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Stroke mechanism in patients with non-valvular atrial fibrillation according to the $CHADS_2$ and CHA_2DS_2-VASc scores

M.-J. Cha, Y. D. Kim, H. S. Nam, J. Kim, D. H. Lee and J. H. Heo
Department of Neurology, Yonsei University College of Medicine, Seoul, Korea

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Background and purpose: The $CHADS_2$ and CHA_2DS_2-VASc scores are useful to stratify embolic risks in patients with non-valvular atrial fibrillation (NVAF) and to identify patients eligible for anticoagulation. Although the risk of stoke increases in patients with higher $CHADS_2$ or CHA_2DS_2-VASc scores, it is uncertain why the stroke rate increases in them. Concomitant potential cardiac sources of embolism (PCSE) may be more frequent in patients with higher $CHADS_2$ or CHA_2DS_2-VASc scores because stroke risks increase when concomitant PCSE is present in Atrial fibrillation (AF). On the other hand, atherothrombosis may be the cause when considering that most components of the $CHADS_2$ and CHA_2DS_2-VASc scores are risk factors for atherosclerosis.

Methods: Amongst 5493 stroke patients who were prospectively registered with the stroke registry for 11 years, 860 consecutive patients with NVAF were included for this study. We investigated the mechanisms of stroke according to the $CHADS_2$/CHA_2DS_2-VASc score in stroke patients with NVAF.

Results: Amongst 860 patients, concomitant PCSE were found in 334 patients (38.8%). The number of PCSE increased as the $CHADS_2$/CHA_2DS_2-VASc score increased ($P < 0.001$). Of individual PCSE, akinetic left ventricular segment, hypokinetic left ventricular segment and myocardial infarction <4 weeks were associated with the $CHADS_2$/CHA_2DS_2-VASc score. The presence of possible atherothrombotic mechanism, in addition to AF, was suggested in 27.3%. The proportion of patients with concomitant presence of possible atherothrombosis was increased as the $CHADS_2$/CHA_2DS_2-VASc score increased ($P < 0.001$).

Conclusions: Increased frequency of concomitant PCSE and that of the atherothrombotic mechanism may explain the high risk of stroke in patients with higher $CHADS_2$/CHA_2DS_2-VASc score.

Introduction

Atrial fibrillation (AF) is the most common cardiac source of embolism, and it accounts for about 77% of high-risk potential cardiac sources of embolism (PCSE) in stroke patients [1]. Whilst the incidence of stroke increases by an average fivefold in the presence of AF, embolic risks in patients with AF are different depending on many factors [2,3]. To stratify embolic risks in patients with non-valvular AF (NVAF) and to identify patients eligible for anticoagulation, a scoring system known as the $CHADS_2$ score was developed [4]. $CHADS_2$ is an acronym that means five stroke risk factors and is calculated as the sum of points allocated to each of the following items: one point each for congestive heart failure (CHF), hypertension, age ≥75 years and diabetes mellitus, and two points for previous ischaemic stroke or transient ischaemic attack (TIA) [4]. Recently, the CHA_2DS_2-VASc score was proposed, which adds vascular disease [previous myocardial infarction, complex aortic plaque and peripheral artery disease (PAD)], age 65–74 and female sex to the original $CHADS_2$ score [5]. The CHA_2DS_2-VASc score scheme showed modest improvement for the prediction of thromboembolism over the $CHADS_2$ score [6].

The stroke rate increases as the $CHADS_2$/CHA_2DS_2-VASc score increases [4,7,8]. However, it is uncertain why the stroke rate increases in patients with higher $CHADS_2$/CHA_2DS_2-VASc scores. It can be presumed

Correspondence: J. Hoe Heo, MD, PhD, Department of Neurology, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemoon-ku, 120-752, Seoul, Korea (tel.: 82 2 2228 1605; fax: 82 2 393 0705; e-mail: jhheo@yuhs.ac).

