p
Age, y	64 ± 11	64 ± 11	65 ± 10	0.70
Male, n (%)	141 (74)	88 (74)	53 (75)	1.00
Hypertension, n (%)	121 (64)	78 (66)	43 (61)	0.53
Diabetes mellitus, n (%)	34 (18)	22 (19)	12 (17)	0.85
Smoker, n (%)	101 (53)	66 (56)	35 (49)	0.45
Dyslipidemia, n (%)	65 (34)	45 (38)	20 (28)	0.21
Silent brain infarction, n (%)	50 (26)	26 (22)	24 (34)	0.09
eGFR (mL/min/1.73 m^2)	75 ± 21	76 ± 23	75 ± 18	0.68
CHA_2DS_2-VASc score	1.8 ± 1.2	1.8 ± 1.1	1.8 ± 1.2	0.79
Inappropriately reduced-dose DOACs, n (%)	25 (32)	14 (12)	11 (16)	0.51
Warfarin, n (%)	31 (16)	24 (20)	7 (10)	0.07
PT-INR of warfarin patients	2.31 ± 0.59	2.26 ± 0.44	2.46 ± 0.98	0.39
Ejection fraction, %	58 ± 5	59 ± 5	55 ± 6	<0.001
Left atrial diameter, mm	41 ± 6	39 ± 6	44 ± 6	<0.001
E wave, cm/s	73 ± 20	68 ± 19	83 ± 17	<0.001
e′, cm/s	7.0 ± 2.0	6.6 ± 2.0	7.7 ± 1.9	0.001
E/e′	11.2 ± 4.0	10.9 ± 3.9	11.6 ± 4.3	0.30
Spontaneous echo contrast, n (%)	19 (10)	4 (3)	15 (21)	<0.001
LAA emptying velocity, cm/s	51 ± 21	58 ± 18	37 ± 17	<0.001
Complex arch plaques, n (%)	23 (12)	14 (12)	9 (13)	1.00

eGFR, estimated glomerular filtration rate; DOACs, direct oral anticoagulants; LAA, left atrial appendage; NVAF, nonvalvular atrial fibrillation

Table 2
Clinical and echocardiographic characteristics according to the presence of SBI in all patients and patients with paroxysmal or persistent NVAF.

	All patients			Paroxysmal AF			Persistent AF		
	Without SBI (n = 140)	With SBI (n = 50)	p	Without SBI (n = 93)	With SBI (n = 26)	p	Without SBI (n = 47)	With SBI (n = 24)	p
Age, y	63 ± 11	79 ± 8	<0.001	62 ± 11	70 ± 8	0.002	63 ± 11	68 ± 8	0.06
Male, n (%)	104 (74)	37 (74)	1.00	67 (72)	21 (81)	0.46	37 (79)	16 (67)	0.39
Hypertension, n (%)	82 (59)	39 (78)	0.02	56 (60)	22 (85)	0.02	26 (55)	17 (71)	0.31
Diabetes mellitus, n (%)	18 (13)	16 (32)	0.005	12 (13)	10 (39)	0.008	6 (13)	6 (25)	0.32
Smoker, n (%)	78 (56)	23 (46)	0.25	52 (56)	14 (54)	1.00	26 (55)	9 (38)	0.21
Dyslipidemia, n (%)	50 (36)	15 (30)	0.49	36 (39)	9 (35)	0.82	14 (30)	6 (25)	0.78
eGFR (mL/min/1.73 m^2)	77 ± 21	70 ± 22	0.002	78 ± 23	67 ± 21	0.03	75 ± 16	74 ± 22	0.71
CHA_2DS_2-VASc score	1.6 ± 1.1	2.3 ± 1.2	<0.001	1.6 ± 1.1	2.4 ± 1.1	0.001	1.5 ± 1.1	2.2 ± 1.4	0.03
Inappropriately reduced-dose DOACs, n (%)	16 (11)	9 (18)	0.23	9 (10)	5 (19)	0.19	7 (15)	4 (17)	1.00
PT-INR of warfarin patients	2.13 ± 0.41	2.52 ± 0.72	0.07	2.14 ± 0.43	2.49 ± 0.41	0.07	1.99	2.56 ± 1.05	0.64
Ejection fraction, %	58 ± 5	57 ± 5	0.11	59 ± 4	59 ± 3	0.80	56 ± 6	54 ± 6	0.30
Left atrial diameter, mm	40 ± 6	43 ± 6	0.02	38 ± 6	41 ± 5	0.08	43 ± 6	44 ± 6	0.49
E wave, cm/s	71 ± 17	78 ± 24	0.04	66 ± 15	73 ± 27	0.10	82 ± 17	84 ± 19	0.67
e′, cm/s	7.2 ± 2.1	6.4 ± 1.8	0.02	6.8 ± 2.1	6.0 ± 1.8	0.08	8.1 ± 1.9	6.9 ± 1.7	0.01
E/e′	10.5 ± 3.5	12.9 ± 4.9	<0.001	10.4 ± 3.6	12.7 ± 4.3	0.01	10.7 ± 3.2	13.1 ± 5.6	0.02
Spontaneous echo contrast, n (%)	10 (7)	9 (18)	0.050	1 (1)	3 (12)	0.03	9 (19)	6 (25)	0.56
LAA emptying velocity, cm/s	53 ± 20	43 ± 21	0.002	60 ± 17	51 ± 21	0.02	39 ± 18	34 ± 16	0.22
Complex arch plaques, n (%)	15 (11)	8 (16)	0.49	10 (11)	4 (15)	0.50	5 (11)	4 (17)	0.48

