

Atrial Septal Aneurysm may Cause In-Hospital Recurrence of Cryptogenic Stroke

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Aims: Awareness of potentially embologenic diseases is critical to determining the prognosis of cryptogenic stroke. The clinical significance of atrial septal aneurysm (ASA) in cryptogenic stroke has not been fully studied. Therefore, we explored clinical characteristics and in-hospital recurrence in patients with ASA in cryptogenic stroke.

Methods: A multicenter observational registry of cryptogenic stroke patients was conducted. We obtained baseline characteristics, radiological and laboratory findings, and echocardiographic findings, especially of embolic sources on transesophageal echocardiography. The CHALLENGE ESUS/CS (Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for embolic stroke of undetermined source/cryptogenic stroke) registry was recorded at <http://www.umin.ac.jp/ctr/> (UMIN000032957). Patients' clinical characteristics were compared according to the presence of ASA, and factors associated with in-hospital stroke recurrence were assessed.

Results: The study included 671 patients (age, 68.7 ± 12.7 years; 450 males; median National Institutes of Health Stroke Scale score, 2). ASA was detected in 92 patients (14%), displaying higher age (72.4 ± 11.0 vs. 68.1 ± 12.9 years, $p=0.004$), reduced frequency of diabetes mellitus (16% vs. 27%, $p=0.030$), higher frequency of right-to-left shunt (66% vs. 45%, $p<0.001$), and in-hospital stroke recurrence (8% vs. 3%, $p=0.034$). ASA was relatively associated with in-hospital recurrence (odds ratio 2.497, 95% confidence interval 0.959–6.500, $p=0.061$).

Conclusions: The CHALLENGE ESUS/CS registry indicated that ASA was not rare in cryptogenic stroke, and ASA's clinical characteristics included higher age, reduced frequency of diabetes mellitus, and increased frequency of concomitant right-to-left shunt. ASA may be related to in-hospital stroke recurrence in cryptogenic stroke.

Key words: Stroke, Cryptogenic stroke, Transesophageal echocardiography, Atrial septal aneurysm

Introduction

Cryptogenic stroke comprises 20%–40% of stroke cases¹⁻⁴. Cryptogenic stroke is more likely to represent embolic stroke, in which potential embolo-

genic diseases are latent, rather than thrombotic infarction^{1, 5-8}. In 2014, embolic stroke of undetermined source (ESUS) was advocated as a new clinical entity². Recent clinical trials for ESUS comparing the efficacy of direct oral anticoagulants (DOACs) with

Methods

Study Population

The CHALLENGE ESUS/CS registry is a multicenter, retrospective registry enrolling consecutive patients with cryptogenic stroke who underwent TEE in any of eight participating hospitals in Japan between April 2014 and December 2016¹⁹). Inclusion criteria were: 1) within seven days of stroke onset; 2) non-lacunar stroke on neuroradiological imaging; 3) absence of arterial stenosis $\geq 50\%$ or occlusion in a corresponding large artery; 4) absence of major embologenic cardiac diseases; and 5) absence of other determined stroke etiologies. Elicitation of medical history and diagnostic modalities, including CT/MRI, carotid duplex ultrasonography, 12-lead electrocardiography, blood examinations, and chest X-ray, were performed upon admission for CS diagnosis and enrolment in the study. This study was conducted in accordance with the Declaration of Helsinki. Institutional review boards at all eight participating centers approved the protocol. We used clinical information obtained from medical records, and the need to obtain written informed consent from each patient was, therefore, waived for this retrospective study. This study was registered at <http://www.umin.ac.jp/ctr/> (UMIN000032957).

Atherosclerotic Risk Factors

Atherosclerotic risk factors were defined according to previous studies: hypertension; diabetes mellitus; dyslipidemia; current smoking status; history of ischemic heart disease; and history of ischemic stroke^{20, 21}). Hypertension was defined as a history of using antihypertensive agents, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg at 14 days after stroke. Diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, fasting blood glucose level >126 mg/dL, or glycosylated hemoglobin $\geq 6.5\%$. Dyslipidemia was defined as use of antihyperlipidemic agents, serum low-density lipoprotein cholesterol ≥ 140 mg/dL, high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, or triglyceride ≥ 150 mg/dL.

