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ORIGINAL COMMUNICATION

CHA_2DS_2-VASc score and prognosis in ischemic strokes with atrial fibrillation

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Abstract The CHA_2DS_2-VASc score was developed to improve stroke risk stratification in atrial fibrillation (AF) patients. We sought to analyze the distribution and prognostic value of the CHA_2DS_2-VASc score in a cohort of ischemic stroke patients with AF. In total, 439 consecutive stroke patients with AF were studied. The CHA_2DS_2-VASc score was calculated according to clinical status before stroke onset. Poor outcome was defined as a modified Rankin score of 3 to 6 at 3 months. Association between CHA_2DS_2-VASc score and poor outcome was analyzed using logistic regression analysis. In 95.6% of patients, CHA_2DS_2-VASc was >1 and only 41.8% of those with previously diagnosed AF were using oral anticoagulation at the time of the stroke. Poor outcome was found in 53.1% of the patients. In univariate analysis age, female sex, current smoking, previous stroke, CHA_2DS_2-VASc score, and stroke severity were associated with outcome. In multivariate analysis, CHA_2DS_2-VASc score was independently associated with poor outcome [OR 1.36 (95% CI: 1.14–1.62), $P = 0.001$] as well as NIHSS [OR 1.22 (95% CI: 1.17–1.26), $P < 0.001$]. After removing stroke severity, therapeutic anticoagulation was also associated with stroke prognosis [OR 0.45 (95% CI: 0.23–0.86), $P = 0.016$]. Most patients with ischemic stroke and AF have a high CHA_2DS_2-VASc score. Independent of stroke severity, CHA_2DS_2-VASc score is associated with 3-month outcome. Despite all the available information and guidelines, our AF patients are clearly undertreated.

Keywords CHA_2DS_2-VASc · Stroke · Atrial fibrilation · Prognosis · Anticoagulation

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Introduction

Clinical factors such as age, stroke severity, atrial fibrillation (AF), female sex, diabetes, and congestive heart failure (CHF) have been associated with poor prognosis after an ischemic stroke (IS) [21, 26]. In addition, AF is the main cause of IS in the elderly and is associated with a high mortality and disability rate [12, 17]. Large randomized trials have shown that adjusted-dose warfarin reduces stroke risk by approximately 60% compared with no antithrombotic treatment and by 40% compared to antiplatelet

Table 1 CHA_2DS_2-VASc acronym score

CHA_2DS_2-VASc acronym	Score
Congestive heart failure/LV dysfunction (EF <35%)	1
Hypertension	1
Aged ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease (prior myocardial infarct, complex aortic plaque and peripheral artery disease)	1
Aged 65–74	1
Sex (female)	1

LV left ventricle, *EF* ejection fraction

therapy [10, 19]. Nonetheless, most patients with AF are not taking warfarin at the time of first stroke [6].

The recently published CHA_2DS_2-VASc score, developed to improve stroke risk stratification in patients with AF, has proved to more accurately predict stroke risk, even in patients using oral anticoagulation [14].

This new schema includes more variables (e.g., sex) and gives a double score to advanced age or previous history of stroke or TIA (Table 1). The main consequence of applying the CHA_2DS_2-VASc score in the population is the reclassification as high risk of almost 50% of patients classified as having intermediate risk under the previous $CHADS_2$ scheme, thereby increasing the number of subjects receiving anticoagulation therapy [15].

The aim of the study is to describe the CHA_2DS_2-VASc scoring in a cohort of patients with AF and IS or transient ischemic attack (TIA) registered in our database and to analyze its potential utility as a prognostic tool.