eGFR, estimated glomerular filtration rate; DOACs, direct oral anticoagulants; LAA, left atrial appendage; NVAF, nonvalvular atrial fibrillation; SBI, silent brain infarction

1.02–4.89; p = 0.04) (Model 2). However, no risk factor of SBI was observed when putting CHA_2DS_2-VASc score as a continuous variable (Model 3).

3.3. Clinical and echocardiographic variables associated with SBI in patients with paroxysmal NVAF

Clinical and echocardiographic characteristics by SBI status in patients with paroxysmal NVAF are shown in Table 2. Age, hypertension, diabetes mellitus, CHA_2DS_2-VASc score, E/e′, and spontaneous echo contrast were positively associated with SBI. On the other hand, eGFR and LAA emptying velocity were negatively associated with SBI. Table 3 shows the clinical and echocardiographic variables associated with the presence of SBI and their odds ratios (ORs) obtained on multiple logistic regression analysis. Age (OR, 1.08; 95% confidence interval, 1.01–1.15; p = 0.03) and diabetes mellitus (OR, 5.41; 95% confidence interval, 1.58–18.50; p = 0.007) remained independently associated with the presence of SBI (Model 1). When putting CHA_2DS_2-VASc score instead of age, hypertension, and diabetes mellitus into multivariate analysis, only chronic kidney disease remained independently associated with the presence of SBI in both a binary variable (OR, 3.42; 95% confidence interval, 1.06–11.00; p = 0.04) (Model 2) and a continuous variable (OR, 3.30; 95% confidence interval, 1.03–10.60; p = 0.04) (Model 3). There was no significant interaction between CHA_2DS_2-VASc score $\geq$ 2 (p = 0.07) or NVAF type (p = 0.48) and chronic kidney disease.