TEE Study

TEE was performed in patients who were awake and had fasted for at least 4 h before the examination. To examine the heart and aortic arch, a multiplane

aspirin have failed to show any benefits of DOACs over aspirin^{9, 10}). ESUS displays a high frequency of stroke recurrence compared to other ischemic stroke subtypes, and various underlying embologenic diseases may determine DOACs' therapeutic effects^{11, 12}). Furthermore, factors underlying embologenic diseases related to in-hospital stroke recurrence remain essentially unknown.

Atrial septal aneurysm (ASA) is an anomaly, defined as redundant and mobile interatrial septal tissue in the fossa ovalis region or the entire septum, and frequently with concomitant patent foramen ovale (PFO)¹³⁻¹⁵). The original diagnostic criteria of Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Classification defined ASA as a medium risk for cardioembolism, as is PFO¹⁶). Many studies have shown that PFO was more frequent in patients with cryptogenic stroke, especially young adults, than in healthy adults^{5-7, 17}). Importantly, a previous study demonstrated that the coexistence of ASA and PFO potentially increased the risk of stroke recurrence, while another study reported that patients with PFO alone and patients with both PFO and ASA displayed similar occurrence rates^{8, 18}). To date, however, few studies have focused on ASA or explored associations between ASA and cryptogenic stroke^{13, 14}). Therefore, ASA's clinical characteristics and pathogenicity of in cryptogenic stroke have not been fully elucidated.

Transesophageal echocardiography (TEE) is useful to screen for potential embolic sources in cryptogenic stroke, and TEE is superior to transthoracic echocardiography for diagnosing ASA¹⁴). The present study used the Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for ESUS/Cryptogenic Stroke (CHALLENGE ESUS/CS) registry, a multicenter registry with a comprehensive database of patients with cryptogenic stroke, who underwent TEE to identify potential embolic sources.

Aim

We explored clinical characteristics and in-hospital stroke recurrence among patients with ASA and examined the pathogenic significance of ASA for cryptogenic stroke.

probe was manipulated to provide appropriate views, including axial and sagittal images. ASA was defined as ≥ 10 mm excursion into either the left or right atrium, or a sum of total excursion into the left or right atrium of ≥ 15 mm²²). Right-to-left shunt (RLS) was assessed by injecting agitated saline and having patients perform the Valsalva maneuver; then the numbers of microbubbles, with and without contrast agents, were compared. The number of microbubbles transiting from the right atrium to the left atrium was also counted. PFO was diagnosed when microbubbles were visualized in the left atrium within three cardiac cycles after the Valsalva maneuver. Pulmonary arteriovenous fistula (pAVF) was diagnosed when microbubbles were visualized in the left atrium more than three cardiac cycles after the Valsalva maneuver, or when microbubbles were visualized without the Valsalva maneuver. Plaque thickness was measured, and values ≥ 4 mm were considered to represent large aortic arch plaque. Examinations were performed by two or three experienced sonographers in each institution.

Data Collection and Analyses

Baseline clinical information, laboratory and radiological data on admission, echocardiographic findings, and clinical course on admission were collected from hospital charts or database reviews. In-hospital stroke recurrence was defined as new focal onset of neurological symptoms, corresponding to a lesion on radiological imaging. Baseline characteristics, radiological and laboratory data, echocardiographic findings, and clinical course during admission were compared according to the presence of ASA. Factors related to in-hospital stroke recurrence were analyzed. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Statistical Analysis

Numerical values are reported as mean \pm standard deviation. Data were analyzed using the chi-squared test for categorical variables and the Mann–Whitney test for nonparametric analyses. All variables with values of $p < 0.1$ on univariable analyses were entered into multiple logistic regression analysis to identify independent variables for patients with ASA. Predictors for in-hospital stroke recurrence were also examined, using multiple logistic regression analysis. All statistical analyses were performed using JMP Pro version 14.0.0 software (SAS Institute Inc., Cary, NC). A value of $p < 0.05$ was considered statistically significant.