Materials and methods

From January 2005 to March 2011, 453 patients with a previous modified Rankin Score (mRS) <3, acute IS or TIA, and AF were prospectively registered in the BasicMar database [20], an ongoing hospital register of patients with stroke. We excluded only 14 cases, due to a history of cardiac valve replacement ($n = 8$) and lost to follow-up after hospital discharge ($n = 6$). The final cohort was 439 patients. In 282 cases (64.2%), AF was previously known and in 157(35.8%) was diagnosed with the episode of IS. Following CC/AHA/ESC clinical guidelines, AF was defined as the absence of P waves in the electrocardiogram, with the isoelectric line being replaced by irregular high-frequency oscillations (f waves) and wholly irregular ventricular response. We considered AF when it was documented by an EKG, detected during cardiac monitoring or a previous history based on medical reports of paroxysmal AF.

Clinical methodology

A neurologist diagnosed IS and TIA patients, following the World Health Organization definitions.

All patients were studied with cranial computerized tomography (CT). Further neuroimaging using CT or cranial magnetic resonance (MR) was performed during hospitalization in patients with no lesion in the initial CT.

Initial stroke severity was directly assessed at hospital admission by a trained neurologist using the National Institutes of Health Stroke Scale (NIHSS) [7].

All patients had a complete cardiac study that included 12-lead ECG, chest X-ray and echocardiography. Antithrombotic treatment was started within the first 6 h after stroke onset, following international consensus on neurovascular diseases. Patients with cardioembolic strokes were treated with anticoagulation starting immediately after TIA or minor strokes but postponed up to several weeks after major stroke with significant infarction upon neuroimaging (e.g., more than a third of the MCA territory); antiplatelet therapy was used until anticoagulation could be reintroduced. Existing oral anticoagulation therapy was maintained or stopped using the same criteria. Beginning in 2002, intravenous thrombolytic treatment with recombinant tissue plasminogen activator (rTPA) was administered based on the European Medicines Evaluation Agency Criteria (SITS-MOST) [28] within the first 3 h after stroke onset; following the results of the ECASS-III trial, the time window for rTPA was extended to 4.5 h in 2008 [9]. After thrombolysis, antithrombotic treatment was started at 24 h.

The CHA_2DS_2-VASc score and $CHADS_2$ score were calculated for each patient according to clinical status before onset of stroke. Vascular risk factors were obtained from the patient, relatives, caregivers, or previous medical records. Risk factors were collected in a structured questionnaire, as follows: arterial hypertension (evidence of at least two elevated blood pressure measurements, systolic >140 mm Hg or diastolic >90 mm Hg, recorded on different days before stroke onset; a physician's diagnosis; or use of medication); diabetes (a physician's diagnosis or use of medication); hyperlipidemia (a physician's diagnosis, use of medication, serum cholesterol concentration >220 mg/dL, LDL cholesterol >130 mg/dL, or serum triglyceride concentration >150 mg/dl); current smoking habits; previous ischemic stroke or TIA according to medical records; coronary artery disease (CAD), e.g., prior myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery; previous history of congestive heart failure or left ventricular ejection fraction (LVEF) <35%; and peripheral arterial disease (PAD), which includes previous history of intermittent claudication, arterial thrombosis, and percutaneous or surgical intervention in the thoracic, abdominal aorta or

lower extremity vessels. We also recorded age, sex, and antithrombotic treatment at the time of stroke onset, which was categorized into four groups [none, antiplatelets, therapeutic anticoagulation (Th-OAC) if initial INR $\geq$2, and subtherapeutic anticoagulation (SubTh-OAC) if initial INR <2]. Data at 90 days after stoke onset were obtained from direct patient examination or phone contact. The endpoint of the study was poor outcome, defined as moderate-to-severe disability or death (mRS 3 to 6) at 90 days.

Statistical analysis

Statistical analysis was performed using the SPSS 12.0 software package. Categorical variables are expressed as real numbers and percentages and quantitative variables are expressed with means and standard deviations.

We first performed univariate analysis to test the association between the study variables and stroke outcome using *T* test or Mann–Whitney test (when normal distribution was difficult to assume) for continuous variables and Chi-square for categorical variables.