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that increased risk of stroke in AF patients with higher $CHADS_2/CHA_2DS_2$-VASc scores is mainly associated with an increased risk of cardioembolism. AF is frequently accompanied by other PCSE [1]. AF patients with concomitant PCSE have increased thromboembolic risks [1,3,7]. Therefore, it is assumable that concomitant PCSE may be more frequently accompanied by AF in patients with higher $CHADS_2/CHA_2DS_2$-VASc scores. In contrast, most components of the $CHADS_2/CHA_2DS_2$-VASc score are risk factors of atherosclerosis. The frequency and burden of cerebral artery atherosclerosis were greater in patients with higher $CHADS_2$ scores [9]. In this sense, increased risk of stroke in patients with high $CHADS_2/CHA_2DS_2$-VASc scores may be associated with increased risk of atherothrombosis.

To understand more about mechanisms of increased stroke in higher $CHADS_2/CHA_2DS_2$-VASc scores, in NVAF patients who recently developed stroke, we measured the $CHADS_2/CHA_2DS_2$-VASc score prior to stroke and investigated whether concomitant PCSE were more commonly present in the patient group with higher $CHADS_2/CHA_2DS_2$-VASc scores. We also determined whether potential atherothrombotic mechanisms were more frequently accompanied in them.

Materials and methods

Patients and enrolment

This study was conducted with the approval of the institutional review board of the Severance Hospital, Yonsei University Health System. The subjects in this study were consecutive patients with NVAF who had been registered in the Yonsei Stroke Registry (YSR) from March 1999 to February 2010. The YSR is a prospective hospital-based registry for acute cerebral infarction or TIA patients within 7 days after symptom onset [10]. The accuracy of the data was ensured based on a review of all the data for each case at the weekly stroke conference. All patients were evaluated by medical history, neurological examination, standard blood tests, brain imaging studies, cerebral angiographic studies and 12-lead electrocardiogram. Transesophageal echocardiography (TEE) was a standard evaluation for patients, except for those with poor cooperation because of decreased consciousness, impending brain herniation, poor systemic conditions, swallowing difficulty, tracheal intubation, or lack of informed consent [11,12]. Transcranial Doppler, carotid duplex sonography, transthoracic echocardiography (TTE), Holter monitoring and heart CT scan were performed in selected patients.

The $CHADS_2$ score and CHA_2DS_2-VASc score

In this study, the $CHADS_2$ score and CHA_2DS_2-VASc score were retrospectively calculated. Index cerebral infarction and TIA were not considered in the scoring. CHF was defined when there was a previous history of CHF or CHF was detected during admission based on the medical records or hospital diagnosis code (*International Classification of Disease, 10th Revision* ICD-10-CM codes I50) [4]. Hypertension was defined when a patient had a resting high blood pressure recording (systolic ≥140 mmHg or diastolic ≥90 mmHg) after repeated measurements during admission or when a patient was taking an antihypertensive drug after diagnosis of hypertension. Diabetes mellitus was defined when the fasting plasma glucose was ≥7 mM or a patient was treated with oral hypoglycaemic agents or insulin. Vascular disease, which was one of the components of the CHA_2DS_2-VASc score, was defined when a patient had previous myocardial infarction, complex aortic plaques or PAD including amputation because of PAD, revascularization or angiographically confirmed PAD [5]. Determination of the concomitant PCSE was based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification [13].

Stroke mechanism

Accompaniment of the potential atherothrombotic mechanism in addition to cardioembolic mechanism was determined based on the Yonsei aetiology-based ischaemic stroke classification in each patient [14]. Briefly, atherothrombosis is diagnosed when a patient has intra- or extracranial atherosclerosis of the relevant artery, which is correlated with the patient's symptoms and signs with ischaemic lesions on brain imaging studies. In addition to relevant artery atherosclerosis, one or more evidences of systemic atherosclerosis should be identified. Systemic atherosclerosis includes angiographically documented atherosclerosis in cerebral arteries other than the clinically relevant artery, aortic atheroma demonstrated by TEE, angiographically documented coronary artery disease, and angiographically documented peripheral artery disease [14]. All patients enrolled for this study had AF; therefore, a stroke subtype in each patient was either cardioembolism or stroke of more than two causes (atherothrombosis plus cardioembolism).