3.4. Clinical and echocardiographic variables associated with SBI in patients with persistent NVAF

Clinical and echocardiographic characteristics according to the presence of SBI in patients with persistent NVAF are shown in Table 2. CHA_2DS_2-VASc and E/e′ were positively associated with SBI. On the other hand, e′ was negatively associated with SBI. Table 3 shows the clinical and echocardiographic variables associ-

ated with the presence of SBI and their OR obtained in the multiple logistic regression analysis. Since only e′ or E/e′ and CHA_2DS_2-VASc score were associated with SBI in univariate analysis, we could not perform Model 1. e′ remained independently associated with the presence of SBI when putting CHA_2DS_2-VASc score $\geq$ 2 as a binary variable (OR, 0.71; 95% confidence interval, 0.51–0.98; p = 0.04) (Model 2), while not in a model using CHA_2DS_2-VASc score as continuous variable (OR, 0.73; 95% confidence interval, 0.53–1.01; p = 0.06) (Model 3). When putting E/e′ instead of e′ into multivariate analysis, neither a model of CHA_2DS_2-VASc score $\geq$ 2 (a binary variable) (OR, 2.42; 95% confidence interval, 0.79–7.44; p = 0.12) (Model 2) nor a model of CHA_2DS_2-VASc score (a continuous variable) (OR, 1.11; 95% confidence interval, 0.95–1.30; p = 0.18) (Model 3) was associated with SBI. There was no significant interaction between CHA_2DS_2-VASc score $\geq$ 2 (p = 0.89) or NVAF type (p = 0.43) and e′.

3.5. Relationship between quality of anticoagulation therapy and SBI

Warfarin was used in 31 patients (16%) and there was no significant difference between paroxysmal and persistent NVAF [24 (20%) vs. 7 (10%), p = 0.07]. PT-INR value was optimal in both paroxysmal and persistent NVAF (2.26 ± 0.44 vs. 2.46 ± 0.98, p = 0.39). Moreover, PT-INR value was not associated with SBI in patients with paroxysmal (p = 0.07) and persistent NVAF (p = 0.64). Inappropriately reduced-dose direct oral anticoagulants (DOACs) were observed in 25 patients (14 paroxysmal and 11 persistent) and there was no significant difference between NVAF groups (p = 0.51). Moreover, inappropriately reduced-dose DOACs was not associated with SBI both in patients with paroxysmal (p = 0.19) and persistent NVAF (p = 1.00).

3.6. Size, number, and location of SBI

We have divided into groups based on the differences in size (3 to 5 mm or > 5 mm) (Fig. 3a), number (0, 1–2, or $\geq$ 3) (Fig. 3b), and location (cortex/subcortex, deep white mater, thalamus/basal ganglia, brainstem, and cerebellum) of SBI (Fig. 3c) [32]. SBI was more frequently detected in cortex/subcortex (p = 0.03) in patients with persistent NVAF. Moreover, significantly larger (P = 0.045) and more (P = 0.045) SBI was found in patients with persistent NVAF.

4. Discussion

First, we showed that age, diabetes mellitus, and LAA emptying velocity were significantly associated with the presence of SBI in NVAF patients. Second, we demonstrated that age and diabetes mellitus were significantly associated with the presence of SBI in "paroxysmal" NVAF, but no modifiable risk factors of SBI were observed in "persistent" NVAF. Third, chronic kidney disease was significantly associated with the presence of SBI independent of CHA_2DS_2-VASc score in "paroxysmal" NVAF. Fourth, SBI due to small-vessel occlusive disease (i.e., atherosclerosis) develops from the paroxysmal stage and SBI due to microembolism becomes more apparent from the persistent stage. To our knowledge, this is the first study to demonstrate the difference in risk factors and mechanisms of SBI, which carries an increased risk of symptomatic stroke and cognitive decline, in patients with NVAF.

Age, diabetes mellitus, and LAA emptying velocity were associated with the presence of SBI in all patients. These finding are consistent with previous studies. Vermeer et al. reported that age and diabetes mellitus were associated with the incidence of SBI in elderly people [33]. Similarly, Eguchi et al. showed that diabetes mellitus correlated with SBI in hypertensive population [34]. Miki et al. demonstrated the association between LAA emptying velocity and SBI in NVAF patients [21,22]. However, these studies focused on patients with sinus rhythm or all NVAF patients, and no studies to date have elucidated the differences in prevalence and risk factors of SBI between NVAF types