Variables that reached statistical significance ($P < 0.1$) and pretreatment were included in a multivariate analysis using stepwise logistic regression. To avoid collinearity, $CHADS_2$ and variables already included in the CHA_2DS_2-VASc score were removed. Each antithrombotic pretreatment category (antiplatelets, Th-OAC, SubTh-OAC) was compared with no pretreatment. Because of the strong association between stroke severity and outcome, a second multivariate analysis was undertaken after removing NIHSS score (Table 4). Statistical significance was set at $P < 0.05$. All analyses were two-tailed. Anonymized study data was collected from our clinical protocol, which was approved by the local ethics committee. All patients signed the informed consent.

Results

Patient characteristics and CHA_2DS_2-VASc score

Of the final cohort of 439 patients, 270 (61.5%) were female and 326 (74.3%) were 75 years or older. Final diagnosis was IS in 385 patients and TIA in 54. Only 4.4% of patients in our cohort had a CHA_2DS_2-VASc score $\leq$1. Distribution of CHA_2DS_2-VASc score with pretreatments and outcome rates is detailed in Table 2. The most frequent scores were 4 (29.2%) and 5 (24.6%).

Of patients with previously known AF, 17.7% were not using any antithrombotic treatment (both of the patients with CHA_2DS_2-VASc = 0 and 28.6% of patients with CHA_2DS_2-VASc = 1), 40.4% were using antiplatelets, and 41.8% were using oral anticoagulants. Notably, only 20.2% of the total cohort had INR levels within the therapeutic range.

Outcome

Poor outcome was found in 233 patients (53.1%). The univariate analysis is summarized in Table 3. Variables associated with poor outcome were age ($P < 0.001$), female sex [OR 1.57 (95% CI: 1.07–2.32) $P = 0.022$], previous stroke [OR 2.41 (95% CI: 1.39–4.17) $P = 0.001$], stroke severity ($P < 0.001$), previous antithrombotic treatment ($P = 0.011$), $CHADS_2$ score ($P = 0.012$) and CHA_2DS_2-VASc score ($P = 0.001$).

In the multivariate analysis, CHA_2DS_2-VASc score was found to be an independent predictor of poor outcome [OR 1.36 (95% CI: 1.14–1.62), $P = 0.001$], as was stroke severity [OR 1.22, (95% CI: 1.17–1.26), $P < 0.001$]. Current smoking was included in the model due to a trend in the univariate analysis, but after adjustment in the multivariate model this association did not reach statistical significance.

Removing stroke severity from the analysis (Table 4) did not modify the association between CHA_2DS_2-VASc and stroke outcome [OR 1.29 (95% CI: 1.12–1.49), $P = 0.001$]. Moreover, Th-OAC compared with no antithrombotic treatment appeared as a protective factor for stroke outcome [OR 0.45 (95% CI: 0.23–0.86), $P = 0.016$].

Discussion

The CHA_2DS_2-VASc score may be the most accurate predictor of thromboembolism in AF patients currently available to us [14, 24]. In an effort to assess its predictive value for IS and TIA, our study analyzed the CHA_2DS_2-VASc score of patients diagnosed with AF previous to the IS/TIA registered in our database. We found that most had high scores and that CHA_2DS_2-VASc score is associated with 3-month outcome.

CHA_2DS_2-VASc score in IS patients

As we expected, only 4.4% of our cohort of AF patients with IS/TIA had a CHA_2DS_2-VASc score $\leq$1, which is mainly due to the older age and high prevalence of female sex, hypertension, diabetes, and CHF in this subtype of the stroke population. This percentage is higher than the 0.6% population risk per year reported in the validation study of the CHA_2DS_2-VASc score; [16] however, we cannot calculate the risk of stroke in this subgroup because the CHA_2DS_2-VASc score distribution in our general

Table 2 Distribution of the CHA_2DS_2-VASc scores in our cohort related to pretreatment and poor outcome