Data and statistical analysis

Statistical analysis was performed using Windows SPSS package (version 17.0; SPSS Inc., Chicago, IL, USA). Comparisons between patients with concomitant PCSE and those without PCSE were made using the *t*-test or

chi-square for categorical variables. The association between number of concomitant PCSE and the $CHADS_2/CHA_2DS_2$-VASc score and between frequency of each concomitant PCSE and the $CHADS_2/CHA_2DS_2$-VASc score was analysed using linear-by-linear association (chi-square for trend). For these comparisons, CHF was excluded, because CHF is a component of the $CHADS_2$ and CHA_2DS_2-VASc score.

Results

Demographic characteristics

Of 5493 patients who were registered to the YSR during the 11-year study period, 992 patients had AF. After excluding 132 patients with a concomitant valve disease, 860 (15.7%) patients with NVAF were included for this study. Amongst the 860 patients, at least one special cardiac evaluation was performed in 554 patients (64.4%: TEE in 41.4%, TTE in 28.4%, heart CT in 16% and Holter monitoring in 3.4%). Of 860 patients, 334 (38.8%) patients had at least one concomitant PCSE [one PCSE in 245 (28.5%) patients, two PCSE in 70 (8.1%) patients, three PCSE in 18 (2.1%) patients, and four PCSE in 1 (0.1%) patient]. Diabetes mellitus was more common in patients with concomitant PCSE than in those without concomitant PCSE. Other demographic characteristics were not different between the patients with and without concomitant PCSE (Table 1). Of the concomitant PCSE, CHF was most common (151 patients, 17.6%), followed by spontaneous echo contrast (131 patients, 15.2%), left atrial appendage thrombus (39 patients, 4.5%), and patent foramen ovale (39 patients, 4.5%; Table 2).

Association of the $CHADS_2/CHA_2DS_2$-VASc score with concomitant PCSE

$CHADS_2$ scores of 1 and 2 were most common [0 = 100 (11.6%), 1 = 254 (29.5%), 2 = 247 (28.7%), 3 = 161 (18.7%), 4 = 72 (8.4%), 5 = 24 (2.8%), 6 = 2 (0.2%)]. The mean $CHADS_2$ score was higher in the patients with concomitant PCSE (2.21 ± 1.34) than those without concomitant PCSE (1.74 ± 1.16; $P = 0.004$). The number of concomitant PCSE increased as the $CHADS_2$ score increased ($P < 0.001$; Fig. 1a). We also analysed the association with CHA_2DS_2-VASc score. The most common CHA_2DS_2-VASc scores were 3 and 4 [0 = 28 (3.3%), 1 = 98 (11.4%), 2 = 140 (16.3%), 3 = 189 (22.0%), 4 = 186 (21.6%), 5 = 127 (14.8%), 6 = 64 (7.4%), 7 = 20 (2.3%), 8 = 6 (0.7%), 9 = 2 (0.2%)]. The mean CHA_2DS_2-VASc score was higher in the patients with concomitant PCSE (3.79 ± 1.81) than those without concomitant PCSE (3.13 ± 1.57) ($P = 0.004$). The number of concomitant PCSE increased as the CHA_2DS_2-VASc score increased ($P < 0.001$; Fig. 1b).

Association between the $CHADS_2/CHA_2DS_2$-VASc score and individual PCSE

We classified the concomitant PCSE based on the structure involved and analysed their association with the $CHADS_2/CHA_2DS_2$-VASc score. The concomitant PCSE that were attributed to left ventricular (LV) lesions were associated with higher $CHADS_2/CHA_2DS_2$-VASc scores ($P < 0.001$). In contrast, the concomitant PCSE attributed to left atrial (LA) structures were not associated with the $CHADS_2/CHA_2DS_2$-VASc score.

