Large aortic arch plaques correlate with CHADS$_2$ and CHA$_2$DS$_2$-VASc scores in cryptogenic stroke

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HIGHLIGHTS

- CHALLENGE ESUS/CS registry is a large transesophageal echocardiography (TEE) registry for cryptogenic stroke patients.
- CHALLENGE ESUS/CS registry clarified potential embolic sources.
- Large aortic arch plaques were closely related to CHADS$_2$ and CHA$_2$DS$_2$-VASc scores.
- Paroxysmal atrial fibrillation was linked to CHADS$_2$ and CHA$_2$DS$_2$-VASc scores.
- Right-to-left shunt was inversely associated with CHA$_2$DS$_2$-VASc score.

ARTICLE INFO

ABSTRACT

Background and aims: Current trends have suggested covert atrial fibrillation as a mechanism of cryptogenic stroke. However, etiological heterogeneity regarding the underlying embolic sources remains a critical issue in cryptogenic stroke.
Methods: CHALLENGE ESUS/CS (Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for Embolic Stroke of Undetermined Source/Cryptogenic Stroke) is a multicenter observational registry of cryptogenic stroke patients admitted to participating hospitals, who underwent transesophageal echocardiography between April 2014 and December 2016. We obtained baseline characteristics, radiological and laboratory data, and echocardiographic findings, especially for embolic sources demonstrated on transesophageal echocardiography, and conducted comparisons according to CHADS$_2$ and CHA$_2$DS$_2$-VASc scores (0–1 *vs.* $\geq$ 2, respectively). This study was registered at http://www.umin.ac.jp/ctr/ (UMIN000032957).
Results: The study comprised 677 patients (age, 68.7 $\pm$ 12.8 years; 455 males; median National Institutes of Health Stroke Scale score, 2) with cryptogenic stroke. On multiple logistic regression analysis, large aortic arch plaque $\geq$ 4 mm (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.51–3.36; $p < 0.001$), with ulcerative or mobile components (OR, 2.37; 95%CI, 1.38–4.06; $p = 0.002$), was associated with CHADS$_2$ score $\geq$ 2. Large aortic arch plaque $\geq$ 4 mm (OR, 3.88; 95%CI, 2.07–7.27; $p < 0.001$) and ulcerative or mobile components (OR, 3.25; 95%CI, 1.44–7.34; $p = 0.005$) were linked to CHA$_2$DS$_2$-VASc score $\geq$ 2.
Conclusions: The CHALLENGE ESUS/CS registry is a large TEE registry, and clarifies potential embolic etiologies

of cryptogenic stroke using TEE. Large aortic arch plaques were associated with high $CHADS_2$ and CHA_2DS_2-VASc scores, and represented important embolic sources in cryptogenic stroke.

1. Introduction

Ischemic stroke with an undetermined etiology is not uncommon, comprising about a quarter of all ischemic strokes [1]. Cryptogenic stroke (CS) was first named by Mohr more than a quarter of a century ago, and many studies since have focused on identifying culprits such as patent foramen ovale (PFO), atrial septal aneurysm (ASA), and aortic arch plaques as potential contributors to stroke occurrence [2–5]. In 2014, embolic stroke of undetermined source (ESUS) was advocated as a new clinical entity [1]. Underlying paroxysmal atrial fibrillation (PAF) has recently been detected in around 30% of ESUS and CS using novel devices [6–8]. Importantly, recent large-scale clinical trials for ESUS aimed at comparing efficacy between direct oral anticoagulants (DOACs) and aspirin failed to show comparable benefits of DOACs with aspirin [9,10]. On the contrary, a sub-analysis of the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial *vs.* ASA to Prevent ESUS (NAVIGATE-ESUS) suggested that rivaroxaban reduced stroke recurrence in ESUS patients with PFO [11]. Optimal treatments for ESUS and CS are thus yet to be elucidated, and clarifying the embolic etiological heterogeneity of ESUS and CS may be critical to secondary prevention efforts.

Transesophageal echocardiography (TEE) remains the gold standard for screening these potential embolic sources, and has given great insights into the associations of potential embolic etiologies in not only CS, but also ESUS [4,12–14]. Taking advantage of the utility of TEE, we created a multicenter registry with a comprehensive database of patients with CS for whom potential embolic etiologies were detected on TEE.