Since NVAF is a progressive disease that progresses with structural and electrical remodeling through underlying cardiovascular conditions such as hypertension, followed by the self-terminating stage (paroxysmal) and the persistent stage [35], we examined whether there were any differences in the mechanisms and risk factors of SBI between NVAF types. SBI was more frequently detected in cortex/subcortex, which may be more likely to arise from microembolism in patients with persistent NVAF. Moreover, significantly larger and more SBI was found in patients with persistent NVAF. These findings indicate that SBI due to microembolism becomes more apparent at the persistent stage. e′ remained independently associated with SBI when putting CHA_2DS_2-VASc score $\geq$ 2 as a binary variable (Model 2), while not in a continuous variable (Model 3). These results indicate that e′ is superior than CHA_2DS_2-VASc score $\geq$ 2 for risk stratification of SBI, while not than CHA_2DS_2-VASc score as a continuous variable. Moreover, when putting E/e′ instead of e′ into multivariate analysis, neither Model 2 nor Model 3 was associated with SBI. It is undeniable that e′ may be associated with SBI; however, since E/e′ and e′ were not associated with SBI in the model which includes CHA_2DS_2-VASc score as a continuous variable, it is difficult to conclude that diastolic dysfunction is superior than CHA_2DS_2-VASc score for risk stratification of SBI in patients with persistent NVAF. Therefore, we suggest ablation therapy at the time of paroxysmal stage to prevent progression to persistent NVAF may reduce lifetime SBI risk and consequently reduce the risk of future symptomatic stroke.

In paroxysmal NVAF, Model 2 and Model 3 indicated that chronic kidney disease was more useful than CHA_2DS_2-VASc score regardless of a binary or a continuous variable for risk stratification of SBI. However, Model 1 indicated that age and diabetes mellitus were better indicators of SBI than chronic kidney disease. This may be because chronic kidney disease is the consequences of microvascular damage mediated by aging and diabetes mellitus. These findings suggest that both diabetes mellitus and chronic kidney disease are useful for risk stratification of SBI, and intervention for diabetes mellitus to prevent progression to chronic kidney disease may prevent SBI and consequently reduce the risk of future symptomatic stroke. Since age and diabetes are well-known risk factors for atherosclerosis, these findings suggest that SBI due to small-vessel occlusive disease (i.e., atherosclerosis) develops from the paroxysmal stage. As for renal impairment, Wada et al. reported that the presence of chronic kidney disease was associated with SBI in a general population [36]. Similarly, Kobayashi et al. showed a negative association between eGFR and SBI in patients with chronic kidney disease [37]. However, these studies focused on patients with sinus rhythm, and no studies to date have elucidated in patients with NVAF. Since renal impairment and SBI are microvascular damage mediated by similar mechanisms (i.e., endothelial dysfunction [38] and lipohyalinosis resulting from exposure to highly pulsatile pressure and flow) [39], the existence of chronic kidney disease indicates that SBI may exist as well. Moreover, the presence of chronic kidney disease may accelerate the secretion of inflammatory cytokines and oxidative stress markers that lead to arteriosclerosis and endothelial dysfunction [40].

5. Limitations

This study had several limitations. First, because we used cross-sectional data, we could not evaluate the causal relationship between chronic kidney disease or decreased e′, and SBI. Prospec-

Table 3
Multiple logistic regression analysis of SBI in all patients and patients with paroxysmal or persistent NVAF.