Amongst individual PCSE, akinetic LV segment, hypokinetic LV segment and myocardial infarction (MI) <4 weeks were associated with $CHADS_2$ scores. As the $CHADS_2$ scores increased, their frequencies increased [akinetic LV segment ($P < 0.001$), hypokinetic left ventricular segment ($P < 0.001$) and myocardial infarction <4 weeks ($P = 0.001$)]. In comparison, using the CHA_2DS_2-VASc score, similar associations were found in that the frequency of akinetic LV segment ($P = 0.001$), hypokinetic LV segment

Table 1 Baseline characteristics of the patients

	Total (N = 860)	With PCSE (N = 334)	Without PCSE (N = 526)	P-value
Age, year, mean ± SD	70.23 ± 10.47	69.66 ± 10.86	70.59 ± 10.21	0.259
Sex, Men	490 (48.6)	191 (57.2)	299 (56.8)	0.921
Hypertension	641 (74.5)	245 (73.4)	396 (75.3)	0.526
Diabetes mellitus	213 (24.8)	96 (28.7)	117 (22.2)	0.031
Smoking	248 (28.8)	102 (30.5)	146 (27.8)	0.380
Hypercholesterolaemia	49 (5.7)	20 (6.0)	29 (5.5)	0.770
History of CAD	149 (17.3)	68 (20.4)	81 (15.4)	0.061
Previous TIA/infarction	184 (21.4)	69 (20.7)	115 (21.9)	0.675

Numbers in parenthesis are percentages.

PCSE, potential cardiac sources of embolism; CAD, coronary artery disease; TIA, transient ischaemic attack.

Table 2 The association of concomitant potential cardiac sources of embolism with the $CHADS_2$ score

	CHADS2 score					
Structure	PCSE	0–1 (n = 354)	2–3 (n = 408)	4–6 (n = 98)	Total (860)	P-value
LA disease	LA thrombus	19 (5.4)	16 (3.9)	4 (4.1)	39 (4.5)	0.401
	Spontaneous echo contrast	64 (18.1)	53 (13.0)	14 (14.3)	131 (15.2)	0.114
	Atrial septal aneurysm	0 (0)	1 (0.2)	0 (0)	1 (0.1)	0.652
	Patent foramen ovale	19 (5.4)	15 (3.7)	5 (5.1)	39 (4.5)	0.554
LV disease	Akinetic LV segment	3 (0.8)	5 (1.2)	6 (6.1)	14 (1.6)	0.004
	Dilated cardiomyopathy	5 (1.4)	3 (0.7)	1 (1.0)	9 (1.0)	0.503
	MI (<4 weeks)	1 (0.3)	2 (0.5)	4 (4.1)	7 (0.8)	0.004
	LV thrombus	0 (0)	3 (0.7)	0 (0)	3 (0.3)	0.435
	Hypokinetic LV segment	7 (2.0)	13 (3.2)	11 (11.2)	31 (3.6)	0.001
	MI (>4weeks but 6 months)	0 (0)	1 (0.2)	0 (0)	1 (0.1)	0.652
Arrhythmia	Atrial flutter	4 (1.1)	9 (2.2)	0 (0)	13 (1.5)	0.956
	Sick sinus syndrome	0 (0)	4 (1.0)	0 (0)	4 (0.5)	0.108

Numbers in parenthesis are percentages.
LA, left atrial; LV, left ventricular; MI, myocardial infarction; PCSE, potential cardiac sources of embolism.