$CHADS_2$ and CHA_2DS_2-VASc scores are commonly used risk scores for stroke and optimal therapeutic indications in patients with AF [15,16]. Emerging data have shown that $CHADS_2$ and CHA_2DS_2-VASc scores allow stratification of the risk of stroke recurrence and death in ESUS [17]. So far, the associations of underlying embologenic diseases in ESUS and CS with $CHADS_2$ and CHA_2DS_2-VASc scores have remained essentially unknown [3–5]. Collectively, we explored potential embolic sources according to $CHADS_2$ and CHA_2DS_2-VASc scores in CS patients, and elucidated embolic sources related to high $CHADS_2$ and CHA_2DS_2-VASc scores from our multicenter TEE registry.

2. Patients and methods

2.1. Study population

The Mechanisms of Embolic Stroke Clarified by Transesophageal Echocardiography for Embolic Stroke of Undetermined Source/Cryptogenic Stroke (CHALLENGE ESUS/CS) registry is a multicenter registry enrolling consecutive patients with CS who underwent TEE among 8 hospitals in Japan, between April 2014 and December 2016. Inclusion criteria were: 1) within 7 days of stroke onset; 2) non-lacunar stroke on neuroradiological imaging; 3) absence of arterial stenosis ≥ 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 the medical history and diagnostic modalities including CT/MRI, carotid duplex ultrasonography, 12-lead electrocardiography, blood examinations, and chest X-ray was performed on admission for the diagnosis of CS and enrollment to the study. Institutional review boards in all eight participating centers approved the protocol. As clinical information obtained from medical records was used for all analyses in this retrospective study, the need to obtain written informed consent from each patient was waived. The

study protocol and the informed consent statement were provided on the website of each institution. This study was registered at http://www.umin.ac.jp/ctr/(UMIN000032957).

2.2. TEE study

TEE was performed in patients who were awake and had fasted for at least 4 h before the examination. Lidocaine spray was given, but no premedication was used. To examine the heart and aortic arch, a multiplane probe was manipulated to provide appropriate views, including axial and sagittal images. ASA was diagnosed when the atrial septum extended into the left or right atrium, or both. Right-to-left shunt (RLS) was assessed by injecting agitated saline and having patients perform the Valsalva maneuver, then 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 3 cardiac cycles after the Valsalva maneuver. Pulmonary arteriovenous fistula was diagnosed when microbubbles were visualized in the left atrium more than 3 cardiac cycles after the Valsalva maneuver or when microbubbles were visualized without Valsalva maneuver. Plaque thickness was measured, and plaque thickness ≥ 4 mm were considered as large aortic arch plaques. Mobile aortic plaques were diagnosed as having a mobile component swinging on a peduncle. Ulcerative plaques were diagnosed as a discrete indentation on the luminal surface of the plaque with base width and maximum depth of ≥ 2 mm each. Examinations were performed by 2 or 3 experienced sonographers in each institution.

2.3. Data collection and analyses

Collection of baseline clinical information, and laboratory, radiological, and echocardiographic data on admission was conducted through hospital chart or database reviews. Clinical courses including neurological deterioration, detection of PAF, and stroke recurrence were evaluated during admission. These data were retrospectively obtained during the study period from May 2017 to July 2018. $CHADS_2$ score was determined from congestive heart failure, hypertension, age ≥ 75 years, diabetes, and stroke or transient ischemic attack (2 points). CHA_2DS_2-VASc score was determined from congestive heart failure, age ≥ 75 years (2 points), diabetes, stroke or TIA (2 points), vascular disease, age 65–74 years, and female sex prior to stroke onset at enrollment. Baseline characteristics, radiological and laboratory data, echocardiographic findings including potential embolic diseases, and clinical course were compared according to $CHADS_2$ score (0–1 *vs.* ≥ 2), and CHA_2DS_2-VASc score (0–1 *vs.* ≥ 2), respectively. Correlations between $CHADS_2$ and CHA_2DS_2-VASc scores and frequencies of potential embolic diseases were analyzed.

2.4. Statistical analysis

Numerical values are reported as mean ± 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 univariate analyses were entered into multiple logistic regression analysis to identify independent variables for $CHADS_2$ and CHA_2DS_2-VASc scores ≥ 2, respectively. A two-sided probability value of $p < 0.05$ was considered significant. All data were analyzed using SPSS for Windows version 15.0 software (SPSS, Chicago, IL).

