Original Article

Relationship between CHA_2DS_2-VASc Score and Echocardiography Parameters with Ischemic Stroke Development

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Abstract

Context: Atrial fibrillation (AF) is the most common persistent rhythm disorder that has been shown to be associated with a significant increase in stroke risk. CHA_2DS_2-VASc is a scoring system to identify the risk of thromboembolism in nonvalvular AF patients. **Aims:** The aim of our study was to investigate the relationship between the demographic properties, transthoracic and transesophageal echocardiography parameters, the patients' CHA_2DS_2-VASc scores, and cerebrovascular events. **Subjects and Methods:** There were 48 patients with previous stroke and 217 patients without. We compared patients' demographic data, echocardiographic parameters, presence of patent foramen ovale (PFO) in transesophageal echocardiography, medications, AF categories, and CHA_2DS_2-VASc scores. **Results:** The mean age of the stroke group was 64.8 ± 12.3 years; the mean age of the control group was 63.2 ± 12.8 years ($P = 0.417$). The CHA_2DS_2-VASc score was 3.25 ± 2.06 in the stroke group and 2.49 ± 1.54 in the nonstroke group ($P < 0.001$). As for the presence of PFO, it was present in 45.8% of patients who had a stroke, but only 17.9% in the nonstroke group ($P < 0.001$). **Conclusions:** CHA2DS2-VASc score increases the risk of stroke in a broader sense, but not only in patients with AF. It is reasonable to think that the higher the score, the higher the risk of stroke. Furthermore, the presence of PFO in a patient is a facilitating factor for stroke, which may be considered for closure in the case of recurrent stroke episodes.

Keywords: Anticoagulants, atrial fibrillation, stroke, thrombus

Introduction

Atrial fibrillation (AF) is the most common persistent rhythm disorder that has been shown to be associated with a significant increase in stroke risk.[1] Left atrial appendage (LAA) thrombi are responsible for most strokes of cardiac origin.[2] CHA_2DS_2-VASc is a scoring system to identify the risk of thromboembolism and thus the indications for anticoagulation in nonvalvular AF patients. CHA_2DS_2-VASc score ranges from 0 to 9 points, where congestive heart failure or left ventricular ejection fraction (EF) ≤0.40, hypertension, age 65–74 years, diabetes mellitus, vascular disease, and female sex are each assigned 1 point; age ≥75 years,

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prior stroke, transient ischemic attack, and thromboembolism are each assigned 2 points.[3] Anticoagulation is recommended in patients with a CHA_2DS_2-VASc score of 2 and above.[4] In addition, patent foramen ovale (PFO) is detected in some patients with cryptogenic stroke. PFO prevalence is 6 times greater in cryptogenic stroke under the age of 55 than other causes of stroke.[5] PFO is a defect located at the interatrial septum that provides right-to-left shunt in fetal circulation and persists after birth in 27% of the general population.[6] Paradoxical embolism through a PFO generally originates from deep vein thrombosis, although air, amniotic fluid, and fat embolism may rarely cause a stroke by right-to-left shunting, especially during a Valsalva maneuver.[7]

The aim of our study was to investigate the relationship between the demographic properties, the presence of left atrial thrombus, and the presence of PFO in patients undergoing transesophageal echocardiography (TEE); we also aimed to examine the relationship between the patients' CHA_2DS_2-VASc scores and cerebrovascular events.

Subjects and Methods

This study enrolled a total of 265 patients who were admitted to our adult cardiology outpatient clinic and who underwent TEE procedure for any indication between June 2017 and June 2019. Patient's demographic data, transthoracic and transesophageal echocardiographic examinations, and laboratory test results were recorded retrospectively. Patients with missing medical data, cancer with ongoing treatment, hematological thrombotic disorders, and catheter thrombus surveilled by successive TEE examinations were excluded.

The patients were divided into two groups according to their previous stroke. There were 48 patients with previous stroke specified as Group I and 217 patients without stroke specified as Group II. We compared patient's demographic data, echocardiographic parameters, presence of PFO in TEE, medications, AF categories, and CHA_2DS_2-VASc scores.

AF was categorized on the basis of patient history and ESC AF Guidelines.[8] Accordingly, paroxysmal AF was defined by symptoms lasting up to 7 days, persistent AF between 7 days and 1 year, long-standing persistent AF more than 1 year, and permanent AF for an undetermined period of time. Newly diagnosed AF was diagnosed by a new onset of symptoms and the absence of any previous history of AF.

For all patients, hemoglobin, hematocrit, white blood cell count, platelet count, creatinine, high-density lipoprotein, triglyceride, and low-density lipoprotein levels were recorded. Study protocols approved by the local ethics committee were utilized throughout the study. A standardized questionnaire was used to collect clinical and demographic information, including medication history.