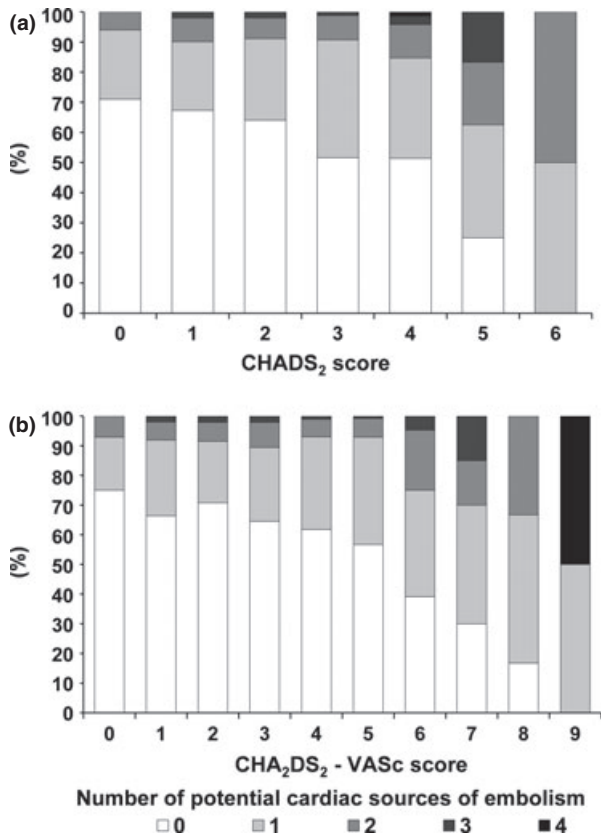

Figure 1 Association between (a) the $CHADS_2$ score or (b) the CHA_2DS_2-VASc score and the number of concomitant potential cardiac sources of embolism (PCSE). The number of concomitant PCSE increased as the $CHADS_2$/CHA_2DS_2-VASc score increased (P < 0.001).

(P = 0.010) and myocardial infarction <4 weeks (P = 0.003) increased as the CHA_2DS_2-VASc score increased.

In the original study of the $CHADS_2$ score, based on stroke risks, seven $CHADS_2$ strata were categorized into low risk ($CHADS_2$ 0 or 1), medium risk ($CHADS_2$ 2 or 3) and high risk ($CHADS_2$ 4, 5 or 6) [4]. In the analysis with categorization based on $CHADS_2$ scores into 0–1, 2–3 and ≥4, the differences were also significant between the three groups (Table 2).

Detection of PCSE depends on TEE examination. We performed subgroup analysis on the concomitant PCSE and the $CHADS_2$ score in 356 patients who underwent TEE. Total number of PCSE increased as the $CHADS_2$ score increased (P < 0.001). As the $CHADS_2$ scores increased, the frequencies of akinetic LV segment (P = 0.003) and myocardial infarction <4 weeks (P = 0.003) also increased (Table S1).

Stroke mechanism

After excluding 28 patients with TIA, stroke mechanisms could be determined in 832 patients. Amongst them, atherothrombotic mechanism in addition to cardioembolism was suspected in 235 patients (28.2%). The proportion of a stroke subtype of more than two causes (atherothrombosis plus cardioembolism) significantly increased as the $CHADS_2$ and CHA_2DS_2-VASc scores increased (P < 0.001; Fig. 2).

Discussion

We investigated the association between concomitant PCSE and $CHADS_2$/CHA_2DS_2-VASc score in stroke patients with NVAF and sought possible stroke mechanisms according to the $CHADS_2$/CHA_2DS_2-VASc score. In this study, the number of concomitant PCSE increased as the $CHADS_2$/CHA_2DS_2-VASc score