3. Results

A total of 677 patients with cryptogenic stroke were enrolled into the study, and no patients from any institution contacted us to decline participation. Median duration of hospitalization was 17 days. Among them, 565 patients (83%) fulfilled the diagnostic criteria for ESUS [1]. Baseline characteristics of the entire study population are summarized in Table 1. Mean age was 68.7 ± 12.8 years, and 456 males (67%) were enrolled. Median baseline National Institutes of Health Stroke Scale (NIHSS) score was 2. Age, gender, risk factors, NIHSS score, and clinical course during admission were registered, and only a few values were lacking on radiological, echocardiographic, and laboratory data ($< 4\%$).

3.1. CHADS2 and CHA2DS2-VASc scores and frequency of potential embolic sources

The distribution of enrolled patients, and representative embologenic diseases such as RLS, ASA, and aortic arch plaques on TEE, as well as PAF detected during admission according to CHADS2 and CHA2DS2-VASc scores, are shown in Fig. 1. Among the enrolled patients, CHADS2 and CHA2DS2-VASc scores peaked at 1 or 2, and 3 points, respectively. In terms of embolic sources, overall RLS and aortic arch plaques were more frequent than ASA and PAF. Frequency of ≥ 4 mm, ulcerative, or mobile aortic arch plaque increased in correlation with CHADS2 score (19%, 0 points; 33%, 1; 40%, 2; 49%, 3; 59%, 4–6; $p < 0.001$) and CHA2DS2-VASc score (11%, 0 points; 19%, 1; 35%, 2; 39%, 3; 45%, 4; 55%, 5–8; $p < 0.001$). Frequency of RLS decreased in inverse correlation with CHA2DS2-VASc score (60%, 1; 45%, 2; 47%, 3; 44%, 4; 40%, 5–8; $p = 0.018$). Distribution of ASA did not differ between CHADS2 and CHA2DS2-VASc scores. Fig. 2 shows that frequency of large aortic arch plaque ≥ 4 mm increased in correlation with CHADS2 score (15%, 0 points; 22%, 1; 25%, 2; 33%, 3; 42%, 4–6) and CHA2DS2-VASc score (8%, 0 points; 12%, 1; 23%, 2; 25%, 3; 30%, 4; 39%, 5–8). Ulcerative or mobile aortic plaques also tended to increase according to developments of CHADS2 (4%, 0 points; 12%, 1; 15%, 2; 16%, 3; 17%, 4–6) and CHA2DS2-VASc scores (3%, 0 points; 7%, 1; 12%, 2; 14%, 3; 15%, 4; 15%, 5–8). Neurological deterioration and stroke recurrence did not differ significantly among each CHADS2 and CHA2DS2-VASc score.

3.2. Clinical characteristics according to CHADS2 and CHA2DS2-VASc scores

Baseline characteristics and radiological, echocardiographic and laboratory findings were compared among 321 and 356 patients with CHADS2 score 0–1 and ≥ 2, and 136 and 541 patients with CHA2DS2-VASc scores 0–1 and ≥ 2 points, respectively (Table 2). Age, frequency of hypertension, diabetes, dyslipidemia, coronary artery diseases, and previous history of ischemic stroke were higher with CHADS2 and CHA2DS2-VASc scores ≥ 2 (p 0.001). Male gender and current smoking habits were lower in patients with CHA2DS2-VASc scores ≥ 2 ($p < 0.001$). Significant differences in NIHSS score were evident between CHA2DS2-VASc scores 0–1 and ≥ 2 ($p = 0.031$). Carotid stenosis on duplex ultrasonography and MRI findings did not differ between comparable CHADS2 and CHA2DS2-VASc score groups. In terms of echocardiographic data, mitral regurgitation and ASA did not differ between groups of CHADS2 and CHA2DS2-VASc scores. Presence of RLS was lower in patients with CHA2DS2-VASc score ≥ 2 ($p < 0.001$). Aortic arch plaques ≥ 4 mm and with ulceration or mobile components were significantly higher in patients with CHADS2 score ≥ 2 (31% and 15%, respectively) rather than 0–1 (19% and 9%, respectively; $p < 0.001$) and in patients with CHA2DS2-VASc score ≥ 2 (29% and 14%, respectively) rather than 0–1 (11% and 6%, respectively; $p < 0.001$).