Statistical analyses

Laboratory data and echocardiographic variables were compared between the two groups using Kruskal–Wallis test, with paired Mann–Whitney U-test being performed as the *post hoc* analysis to identify significantly different pairs. Categorical data were analyzed with the Fisher's exact test and Chi-squared test. Normally distributed continuous variables were expressed as the mean ± standard deviation; nonnormally distributed continuous variables were expressed as median (minimum–maximum); and categorical variables were presented as percentage (%). Backward stepwise logistic regression analysis method was used for multivariate analysis. $P < 0.05$ was considered statistically significant. All analyses were performed using the SPSS statistical software package (version 25; SPPS, Chicago, IL, USA).

Results

The mean age of the Group I was 64.8 ± 12.3 years; the mean age of the Group II was 63.2 ± 12.8 years ($P = 0.417$). The percentage of men was 64.5% in Group I and 62.2% in Group II ($P = 0.869$) [Table 1]. The rate of AF was much higher in Group II because the most common indication for TEE was for thrombus evaluation for AF rhythm control. Thus, AF was present in 35.4% of patients with a history of stroke and 78.8% of patients without ($P < 0.001$). As for the presence of PFO, it was present in 45.8% of patients who had a stroke, but only 17.9% in the nonstroke group ($P < 0.001$). Thrombus was detected by TEE in 5 (10.4%) patients

Table 1: Demographic characteristics and drug usage of patients

Parameters	Group I (*n*=48)	Group II (*n*=217)	*P*
Sex, male (%)	31 (64.5)	135 (62.2)	0.869
Age (years)	64.8±12.3	63.2±12.8	0.417
Hypertension (%)	31 (64.5)	132 (60.8)	0.743
Diabetes mellitus (%)	14 (29.1)	45 (20.7)	0.249
Hyperlipidemia (%)	21 (43.7)	61 (28.1)	0.039
Smoking (%)	15 (31.2)	55 (25.3)	0.469
CAD history in family (%)	10 (20.8)	33 (15.2)	0.385
Presence of AF (%)	17 (35.4)	171 (78.8)	<0.001
Presence of PFO (%)	22 (45.8)	39 (17.9)	<0.001
Presence of prosthesis valves (%)	4 (8.3)	14 (6.4)	0.432
CAD (%)	12 (25.0)	58 (26.7)	0.859
Systolic dysfunction (%)	6 (12.5)	83 (38.2)	0.001
Vascular disease (%)	3 (6.2)	14 (6.4)	0.629
Renal failure (%)	1 82.0)	11 (5.0)	0.700
Presence of thrombus in TEE	5 (10.4)	34 (15.6)	0.500
Antiaggregant drug use	30 (62.5)	77 (35.4)	0.006
Anticoagulant drug use	14 (29.1)	100 (46.0)	0.037
ACEI/ARB	23 (47.9)	112 (51.6)	0.750
Beta-blocker	23 (47.9)	153 (70.5)	0.004
Calcium channel blocker	14 (29.1)	49 (22.5)	0.351
Statin	14 (29.1)	51 (23.5)	0.459
Spironolactone	3 (6.2)	39 (17.9)	0.049

CAD: Coronary artery disease, PFO: Patent foramen ovale, TEE: Transeosephageal echocardiography, TTE: Transthoracic echocardiography, AF: Atrial fibrillation

in Group I (n = 48) and 34 patients (15.6%) in Group II (n = 217) (P = 0.500).

An analysis of AF types in Group I showed that paroxysmal AF was present in eight patients, persistent AF in four patients, and chronic AF in five patients [Table 2].

Considering other echo parameters, left ventricular EF was significantly higher in the stroke group (56.9 ± 9.19 vs. 51.9 ± 10.87; P = 0.002). Regarding the end-diastolic volume, left atrial, and right atrial diameter, there was no significant difference between the two groups (P = 0.059, 0.081, and 0.061, respectively) [Table 3].

The CHA_2DS_2-VASc score was 3.25 ± 2.06 in Group I and 2.49 ± 1.54 in Group II (P < 0.001).

Beta-blocker use was found to be higher in Group II since the number of patients with AF was correspondingly high. Similarly, oral anticoagulant and antiaggregant use was also significantly higher in Group II. A total of 17 patients were using oral anticoagulants in Group I. Three of them received oral anticoagulation with acetyl salicylic acid combination. Six patients did not receive any treatment. Of the five patients with thrombus, two were using warfarin; two were using acetyl salicylic acid and clopidogrel; and a patient was using acetyl salicylic acid alone [Table 4].