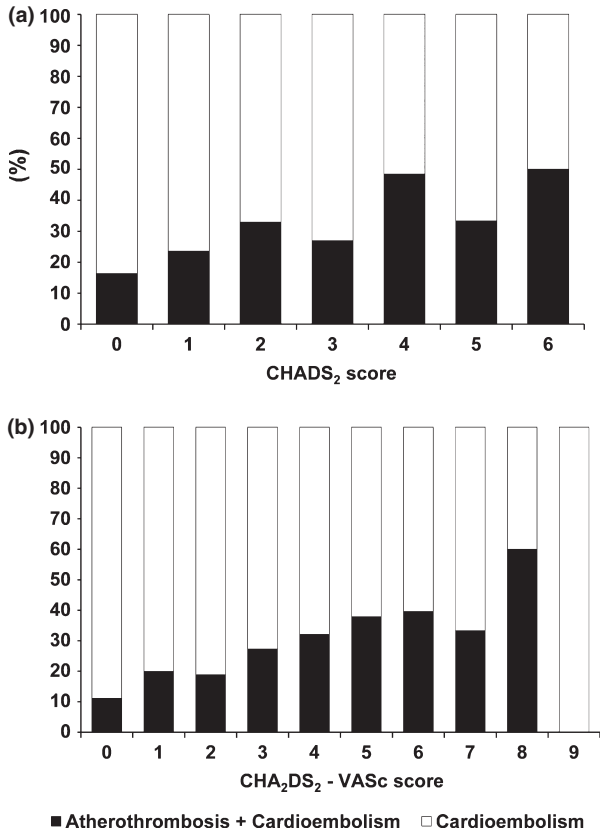

Figure 2 The stroke mechanism according to the $CHADS_2/CHA_2DS_2$-VASc score. The stroke subtype of more than two causes (atherothrombosis plus cardioembolism) increased as (a) the $CHADS_2$ score or (b) the CHA_2DS_2-VASc score increased.

increased. We further investigated which concomitant PCSE are associated with $CHADS_2/CHA_2DS_2$-VASc scores in stroke patients with NVAF. PCSE of the left ventricular origin, which were akinetic LV segment, hypokinetic LV segment and MI < 4 weeks, were related to higher $CHADS_2/CHA_2DS_2$-VASc scores in our study.

Our findings suggest that increased risk of stroke in patients with higher $CHADS_2/CHA_2DS_2$-VASc scores may, in part, be ascribed to the presence of concomitant PCSE. However, concomitant PCSE, akinetic/hypokinetic LV segment and MI < 4 weeks, which were associated with $CHADS_2$ scores in this study, comprised only 4.9% of our study group. These findings suggest that the increased risk associated with higher $CHADS_2/CHA_2DS_2$-VASc score may not be simply due to increased risk of embolism from the cardiac chamber associated with concomitant PCSE. Old age is independently associated with decreased left atrial appendage flow velocities, and hypertension is also associated with stasis of flow and thrombus in the left atrial appendage [15,16]. CHF and diabetes mellitus are associated with a significantly increased risk of left atrial appendage thrombi [3,17]. These findings suggest that intrinsic factors related to components of the $CHADS_2/CHA_2DS_2$-VASc score may partly play roles in increased risk of thrombus formation in the cardiac chamber.

Atherothrombosis and AF are common diseases that coexist in many stroke patients [18]. Components of the $CHADS_2$ score, such as age, hypertension and diabetes mellitus, are also risk factors for atherosclerosis. Components of the CHA_2DS_2-VASc score, which were added to the original $CHADS_2$ scoring system, include vascular disease (previous myocardial infarction, complex aortic plaques and PAD) [5]. They are results of atherosclerosis of the coronary artery, the peripheral artery, or the aorta. Given that atherosclerosis is a systemic disease, the incidence of cerebral atherosclerosis may be higher in patients with higher $CHADS_2/CHA_2DS_2$-VASc scores. In our previous study, we showed that the $CHADS_2$ score was predictive of concomitant cerebral artery atherosclerosis and that atherosclerosis of the proximal symptomatic artery was more frequent in the stroke patients with high $CHADS_2$ scores [9]. In this study, the frequency of the stroke subtype of more than two causes, which was the atherothrombosis plus cardioembolism, increased in the patient group with higher $CHADS_2/CHA_2DS_2$-VASc scores. The actual mechanism of stroke is difficult to determine in patients who have both AF and atherosclerosis of the relevant artery. However, increased proportion of patients with concomitant arterial sources of thromboembolism in patients with higher $CHADS_2/CHA_2DS_2$-VASc scores suggests that atherothrombosis might be the actual cause of stroke in some of them. Our findings also suggest that the risk of stroke in patients with NVAF should involve not only the traditional $CHADS_2$ and/or CHA_2DS_2-VASc scores but also the whole atherosclerotic spectrum.