For laboratory data, significant differences were seen in HDL-C between degrees of CHADS2 score ($p < 0.001$), in glucose between degree of CHADS2 and CHA2DS2-VASc scores ($p < 0.001$), and in D-dimer between degree of CHADS2 and CHA2DS2-VASc scores ($p < 0.01$).

Regarding clinical course, detection of PAF was higher with CHADS2 and CHA2DS2-VASc scores ≥ 2 ($p = 0.028$ and $p = 0.025$, respectively).

3.3. Independent factors linked to high CHADS2 and CHA2DS2-VASc scores

Dyslipidemia, current smoking, coronary artery disease, aortic arch plaques, HDL-C, glucose, D-dimer, and PAF were selected for multiple logistic regression analyses to explore factors related to CHADS2 score ≥ 2 (Model 1). Dyslipidemia, current smoking, NIHSS score, RLS, aortic arch plaques, HDL-C, glucose, D-dimer, and PAF were selected for multiple logistic regression analyses for CHA2DS2-VASc score ≥ 2 (Model 2). In Model 1, large aortic arch plaque ≥ 4 mm (odds ratio [OR], 2.25; 95% confidence interval [CI], 1.51–3.36; $p < 0.001$) and with ulcerative or mobile components (OR, 2.37; 95%CI, 1.38–4.06; $p = 0.002$), and detection of PAF during admission (OR, 2.13; 95%CI, 1.18–3.84; $p = 0.012$) were independently associated with CHADS2 score ≥ 2 (Table 3). Dyslipidemia and glucose levels were related to CHADS2 score ≥ 2, but current smoking and HDL-C levels were inversely associated with CHADS2 score ≥ 2 ($p < 0.05$). In Model 2, large aortic arch plaque ≥ 4 mm (OR, 3.88; 95%CI, 2.07–7.27; $p < 0.001$) and with ulcerative or mobile components (OR, 3.25; 95%CI, 1.44–7.34; $p = 0.005$), and PAF during admission (OR, 3.33; 95%CI, 1.11–10.02; $p = 0.032$) were linked to CHA2DS2-VASc score ≥ 2. Dyslipidemia and glucose levels were related to CHADS2 score ≥ 2, but current smoking and RLS were inversely associated with CHADS2 score ≥ 2 ($p < 0.05$) (Table 4).

Table 1
Baseline characteristics, MRI and echocardiographic findings, laboratory data, and clinical course during admission for the CHALLENGE ESUS/CS study population.

Characteristics	Number with data	Summary
Sociodemographic		
Age, y,[a]	677	68.7 ± 12.8
Gender, male, no (%)	677	455 (67)
Risk factors, no (%)	677	
Hypertension	677	484 (71)
Diabetes mellitus	677	172 (25)
Dyslipidemia	677	345 (51)
Cigarette smoking	677	181 (27)
Coronary artery disease	677	68 (10)
Previous history of ischemic stroke	677	123 (18)
NIHSS score on admission, median (IQR)	677	2 (1–5)
Carotid stenosis on duplex ultrasonography	677	33 (5)
MRI, no (%)		
Cortical infarction	672	539 (80)
Large infarction ≥ 3 cm in diameter	672	201 (30)
Intracranial arterial stenosis on MRA	672	72 (11)
Echocardiographic findings, no (%)		
Mitral regurgitation	676	362 (53)
Atrial septal aneurysm	671	92 (14)
Right to left shunt	654	302 (46)
Aortic arch plaques	675	254 (38)
Laboratory findings,[a]		
HDL-C, mg/dL	669	51.2 ± 15.0
TG, mg/dL	672	132.8 ± 107.6
Glucose, mg/dL	672	132.0 ± 51.0
D-dimer, µg/mL	677	3 ± 16.3
Clinical course during admission, no (%)		
Neurological deterioration	677	27 (4)
Detection of PAF	677	64 (9)
Stroke recurrence	677	25 (4)