Results

From the eight university hospitals or stroke centers, 677 patients with cryptogenic stroke were enrolled in the CHALLENGE ESUS/CS registry. Among these, six patients were not evaluated for the presence of ASA in each TEE examination and were, thus, excluded from our study. Thus, 671 patients (age, 68.7 ± 12.7 years; 450 males; median National Institutes of Health Stroke Scale score, 2) were finally analyzed. The median duration of hospitalization was 17 days. ASA was found in 92 patients (14%). **Table 1** shows the enrolled patients' clinical characteristics. In-hospital stroke recurrence occurred at a mean of 4.2 ± 9.2 days after admission. Age, sex, risk factors, National Institutes of Health Stroke Scale (NIHSS) score, and clinical course during admission were completely registered, and only a few percent of values were missing among radiological, echocardiographic, and laboratory data ($< 3\%$).

Frequency of ASA Stratified by Age

Distributions of enrolled patients and ASA on TEE according to age are shown in **Fig. 1**. The number of enrolled patients with ASA increased from age < 50 years and peaked at 70–79 years, then decreased. ASA frequency significantly increased in correlation with increasing age (6%, age < 50 years; 8%, 50–59 years; 12%, 60–69 years; 16%, 70–79 years; 19%, ≥ 80 years; $p = 0.040$; **Fig. 1**).

Clinical Characteristics According to Presence of Asa

Baseline characteristics, MRI and echocardiographic findings, and laboratory data were compared among 92 patients in the ASA group and 579 patients in the nonASA group (**Table 1**). In univariable analyses, age was higher among ASA patients (72.4 ± 11.0 years vs. 68.1 ± 12.9 years, $p = 0.004$), and there was no significant difference in males vs. females. As vascular risk factors for atherosclerosis, the frequency of diabetes mellitus was significantly lower in patients with ASA (16%) than in patients without ASA (27%, $p = 0.030$), while hypertension, dyslipidemia, cigarette smoking, chronic renal failure, coronary artery diseases, and previous history of ischemic stroke did not differ significantly between groups. In terms of MRI findings, frequencies of cortical infarction, large infarction > 3 cm in diameter, and intracranial arterial stenosis ($> 50\%$ stenosis in an area not relevant to the infarction area) showed no significant differences. For echocardiographic findings, frequencies of mitral and atrial regurgitation did not differ significantly between groups. RLS was more frequent in patients with ASA

Table 1. Baseline characteristics, MRI and echocardiographic findings, laboratory data, and clinical course during admission of study subjects for atrial septal aneurysm