Figure 1 shows a receiver operating characteristic (ROC) curve for CHA_2DS_2-VASc score. According to it, an international normalized ratio (INR) level above 3.5 has a sensitivity of 42% and a specificity of 73% for stroke prediction.

A univariate regression analysis showed that PFO, CHA_2DS_2-VASc category, pulmonary artery pressure, tricuspid insufficiency, diastolic dysfunction, and EF category were significant univariate predictors of stroke. INR level of 3.5 found in the ROC analysis was taken as the cutoff level. EF category was based on the normal EF level of 55%. A multiple regression analysis for the risk factors revealed that PFO, CHA2DS2-VASc category emerged as significant independent predictors of cerebrovascular event [Table 5]. Accordingly, having a PFO increased the cerebrovascular event risk by 4.02 times (95% confidence interval [CI], 1.99–8.11), while a CHA_2DS_2-VASc score above 3.5 increased the same risk by 3.52 times (95% CI, 1.64–7.57).

Table 2: Atrial fibrillation classification of patients

AF classification	Group I (n=48)	Group II (n=217)
Paroxysmal AF	8	65
Persistent AF	4	74
Long-standing persistent AF	-	5
Chronic AF	5	29

AF: Atrial fibrillation

Table 3: Comparison of CHA2D2S VASc scores, echocardiographic, and laboratory parameters of patients

Parameters	Group I (n=48)	Group II (n=217)	P
CHA2DS2-VASc	3.25±2.06	2.49±1.54	0.004
Ejection fraction (%)	56.9±9.19	51.9±10.87	0.002
End-diastolic volume (ml)	94.2±20.5	104.4±35.8	0.059
Left atrium diameter (mm)	42.8±12.5	44.9±6.2	0.081
Right atrium diameter (mm)	38.1±4.2	40.7±5.0	0.061
Pulmonary artery pressure in TTE (mmHg)	37.6±7.6	39.4±10.8	0.458
Left ventricular hypertrophy in TTE	32 (66.6)	155 (71.4)	0.162
Diastolic dysfunction, TTE	24 (50.0)	65 (29.9)	0.086
Mitral insufficiency, TTE	32 (66.6)	160 (73.7)	0.005
Tricuspid insufficiency, TTE	21 (43.7)	157 (72.3)	0.001
Creatinine (mg/dl)	0.99±0.53	1.18±0.96	0.181
Hemoglobine (g/dl)	13.4±1.99	13.5±1.9	0.897
Hemotocrite (%)	40.3±23.5	41.5±25.6	0.457
White blood cell (10^3×µl)	8.4±2.8	7.8±5.7	0.483
Platelets (10^3×µl)	224±68	227±167	0.893
LDL (mg/dl)	117.0±35.0	115.3±30.3	0.810
HDL (mg/dl)	41.6±9.2	42.4±11.5	0.654
Triglycerides (mg/dl)	133.5±47.3	128.4±65.7	0.612

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TTE: Transthoracic echocardiography

Discussion

In a study investigating the risk of stroke based on the CHA_2DS_2-VASc score, which determines the risk of stroke in AF, Olesen *et al*.[9] found a 1-year stroke risk of 0.84 for a CHA_2DS_2-VASc score of 0 point; 1.79 for 1 point; 3.67 for 2 points; 5.75 for 3 points; and 8.18% for 4 points. Therefore, 2016 European Society of Cardiology AF guideline[8] assigned a Class I indication for long-term anticoagulation when the CHA_2DS_2-VASc score is equal to or >2 for men and equal to or >3 for women, and a Class IIa recommendation for a CHA_2DS_2-VASc score of 1 for men and 2 for women. The type of AF is currently not taken into consideration for initiating long-term anticoagulation.

In a study by Paciaroni *et al*.,[10] where 713 patients were compared with 700 controls, patients with CHA_2DS_2-VASc

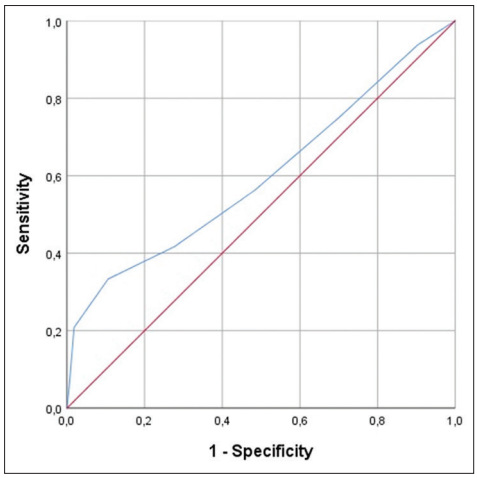

Figure 1: Receiver operating characteristic curve of CHA2DS2-VASc score Area under curve 0.598 (95% Confidence Interval 0.500-0.696)