NIHSS = NIH Stroke scale; IQR = interquartile range, HDL-C = high-density lipoprotein cholesterol; TG = triglyceride; PAF = paroxysmal atrial fibrillation.
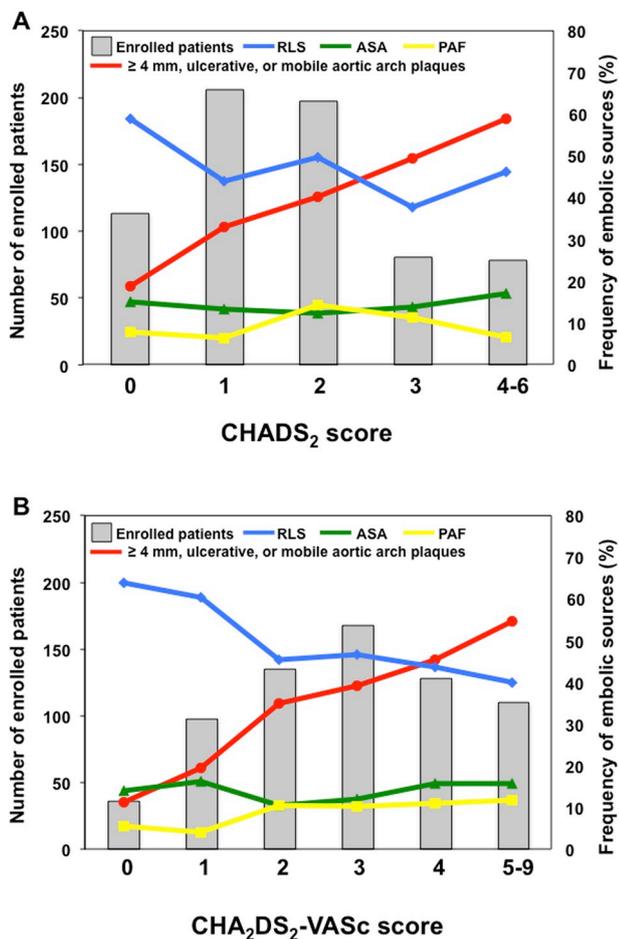[a] Mean $\pm$ SD.

Fig. 1. Proportion of enrolled patients and embologenic diseases by CHADS$_2$ and CHA$_2$DS$_2$-VASc scores.
Histograms and line graphs showing the number of enrolled patients and frequency of right-to-left shunt (RLS), atrial septal aneurysm (ASA), paroxysmal atrial fibrillation (PAF), and aortic arch plaques according to (A) CHADS$_2$ and (B) CHA$_2$DS$_2$-VASc scores.

Fig. 2. Proportion of neurological deterioration and stroke recurrence, and large and complex aortic arch plaques by CHADS$_2$ and CHA$_2$DS$_2$-VASc scores. Histograms and line graphs showing proportions of patients with neurological deterioration and stroke recurrence during admission, and frequency of large aortic arch plaques ≥4 mm and with ulcerative or mobile components according to (A) CHADS$_2$ and (B) CHA$_2$DS$_2$-VASc scores.

4. Discussion

In the present study, a number of CS patients were enrolled into the CHALLENGE ESUS/CS registry. Our data indicated that not only aortic arch plaques ≥4 mm, but also aortic arch plaques with ulcerative or mobile components were closely related to CHADS$_2$ and CHA$_2$DS$_2$-VASc scores ≥2 in our TEE registry patients with CS. In addition, PAF, dyslipidemia, and glucose levels were linked to CHADS$_2$ and CHA$_2$DS$_2$-VASc scores, while RLS was inversely associated with CHA$_2$DS$_2$-VASc score.