Characteristics	Total N=671	ASA		p
		Positive n=92 (14%)	Negative n=579 (86%)	
Sociodemographic				
Age, y, mean ± SD	68.7 ± 12.7	72.4 ± 11.0	68.1 ± 12.9	0.004
Gender, male, no (%)	450 (67)	58 (63)	392 (68)	0.377
Risk factors, no (%)				
Hypertension	481 (72)	65 (71)	416 (72)	0.813
Diabetes mellitus	171 (25)	15 (16)	156 (27)	0.030
Dyslipidemia	343 (51)	43 (47)	300 (52)	0.366
Cigarette smoking	180 (27)	20 (22)	160 (28)	0.236
Chronic kidney disease	249 (37)	35 (38)	214 (37)	0.842
Coronary artery disease	68 (10)	5 (5)	63 (11)	0.108
Previous history of ischemic stroke	122 (18)	20 (22)	102 (18)	0.341
NIHSS score on admission, median (IQR)	2 (1–5)	2 (1–5)	2 (1–5)	0.615
Carotid stenosis on duplex ultrasonography	33 (5)	3 (3)	30 (5)	0.429
MRI, no (%)				
Cortical infarction ^a	533 (80)	70 (78)	463 (81)	0.425
Large infarction ≥ 3 cm in diameter ^a	199 (30)	28 (31)	171 (30)	0.842
Intracranial arterial stenosis on MRA ≥ 50% area stenosis ^a	72 (11)	7 (8)	65 (11)	0.303
Echocardiographic findings, no (%)				
Mitral regurgitation ^b	357 (53)	48 (52)	309 (53)	0.818
Aortic regurgitation ^c	206 (31)	30 (33)	176 (30)	0.629
Right-to-left shunt ^d	311 (48)	60 (66)	251 (45)	<0.001
Patent foramen ovale ^d	301 (46)	60 (66)	241 (43)	<0.001
Aortic arch plaques ≥ 4 mm ^b	251 (37)	34 (37)	217 (38)	0.914
Laboratory findings,[†]				
Leukocyte count, × 10 ⁹ /L	7.3 ± 2.7	6.9 ± 2.5	7.3 ± 2.7	0.080
HDL-C, mg/dL ^c	51.2 ± 15.1	50.7 ± 14.3	51.3 ± 15.2	0.746
TG, mg/dL ^a	133.1 ± 107.9	115.3 ± 69.2	135.9 ± 112.6	0.087
Glucose, mg/dL ^a	131.8 ± 51.1	123.8 ± 34.9	133.1 ± 53.2	0.237
BNP ^f	97.9 ± 160.8	61.4 ± 68.9	103.7 ± 170.2	0.204
D-dimer, µg/mL	2.9 ± 16.3	3.3 ± 12.5	2.8 ± 16.9	0.219
Clinical course during admission, no (%)				
Stroke recurrence	25 (4)	7 (8)	18 (3)	0.034
Detection of PAF	64 (10)	5 (5)	59 (10)	0.149
mRS on discharge ≥ 3	145 (22)	27 (29)	118 (20)	0.052

Chi-square test, and the Mann–Whitney *U* test were used for comparison. ASA=atrial septal aneurysm; NIHSS=NIH Stroke scale; IQR=interquartile range; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; BNP=brain natriuretic peptide; mRS=modified Rankin Scale; PAF = paroxysmal atrial fibrillation. Missing values: a, n=5; b, n=1; c, n=2; d, n=20; e, n=8; f, n=92. Chronic kidney disease was defined as eGFR < 60 ml/min/1.73 m².

(66%) than in patients without ASA (45%, *p* < 0.001). PFO and pAVF were found in 60 and 0 patients with ASA, respectively, while PFO and pAVF were found in 241 and 10 patients without ASA, respectively. Frequency of aortic arch plaque did not differ significantly between groups. In terms of laboratory data, no significant differences in leukocyte count, HDL-C, triglyceride or glucose levels were evi-

dent.

Cryptogenic stroke patients with ASA exhibited a higher frequency of in-hospital stroke recurrence than those without ASA (8% vs. 3%, *p*=0.034). Poor functional outcome (modified Rankin scale (mRS) score ≥ 3) on discharge was relatively higher (29% vs. 20%, *p*=0.052) in cryptogenic stroke patients with ASA.