	All patients (n = 190)						Paroxysmal AF (n = 119)						Persistent AF (n = 71)					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3		Model 2		Model 3		Model 2		Model 3	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Chronic kidney disease	1.54 (0.56–4.26)	0.41	2.47 (0.96–6.33)	0.06	2.37 (0.91–6.14)	0.08	1.62 (0.43–6.13)	0.48	3.42 (1.06–11.03)	0.04	3.30 (1.03–10.60)	0.04								
Age	1.06 (1.01–1.10)	0.02					1.08 (1.01–1.15)	0.03												
Hypertension	1.43 (0.62–3.31)	0.41					1.65 (0.44–6.16)	0.45												
Diabetes mellitus	3.00 (1.21–7.44)	0.02					5.41 (1.58–18.50)	0.007												
CHA_2DS_2-VASc score ≥ 2			2.24 (1.02–4.89)	0.04					2.21 (0.70–6.94)	0.17			2.84 (0.96–8.44)	0.06			1.12 (0.96–1.30)	0.14		
CHA_2DS_2-VASc score					1.37 (0.98–1.91)	0.07					1.44 (0.89–2.33)	0.14			1.41 (0.90–2.21)	0.13			1.36 (0.84–2.19)	0.21
e′ (per 1 cm/s)													0.71 (0.51–0.98)	0.04	0.73 (0.53–1.01)	0.06				
E/e′ (per 1 point)	1.06 (0.96–1.17)	0.26	1.09 (0.99–1.20)	0.09	1.08 (0.98–1.19)	0.15	1.06 (0.93–1.19)	0.38	1.10 (0.97–1.24)	0.13	1.08 (0.96–1.23)	0.21					2.42 (0.79–7.44)	0.12	1.11 (0.95–1.30)	0.18
LAA emptying velocity	0.98 (0.96–0.998)	0.03	0.98 (0.96–1.00)	0.06	0.98 (0.96–1.00)	0.07	0.98 (0.95–1.01)	0.14	0.99 (0.96–1.01)	0.31	0.99 (0.96–1.02)	0.45								
Left atrial diameter	1.04 (0.97–1.11)	0.30	1.03 (0.97–1.10)	0.37	1.03 (0.97–1.10)	0.35														
Spontaneous echo contrast							7.36 (0.60–89.90)	0.12	4.96 (0.40–61.35)	0.21	5.60 (0.44–70.60)	0.18								

OR, Odds Ratio; CI, confidence interval; LAA, left atrial appendage; NVAF, nonvalvular atrial fibrillation; SBI, silent brain infarction
Model 1; Multivariate analysis without CHA_2DS_2-VASc score.
Model 2; Multivariate analysis with CHA_2DS_2-VASc score as a binary variable (i.e., CHA_2DS_2-VASc score ≥ 2).
Model 3; Multivariate analysis with CHA_2DS_2-VASc score as a continuous variable.

tive studies are necessary to assess whether chronic kidney disease or decreased e′ indeed predicts SBI in patients with paroxysmal or persistent NVAF. Second, as our study population consisted of patients who were scheduled to undergo their first ablation, the generalizability of our results to permanent NVAF patients without indications for ablation is limited. Third, although there was no significant difference in the prevalence of SBI between patients performed echocardiography in sinus rhythm and AF (63% vs. 30%, p = 0.11) in persistent NVAF, the difference in rhythm during echocardiography may affect the results.

6. Conclusions

Age and diabetes mellitus or renal impairment, which represents microvascular disease, is associated with SBI in patients with paroxysmal NVAF. No modifiable risk factors of SBI were observed after progression to persistent NVAF. These findings suggest that intervention for diabetes mellitus and renal impairment from the paroxysmal stage and ablation therapy at the time of paroxysmal stage to prevent progression to persistent NVAF may prevent SBI and consequently reduce the risk of future symptomatic stroke.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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CRediT authorship contribution statement

Andrew T Kim: Conceptualization, Methodology, Investigation, Writing - original draft. **Shinichi Iwata:** Validation, Writing - review & editing. **Sera Ishikawa:** Formal analysis, Investigation, Data curation. **Soichiro Tamura:** Formal analysis, Investigation, Data curation. **Masanori Matsuo:** Formal analysis, Investigation, Data curation. **Tomotaka Yoshiyama:** Formal analysis, Investigation, Data curation. **Shinichi Nonin:** Formal analysis, Investigation, Data curation. **Asahiro Ito:** Formal analysis, Investigation, Data curation. **Yasuhiro Izumiya:** Supervision. **Minoru Yoshiyama:** Project administration.

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