A considerable number of studies have examined TEE for CS, while a few studies using TEE in the ESUS population have been available [4,14,18,19]. Sample size in these studies was ≈581 patients [20–22]. The main strengths of our multicenter study were that 677 consecutive patients with CS who underwent TEE with comprehensive data by experienced stroke physicians were enrolled in 8 stroke registries. Although TEE is a semi-invasive method and younger stroke patients tended to be prioritized to perform TEE in previous studies [19–22], CS patients enrolled in our registry were 69 ± 13 years old, and frequency of atherosclerotic vascular risk factors was relatively higher than in previous TEE studies [19–22]. Importantly, our baseline characteristics were mostly identical to those in the NAVIGATE ESUS [23]. To the best of our knowledge, the CHALLENGE ESUS/CS registry is the largest TEE registry to enroll patients with CS, and our data may reflect real-world clinical practice in CS, and possibly ESUS.
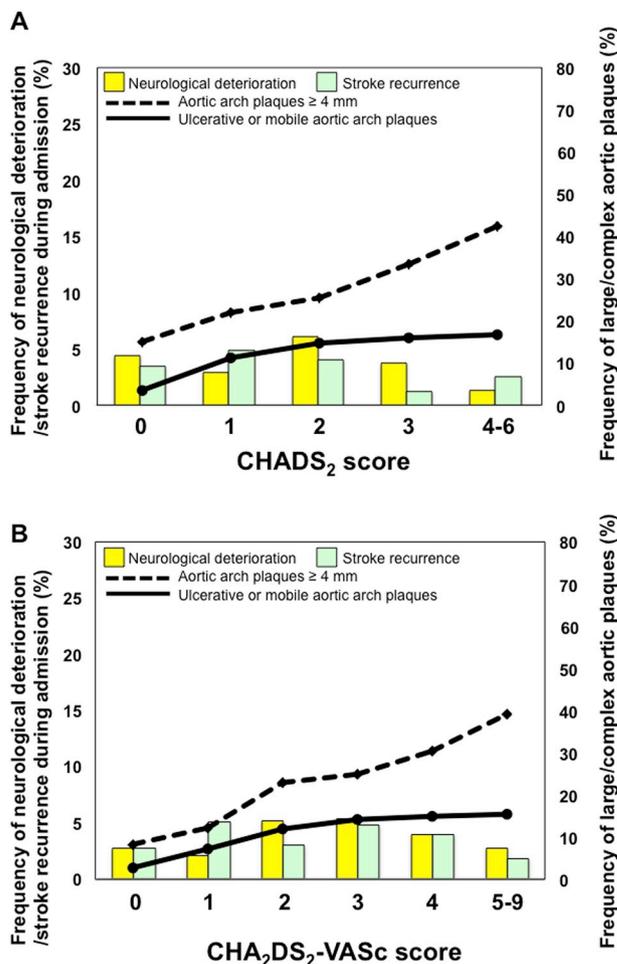
The current study showed that large aortic arch plaques ≥4 mm and with ulcerative or mobile components were closely associated with CHADS$_2$ and CHA$_2$DS$_2$-VASc scores ≥2. CHADS$_2$ score has been widely used in evaluating risk of stroke in AF patients since 2001 [16]. CHA$_2$DS$_2$-VASc score, which included additional risk factors, determined risk stratification of low-risk patients by CHADS$_2$ score [24]. CHADS$_2$ and CHA$_2$DS$_2$-VASc scores ≥2 could be considered as showing a high risk of stroke [25]. Emerging data have indicated that CHADS$_2$ and CHA$_2$DS$_2$-VASc scores predicted mortality and stroke recurrence in ESUS and non-AF stroke patients [17,26]. In these studies, however, underlying aortic atherosclerosis has yet to be elucidated. Large aortic arch plaques ≥4 mm are well known to be related to ischemic stroke of unknown cause and stroke recurrence [2,4,13]. In particular, mobile or ulcerated aortic plaques were considered as a major source of brain embolism [4,18,27]. From our TEE registry data, CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were shown to be useful in stratifying the degree of advanced aortic plaques as critical embolic sources in CS patients for the first time, with potential contributions to poor prognosis.

Low CHA$_2$DS$_2$-VASc scores were associated with a high frequency of RLS. An autopsy study of 965 subjects showed the prevalence of PFO is higher in the first three decades of life and gradually decreases with age until the 10th decade [28]. The CHA$_2$DS$_2$-VASc score was more reflective of age than CHADS$_2$ score was, which might be linked to the clear inverse association between RLS frequency and CHA$_2$DS$_2$-VASc

Table 2

Baseline characteristics, MRI and echocardiographic findings, laboratory data, and clinical course during admission.