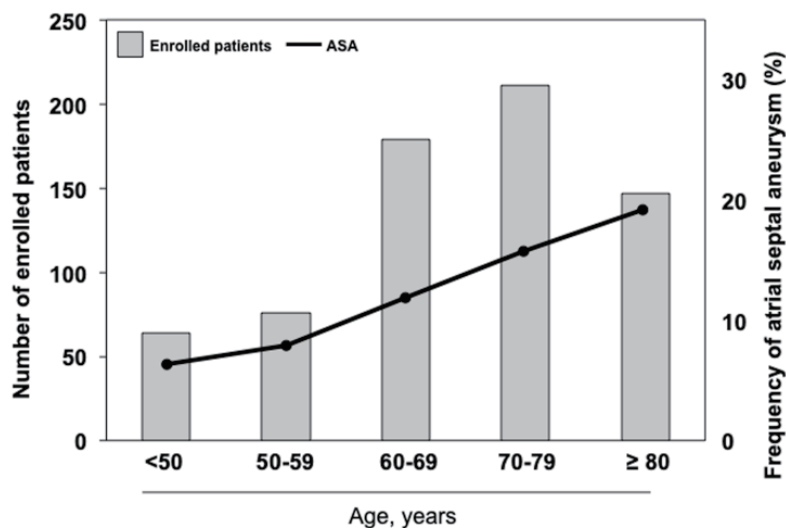


Fig. 1. Proportion of enrolled patients and frequency of atrial septal aneurysm

Histograms and line graphs show the number of enrolled patients and frequency of atrial septal aneurysm according to age.

Table 2. Multiple logistic regression analysis predicting atrial septal aneurysm in cryptogenic stroke patients

Variables	OR	95% CI	<i>p</i>
Age	1.032	1.011–1.054	0.003
Diabetes mellitus	0.521	0.282–0.962	0.037
Right-to-left shunt	2.528	1.563–4.090	<0.001
Leukocyte count	1.000	1.000–1.000	0.323
Triglyceride	0.998	0.995–1.001	0.185
In-hospital stroke recurrence	3.255	1.212–8.743	0.019
mRS on discharge ≥ 3	1.332	0.764–2.320	0.312

OR=odds ratio, CI=confidence interval.

Independent Factors Associated with Patients with Asa

Age, diabetes mellitus, RLS, leukocyte count, triglyceride, in-hospital stroke recurrence, and mRS score ≥ 3 on discharge were selected for multiple logistic regression analyses to explore factors related to ASA. Age (odds ratio [OR], 1.032; 95% confidence interval [CI], 1.011–1.054; $p=0.003$), diabetes mellitus (OR, 0.521; 95% CI, 0.282–0.962; $p=0.037$), RLS (OR, 2.528; 95% CI, 1.563–4.090; $p<0.001$), and in-hospital stroke recurrence (OR, 3.255; 95% CI, 1.212–8.743; $p=0.019$) were independently associated with ASA (Table 2).

Association of In-Hospital Stroke Recurrence with Septal Abnormality

In univariable analyses, NIHSS score, mitral regurgitation, ASA, and leukocyte count tended to be

associated with the presence of in-hospital stroke recurrence ($p<0.1$) (Table 3). No significant differences in frequency of ASA with RLS, or ASA with large RLS (≥ 26 microbubbles), were evident between patients with and without in-hospital stroke recurrence. Next, we used multiple logistic regression analysis to analyze ASA's contribution to in-hospital stroke recurrence. Multiple logistic regression analysis showed that the NIHSS score (OR, 1.074; 95% CI, 1.024–1.127; $p=0.003$), ASA (OR, 2.497; 95% CI, 0.959–6.500; $p=0.061$), and D-dimer levels (OR, 1.029; 95% CI, 0.098–1.062; $p=0.068$) tended to be associated with in-hospital stroke recurrence (Table 4). To analyze the impact of concomitant RLS for in-hospital stroke recurrence in patients with ASA, we entered ASA with RLS and ASA without RLS into multiple logistic regression analyses, showing no significant differences (OR, 1.925; 95% CI, 0.583–

Table 3. Baseline characteristics, MRI and echocardiographic findings, laboratory data, and clinical course during admission of study subjects for in-hospital stroke recurrence