In this study, akinetic/hypokinetic LV segment and MI < 4 weeks were associated with higher $CHADS_2/CHA_2DS_2$-VASc scores. Those cardiac conditions are frequently the results of coronary artery disease [19–21]. In this regard, association of those PCSE with higher $CHADS_2/CHA_2DS_2$-VASc scores may, in part, represent the presence of the concomitant atherosclerosis of the coronary artery. These findings support our previous observations that showed higher frequency of fatal ischaemic heart disease as well as fatal ischaemic stroke in stroke patients with higher $CHADS_2/CHA_2DS_2$-VASc scores [22].

The values and limitations of the $CHADS_2$ score have been discussed in a recent review paper [23]. Despite some limitations, $CHADS_2$ score and CHA_2DS_2-VASc score, which have advantages of its

simplicity and broad applicability, are used and validated for stratification of patients who require oral anticoagulation; oral anticoagulation is recommended for those with a $CHADS_2/CHA_2DS_2$-VASc score ≥2. The $CHADS_2$ score stratifies a patient from 0 to 6, and the CHA_2DS_2-VASc score does from 0 to 9. Although they have a wide range of strata, the cut-off score for the determination of oral anticoagulation is set at the low score 2. It is uncertain whether the same treatment strategy should be applied to all patients with score ≥2. In addition, all AF patients with stroke history, unless they have contraindication for anticoagulation treatment, are indicated for oral anticoagulation, because two points are given for stroke or TIA in calculating the $CHADS_2/CHA_2DS_2$-VASc score. In this regard, the risk stratification using a $CHADS_2/CHA_2DS_2$-VASc scoring system may be regarded as being unhelpful for planning treatment in stroke patients. However, many stroke patients with AF develop recurrent strokes despite adequate oral anticoagulation. Risks of thromboembolism increase as the $CHADS_2/CHA_2DS_2$-VASc score increases. Stroke is more severe when stroke patients with AF have concomitant PCSE [16,24,25]. More patients have poor outcomes during follow-up when the $CHADS_2$ score is high [26,27]. In this regard, AF patients with higher risks may require more intense antithrombotic treatment [28]. However, no definite clinical guidelines for secondary stroke prevention are available for stroke patients with AF who experience recurrent stroke or who have concomitant PCSE and/or higher $CHADS_2/CHA_2DS_2$-VASc score. Those patients with high risks may be good candidates for a new oral direct thrombin inhibitor, such as dabigatran with a higher dose, which showed similar bleeding risks but better stroke prevention, as compared to warfarin [29]. Whilst the effects of combined treatment of antiplatelet agents and oral anticoagulants in patients with AF are controversial [28], such a combined treatment strategy may be considered in selected patients with higher $CHADS_2/CHA_2DS_2$-VASc scores, because atherothrombosis, as well as cardioembolism, can be a mechanism of stroke.

In this study, we found that the number of concomitant PCSE and the stroke subtype of atherothrombosis plus cardioembolism increased with ascending $CHADS_2/CHA_2DS_2$-VASc score in stroke patients with NVAF. This may, in part, explain the high risk of stroke in patients with higher $CHADS_2/CHA_2DS_2$-VASc scores. Our findings also suggest the necessity of coronary artery evaluation in patients with higher $CHADS_2/CHA_2DS_2$-VASc scores because PCSE, which are associated with coronary artery disease, were more common in them.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The association of concomitant potential cardiac sources of embolism which was detected by transesophageal echocardiography and the $CHADS_2$ score.

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