Characteristics	CHADS$_2$ score, points		p	CHA$_2$DS$_2$-VASc score		p
	0–1	≥2		0–1	≥2	
	n = 321, 47%	n = 356, 53%		n = 136, 20%	n = 541, 80%	
Sociodemographic						
Age, y,[a]	62.4 ± 11.9	74.3 ± 10.7	< 0.001	54.2 ± 10.7	72.3 ± 10.5	< 0.001
Gender, male, no (%)	211 (66)	244 (69)	0.437	114 (84)	341 (63)	< 0.001
Risk factors, no (%)						
Hypertension	158 (49)	326 (92)	< 0.001	43 (32)	441 (82)	< 0.001
Diabetes mellitus	17 (5)	155 (44)	< 0.001	4 (3)	168 (31)	< 0.001
Dyslipidemia	136 (42)	209 (59)	< 0.001	44 (32)	301 (56)	< 0.001
Cigarette smoking	96 (30)	85 (24)	0.077	53 (39)	128 (24)	< 0.001
Coronary artery disease	18 (6)	50 (14)	< 0.001	0 (0)	68 (13)	< 0.001
Previous history of ischemic stroke	0 (0)	123 (35)	< 0.001	0 (0)	123 (23)	< 0.001
NIHSS score on admission, median (IQR)	2 (1–5)	2 (1–5)	0.111	2 (0–5)	2 (1–5)	0.031
Carotid stenosis on duplex ultrasonography	13 (4)	20 (6)	0.344	4 (3)	29 (5)	0.343
MRI, no (%)						
Cortical infarction	255 (80)	284 (81)	0.747	111 (82)	428 (80)	0.644
Large infarction ≥ 3 cm in diameter	94 (29)	107 (31)	0.772	42 (31)	159 (30)	0.782
Intracranial arterial stenosis on MRA	28 (9)	44 (12)	0.116	10 (7)	62 (11)	0.156
Echocardiographic findings, no (%)						
Mitral regurgitation	182 (57)	180 (51)	0.119	74 (54)	288 (53)	0.822
Atrial septal aneurysm	44 (14)	48 (14)	0.88	21 (15)	71 (13)	0.461
Right to left shunt	150 (48)	152 (44)	0.352	80 (61)	222 (43)	< 0.001
Aortic arch plaques			< 0.001			< 0.001
≥ 4 mm in thickness	60 (19)	110 (31)		15 (11)	155 (29)	
with ulceration or mobile components	29 (9)	55 (15)		8 (6)	76 (14)	
Laboratory findings[a]						
HDL-C, mg/dL	53.4 ± 15.4	49.3 ± 14.4	< 0.001	53.3 ± 16.3	50.7 ± 14.7	0.076
TG, mg/dL	133.3 ± 109.3	132.2 ± 106.2	0.719	130.0 ± 95.3	133.5 ± 110.5	0.443
Glucose, mg/dL	118.4 ± 32.0	144.1 ± 60.9	< 0.001	115.3 ± 25.8	136.1 ± 54.7	< 0.001
D-dimer, μg/mL	3.8 ± 23.3	2.2 ± 4.0	0.002	4.5 ± 33.7	2.6 ± 6.9	< 0.001
Clinical course during admission, no (%)						
Neurological deterioration	11 (3)	16 (4)	0.478	3 (2)	24 (4)	0.346
Detection of PAF	22 (7)	42 (12)	0.028	6 (4)	58 (11)	0.025
Stroke recurrence	14 (4)	11 (3)	0.381	6 (4)	19 (4)	0.619

Chi-square test and the Kruskal-wallis test were used for comparison.

NIHSS = NIH Stroke scale; IQR = interquartile range, HDL-C = high-density lipoprotein cholesterol; TG = triglyceride; PAF = paroxysmal atrial fibrillation.

[a] Mean ± SD.

Table 3

Multiple logistic regression analysis predicting CHADS2 score ≥2 in CS patients.

Variables	OR	95% CI	p
Dyslipidemia	1.46	1.04–2.06	0.029
Current smoking	0.54	0.36–0.8	0.002
Coronary artery diseases	1.68	0.91–3.1	0.097
Aortic arch plaques	1 (reference)	1 (reference)	
≥ 4 mm in thickness	2.25	1.51–3.36	< 0.001
with ulceration or mobile components	2.37	1.38–4.06	0.002
Glucose	1.02	1.01–1.02	< 0.001
HDL-C	0.99	0.98–1.00	0.019
D-dimer	0.99	0.96–1.01	0.331
PAF	2.13	1.18–3.84	0.012

CS = cryptogenic stroke; PAF = paroxysmal atrial fibrillation.

Table 4

Multiple logistic regression analysis predicting CHA2DS2-VASc score ≥2 in CS patients.