Characteristics	Total <i>N</i> =671	In-hospital stroke recurrence		<i>p</i>
		Positive <i>n</i> =25 (4%)	Negative <i>n</i> =646 (96%)	
Sociodemographic				
Age, y, mean ± SD	68.7 ± 12.7	65.3 ± 13.9	68.9 ± 12.7	0.204
Gender, male, no (%)	450 (67)	15 (60)	435 (67)	0.444
Risk factors, no (%)				
Hypertension	481 (72)	20 (80)	461 (71)	0.347
Diabetes mellitus	171 (25)	9 (36)	162 (25)	0.219
Dyslipidemia	343 (51)	12 (48)	331 (51)	0.751
Cigarette smoking	180 (27)	10 (40)	170 (26)	0.130
Chronic kidney disease	249 (37)	11 (44)	238 (37)	0.467
Coronary artery disease	68 (10)	4 (16)	64 (10)	0.322
Previous history of ischemic stroke	122 (18)	2 (8)	120 (19)	0.179
NIHSS score on admission, median (IQR)	2 (1–5)	3 (2–19)	2 (1–5)	0.028
Carotid stenosis on duplex ultrasonography	33 (5)	1 (4)	32 (5)	0.829
MRI, no (%)				
Cortical infarction ^a	533 (80)	22 (88)	511 (80)	0.287
Large infarction ≥ 3 cm in diameter ^a	199 (30)	5 (20)	194 (30)	0.271
Intracranial arterial stenosis on MRA ≥ 50% area stenosis ^a	72 (11)	2 (8)	70 (11)	0.894
Echocardiographic findings, no (%)				
Mitral regurgitation ^b	357 (53)	9 (36)	348 (54)	0.078
Aortic regurgitation ^c	206 (31)	7 (28)	199 (31)	0.758
ASA	92 (14)	7 (28)	85 (13)	0.034
RLS ^d	311 (48)	10 (42)	301 (48)	0.542
ASA with RLS ^d	60 (9)	4 (17)	56 (9)	0.199
ASA with RLS with large shunt ^{d*}	8 (1)	0 (0)	8 (1)	0.699
Aortic arch plaques ≥ 4 mm ^b	251 (37)	7 (28)	244 (38)	0.319
Laboratory findings, †				
Leukocyte count, × 10 ⁹ /L	7.3 ± 2.7	8.1 ± 2.7	7.2 ± 2.7	0.062
HDL-C, mg/dL ^e	51.2 ± 15.1	48.7 ± 17.7	51.3 ± 15.0	0.288
TG, mg/dL ^a	133.1 ± 107.9	121.0 ± 79.4	133.5 ± 108.9	0.520
Glucose, mg/dL ^a	131.8 ± 51.1	149.6 ± 92.5	131.2 ± 48.9	0.278
BNP, pg/μl ^f	97.9 ± 160.8	78.7 ± 89.0	98.7 ± 163.2	0.844
D-dimer, μg/mL	2.9 ± 16.3	21.7 ± 78.2	2.2 ± 5.9	0.087

Chi-square test, and the Mann–Whitney *U* test were used for comparison. ASA=atrial septal aneurysm; NIHSS=NIH Stroke scale; IQR=interquartile range; RLS=Right-to-left shunt; HDL-C=high-density lipoprotein cholesterol; TG=triglyceride; BNP=brain natriuretic peptide. Missing values: a, *n*=5; b, *n*=1; c, *n*=2; d, *n*=20; e, *n*=8; f, *n*=92. * = more than ≥ 26 microbubbles. Chronic kidney disease was defined as eGFR < 60 ml/min/1.73 m².

Table 4. Multiple logistic regression analysis predicting in-hospital stroke recurrence in cryptogenic stroke patients

Variables	OR	95% CI	<i>p</i>
NIHSS score on admission	1.074	1.024–1.127	0.003
Mitral regurgitation	0.567	0.238–1.354	0.202
ASA	2.497	0.959–6.500	0.061
Leukocyte count	1.000	1.000–1.000	0.550
D-dimer	1.029	0.998–1.062	0.068

OR=odds ratio, CI=confidence interval, NIHSS=NIH Stroke scale, ASA=atrial septal aneurysm.