Table 4: Anticoagulant and antiaggregant usage of stroke patients

	Group I (*n*=48)
Only ASA	14
ASA + varfarin	3
ASA + clopidogrel	6
Only clopidogrel	5
OAC- -warfarin	8
OAC- - apixaban	3
OAC- - rivaroxaban	2
OAC- -edoxaban	1
No treatment	6

ASA: Acetyl salicylic acid, OAC: Oral anticoagulant

Table 5: Multivariate regression analyses of variables

Parameter	Exp (*B*)	95% CI for Exp (*B*)
Patent foramen ovale	4.02	1.99-8.14
CHA2DS2-VASc category	3.52	1.64-7.57

CI: Confidence ınterval

score ≥4 were shown to be significantly higher in the patient group (85.1% vs. 45.4%; $P = 0.0001$). However, that study did not specify average scores. In a multivariate analysis, the CHA_2DS_2-VASc score was found to be 1.72 (1.58–1.88).

In a study comparing the CHA2DS2-VASc scoring system and other scoring systems,[11] the most useful score for determining the risk of stroke was the CHA_2DS_2-VASc score, with a score of 2 and above increasing the risk. Accordingly, 2.2% (5/227) of the patient population had a score of 1 ($P = 0.27$), whereas a score of 2 or above was associated with a thromboembolism rate of 14.67% (333/2300) ($P = 0.0005$). In our study, the mean CHA_2DS_2-VASc score of both groups was above 2, but was found to be 3.25 ± 2.06 in patients with stroke. Studies similar to our study generally recruited patients with AF. However, some authors have advocated that the components of the CHA_2DS_2-VASc score are some general thromboembolism risk factors, which are not specific to AF. For this reason, it is considered that patients without AF but higher CHA_2DS_2-VASc scores have a higher stroke risk than those with lower CHA_2DS_2-VASc scores. Our study data also support this notion. Thus, if a patient has a high CHA_2DS_2-VASc score but no AF, he or she may return with cerebrovascular events even within a short period of time. In addition, another study, where coagulation factors related to LAA thrombus were studied,[12] 32 patients with a history of LAA thrombus were compared with 32 controls. Recurrent thromboembolic events were observed in ten patients in the LAA thrombus group and seven patients in the control group. These events were shown to be associated with high thrombin generation, fibrinogen, plasminogen activator inhibitor-1, and soluble CD40 ligand. Since our study is a retrospective study, coagulation factors could not be investigated, but it should be kept in mind that these factors should be screened in patients who do not have any history of AF but have sustained a thrombotic event. In a study[13] investigated the presence of left atrial thrombus in patients with previous stroke, and found a rate of 5.5% in patients with sinus rhythm. In our study, the rate of thrombus was 10.4% (5/48) in the stroke group. Of these, two patients did not have a history of AF, while the remainder patients had AF. All of five patients were receiving an anticoagulant or antiplatelet.

Our study also detected a significantly higher rate of PFO in the stroke group. PFO is a defect at the interatrial septum, which has been linked with cryptogenic stroke. The presumed mechanism of cryptogenic stroke caused by a PFO is the migration of thrombus from the venous side of the circulation to the left atrium with subsequent systemic embolism, a condition called paradoxical embolization. Provocative maneuvers and preexisting cardiopulmonary disease can cause elevation in right atrial pressures, leading to right-to-left shunting through a PFO. If a patient has cryptogenic stroke and no other risk factor for stroke, the patient should be evaluated for PFO closure. Ozdemir *et al*.[14] examined the association of obstructive sleep apnea and PFO in two patients with stroke. Increased blood viscosity and platelet aggregation in patients with obstructive sleep apnea were implicated as predisposing conditions for clot formation. In a large patient-based meta-analysis, PFO closure and antiplatelet therapy were shown to provide a significant reduction in ischemic stroke, especially among patients under 60 years of age.[14] In another study by Saver *et al*.,[15] PFO closure in adults with a history of cryptogenic stroke was shown to significantly reduce ischemic stroke compared to medical treatment. These data explain the emergence of PFO as one of the important causes of stroke in our study.

Conclusions

The CHA_2DS_2-VASc score increases the risk of stroke in a broader sense, but not only in patients with AF. It is reasonable to think that the higher the score, the higher the risk of stroke. Furthermore, the presence of PFO in a patient is a facilitating factor for stroke, which may be considered for closure in the case of recurrent stroke episodes.

Study limitations

Our study was a retrospective study, so we had not any data about advanced echocardiographic parameters such as left atrial appendage strain rate. We had less patients with stroke and we did not perform Holter monitoring to exclude paroxysmal AF. We evaluate patients with patient history and clinic electrocardiogram.

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Conflicts of interest

There are no conflicts of interest.

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