Variables	OR	95% CI	p
Dyslipidemia	2.21	1.41–3.46	0.001
Current smoking	0.33	0.20–0.52	< 0.001
NIHSS	1.00	0.97–1.04	0.893
Right to left shunt	0.57	0.37–0.88	0.011
Aortic arch plaques ≥ 4 mm	1 (reference)	1 (reference)	
≥ 4 mm in thickness	3.88	2.07–7.27	< 0.001
with ulceration or mobile components	3.25	1.44–7.34	0.005
Glucose	1.02	1.01–1.03	< 0.001
HDL-C	0.99	0.98–1.01	0.261
D-dimer	1.00	0.99–1.01	0.746
PAF	3.33	1.11–10.02	0.032

CS = cryptogenic stroke; NIHSS = NIH Stroke scale; HDL-C = high-density lipoprotein cholesterol; PAF = paroxysmal atrial fibrillation.

score in the present study. Frequency of ASA did not differ according to the severity of CHADS$_2$ and CHA$_2$DS$_2$-VASc scores.

Recent studies have sought to address the presence of covert AF using novel devices, and displayed higher frequency to detect PAF [6,7]. On the other hand, conventional devices including continuous cardiac monitoring and 24-h Holter monitoring revealed that detection rates of PAF were around 7% within 7 days after admission [29,30]. In the current study, PAF was detected in 9% of CS patients during admission. Moreover, our data first demonstrated that CHADS$_2$ and CHA$_2$DS$_2$-VASc scores ≥2 increased the risk of PAF during admission in CS. However, various diagnostic modalities including conventional devices and an insertable cardiac monitor were used in the current study, representing a limitation of this investigation. Future investigations are warranted.

Accordingly, CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were shown to be critical to stratification of the presence of underlying embologenic diseases. In particular, aortic arch plaques and PAF were equally linked to CHADS$_2$ and CHA$_2$DS$_2$-VASc scores ≥2 in CS, while advanced aortic arch plaques were more frequent than PAF. Our data indicated that underlying aortic arch plaques could be important embologenic

diseases in cryptogenic stroke with high CHADS$_2$ and CHA$_2$DS$_2$-VASc scores. On the other hand, long-term cardiac monitoring increased the detection of PAF in CS [6,30]. Thus, long-term follow-up regarding the appearance of PAF and stroke recurrence in CS, and possibly ESUS with high CHADS$_2$ and CHA$_2$DS$_2$-VASc scores would be of importance.

Some potential limitations of the current study must be considered when interpreting the present results. First, this was a retrospective study, and a small amount of radiological, echocardiographic, and laboratory data were lacking. In particular, investigations for potential embolic etiologies were incomplete, including 3.4% missing data for RLS, 0.9% for ASA, and 0.3% for aortic arch plaques. Second, selection bias might have been involved in the performance of TEE for CS patients in each hospital. Third, we used a cut-off value of 50% stenosis for presence of carotid stenosis, and mild carotid atherosclerosis was thus not evaluated.

4.1. Conclusions

The idea of ESUS was based on the integration for diverse underlying embolic mechanisms, but large-scale clinical trials have not shown the efficacy of DOACs in the ESUS population. The CHALLENGE ESUS/CS registry is the largest TEE registry, clarified potential embolic etiologies on TEE, and might reflect real-world clinical characteristics of ESUS/CS. Not only PAF, but also large aortic arch plaques should be considered in CS patients with CHADS$_2$ and CHA$_2$DS$_2$-VASc scores ≥ 2. Underlying large aortic arch plaques would represent important embologenic diseases in cryptogenic stroke with high CHADS$_2$ and CHA$_2$DS$_2$-VASc scores, and evaluating long-term prognosis in such patients is important.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

Study concept and design: YU, YT, RD, AK, TS, MK, and HT. Acquisition of data: YU, YT, RD, AK, TS, MK, YS, HT, EY, MK, YK, MI, AT, KH, KT, YH, and NH. Analysis and interpretation of data: YU, YT, RD, AK, TS, MK, YS, HT, EY, MK, YK, MI, AT, KH, KT, YH, and NH. Drafting of the manuscript: YU, MK, and KT. Critical revision of the manuscript for important intellectual content: TU. Study supervision YU.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.03.009.

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