6.358; $p=0.283$; OR 2.934; 95% CI 0.774–11.125; $p=0.114$).

Discussion

The present study used the CHALLENGE ESUS/CS registry, enrolling a number of cryptogenic stroke patients who underwent TEE to elucidate underlying embolic sources and comprehensive clinical data, and displayed that ASA accounted for 14% of cryptogenic strokes. Clinical characteristics of cryptogenic stroke with ASA included higher age, lower frequency of diabetes mellitus, higher frequency of concomitant RLS, and higher frequencies of in-hospital recurrent stroke. Furthermore, ASA was shown to be comparatively associated with stroke recurrence during hospitalization.

The incidence of ASA is reportedly 0.2%–4% on transthoracic echocardiography, increasing to 2%–8% on TEE^{13–15}. In cryptogenic stroke, the frequency of ASA was increased to 6.4%–39.1%^{7, 23–25}. ASA is considered redundant in the fossa ovalis region and mobile interatrial septal tissue with phasic bulging during the cardiac cycle^{13, 15}. Interestingly, the CHALLENGE ESUS/CS registry showed that ASA frequency increased with aging. Large-scale autopsy and echocardiographic studies have shown ASA in a wide age range, with a higher frequency among middle-aged patients^{13, 14, 26}. Although ASA is generally considered a congenital malformation in the septum primum layer of the interatrial septum, its pathogenesis has yet to be elucidated.

The current study made another crucial finding: ASA was relatively associated with in-hospital stroke recurrence in cryptogenic stroke. Some possible explanations for ASA as a cause of stroke recurrence may be suggested from CHALLENGE ESUS/CS. First, ASA itself can be a potential source of embolism for recurrent stroke. ASA with thromboembolic events has been associated with a higher frequency of intra-atrial thrombus^{14, 27}. In surgical and autopsy studies, thrombus has been confirmed in the aneurysmal sacs of ASA^{26, 28}. Thus, newly reformed thrombus or undetected thrombus on TEE, adhering to the aneurysm or in the left atrium following acute stroke, may cause early stroke recurrence. Second, ASA frequency correlated with increased age and other embologenic diseases, such as covert atrial fibrillation (AF) undetected during admission, or systemic atherosclerosis due to age, might have been involved. In the current study, paroxysmal AF was fundamentally investigated by 12-lead electrocardiography on admission, cardiac monitoring, and 24-h Holter monitoring during admission. According to recent progress in detecting

paroxysmal AF, long-term electrocardiography to elucidate the association of ASA and covert AF is important²⁹. Third, ASA might induce modifications to the electrophysiological substrate and physiological dysfunction in the left atrium, leading to atrial vulnerability^{30–32}. However, there is little evidence associating atrial vulnerability with early stroke recurrence. In general, the coexistence of PFO and ASA increases the risk of stroke recurrence by 7.6%–15.2% during long-term follow-up of cryptogenic stroke^{8, 33–35}. To date, in-hospital stroke recurrence has been essentially unknown among cryptogenic stroke. Our registry focused on stroke recurrence during hospitalization for cryptogenic stroke in terms of potential embolic sources and, for the first time, revealed that ASA might represent a cause of in-hospital stroke recurrence independent from concomitant RLS.

In the current study, acute therapy for cryptogenic stroke was performed by stroke physicians in participating hospitals according to the current stroke guideline and their best medical judgment, assuming that most patients with cryptogenic stroke could be treated with antiplatelet agents^{1, 36, 37}. Interestingly, our data also showed that high NIHSS score (median, 3) was related to in-hospital stroke recurrence. In a subgroup analysis of the Clopidogrel in high-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, which enrolled patients with minor noncardioembolic stroke or transient ischemic attack, high NIHSS score (2–3) was associated with stroke recurrence within 90 days after treatment with dual antiplatelet therapy³⁸. Our data also indicated that high D-dimer levels were related to in-hospital stroke recurrence, possibly because an underlying specific pathogenesis refractory to antiplatelet therapy, such as coagulopathy or Trousseau syndrome, might be present in cryptogenic stroke patients with such clinical features^{39, 40}. On the other hand, there is little or no evidence on secondary prevention in stroke patients with ASA, although treatment with anticoagulants may be a reasonable approach to dissolve the thrombus or prevent fibrin adherence to the septal wall. Furthermore, the long-term prognosis of cryptogenic stroke patients with and without ASA is unknown. Taken together, considering the mechanisms causing in-hospital recurrent stroke and optimal antithrombotic therapy for ASA, high NIHSS score, and D-dimer levels, further studies with a prospective design, larger sample size, and long-term monitoring may be required to clarify its pathogenesis.

This study has some limitations that must be considered when interpreting the results. First, this was a retrospective study, and treatments were nonrandomized. Medications, especially acute antithrombotic

treatments, might, in turn, have affected in-hospital stroke recurrence. Second, regarding TEE examinations, selection of cryptogenic stroke patients for TEE in participating hospitals, and the lack of data on TEE timing during admission (especially in patients with in-hospital stroke recurrence) were certainly biases in the current study. Third, a small proportion of radiological, echocardiographic, and laboratory data (especially for brain natriuretic peptide level) were missing, and relatively few patients with ASA experienced recurrent stroke.

Conclusion

The CHALLENGE ESUS/CS registry enrolled a large number of cryptogenic stroke patients, in whom potential embolic etiologies were identified on TEE. The current results provide new insights in that clinical characteristics of cryptogenic stroke with ASA include older age, lower frequencies of diabetes mellitus, and higher frequency of concomitant RLS. These findings suggested that ASA might be related to in-hospital stroke recurrence in cryptogenic stroke. Our data offer a first insight into elucidating ASA's clinical characteristics in cryptogenic stroke with multicenter registries. However, the pathological contribution of ASA remained, and further study is warranted.

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Potential Conflicts of Interest

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ami Hospital, Shirasawa Hospital, Shiobara Onsen Hospital, Utsunomiya Chuo Hospital, Nishikata Hospital, and Moka. Hospital. K.T. received lecture fees from Bayer Pharmaceutical Co., Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo Co., Ltd. Y.H. received lecture fees from Bayer Pharmaceutical Co. N.H. was an advisory member of Dai-Nippon Sumitomo Pharma Co., Ltd., Hisamitsu Pharmaceutical Co., Inc, Biogen Idec Japan Ltd., received lecture fees from Dai-Nippon Sumitomo Pharma Co., Ltd., Otsuka Pharmaceutical, Co., Ltd., Takeda Pharmaceutical Co., Ltd., Kyowa Hakko-Kirin Co., Ltd., FP Pharmaceutical Corporation, Eisai Co., Ltd., and Novartis Pharma K.K., AbbVie, and received departmental endowments by commercial entities from Kyowa Hakko-Kirin Co., Ltd., Nippon Boehringer Ingelheim, Co., Ltd., AbbVie GK, FP Pharmaceutical Corporation, Otsuka Pharmaceutical, Co., Ltd., Dai-Nippon Sumitomo Pharma Co., Ltd., Eisai Co., Ltd., Nihon Medi-physics Co., Ltd., Asahi Kasei Medical Co., Ltd., Ono Pharmaceutical Co., Ltd., MiZ Co., Ltd., AbbVie GK, OHARA Pharmaceutical Co., Ltd., Nihon Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Boston Scientific Corporation, and Medtronic Inc. T.U. received lecture fees from Daiichi Sankyo Co., Ltd., Boehringer Ingelheim, Otsuka Pharmaceutical Co., Ltd., Bayer Pharmaceutical Co., AstraZeneca K.K., and AbbVie GK., and research funds from Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., Bayer Pharmaceutical Co. Ltd., AbbVie GK., and Eisai Co., Ltd. The remaining authors report no conflicts of interest.

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