CHA_2DS_2-VASc score	*n* (%)	Pretreatment, *n* (%)	Poor outcome, *n* (%)
0	2 (0.5)	None 2 (100)	2 (100)
1	17 (3.9)	None 10 (58.8)	3 (17.6)
		AP 3 (17.6)	
		SubTh-OAC 1 (5.9)	
		Th-OAC 3 (17.6)	
2	41 (9.3)	None 27 (65.9)	19 (46.3)
		AP 7 (17.1)	
		SubTh-OAC 5 (12.2)	
		Th-OAC 2 (4.9)	
3	63 (14.4)	None 33 (52.4)	30 (47.6)
		AP 17 (27)	
		SubTh-OAC 9 (14.3)	
		Th-OAC 4 (6.3)	
4	128 (29.2)	None 49 (38.2)	68 (53.1)
		AP 53 (41.4)	
		SubTh-OAC 12 (9.4)	
		Th-OAC 14 (10.9)	
5	108 (24.6)	None 26 (24.1)	53 (49.1)
		AP 44 (40.7)	
		SubTh-OAC 20 (18.5)	
		Th-OAC 18 (16.7)	
6	51 (11.6)	None 8 (15.7)	35 (68.6)
		AP 26 (51)	
		SubTh-OAC 10 (19.6)	
		Th-OAC 7 (13.7)	
7	22 (5)	None 2 (9.1)	18 (81.8)
		AP 8 (36.4)	
		SubTh-OAC 4 (18.2)	
		Th-OAC 8 (36.4)	
8	7 (1.6)	None 1 (14.3)	5 (71.4)
		AP 4 (57.1)	
		SubTh-OAC 1 (14.3)	
		Th-OAC 1 (14.3)	

AP antiplatelets, *Th-OAC* therapeutic-oral anticoagulation, *SubTh-OAC* Subtherapeutic-oral anticoagulation

population is not known. Therefore, we can only report the score distribution once the stroke has happened.

Prognostic value

To the best of our knowledge, this is the first study to analyze the usefulness of the CHA_2DS_2-VASc score in predicting stroke outcome. Overall, we found that each point increase in the CHA_2DS_2-VASc scale is associated with a 36% increase in the risk for poor 90-day outcome, independent of stroke severity. Although $CHADS_2$ schema might also have a prognostic value according to our results we aimed to analyse the most accurate and comprehensive CHA_2DS_2-VASc score [16, 22, 24].

Surprisingly, we found that both patients in the CHA_2DS_2-VASC = 0 category, with a previous unknown AF, had a bad outcome. Upon further examination, we found that each of these patients had an important comorbidity that was not reflected in the score (e.g., HIV infection and a severe pulmonary hypertension due to chronic obstructive pulmonary disease).

Several factors included in the CHA_2DS_2-VASc score—such as age [2, 3, 11, 13], diabetes [3, 5, 11], CHF [2, 8, 21, 25], and ischemic heart disease [23]—have been previously related with stroke prognosis. Female sex, which for the first time has been included in this risk stratification tool, was associated with higher mortality in strokes due to AF in a previous study from our group [4, 26]. Another variable clearly expected to be associated with prognosis in our study was initial stroke severity [1, 2, 12, 26].

According to our results, CHA_2DS_2-VASc is a useful score to predict not only the risk of IS but also a worse

Table 3 Baseline characteristics of stroke patients and univariate analysis between the study variables and stroke outcome

	Total cohort $n = 439$	Poor outcome $n = 233$	Good outcome $n = 206$	*P*
Mean age, years	78.71 ± 8.74	81.09 ± 8.23	76.02 ± 8.54	<0.001*
Sex, female	270 (61.5)	155 (66.5)	115 (55.8)	0.022*
Smoking	35 (8)	13 (5.6)	22 (10.7)	0.054*
Hypertension	339 (77.2)	182 (78.1)	157 (76.2)	0.636
Diabetes	137 (31.2)	71 (30.5)	66 (32)	0.724
Hyperlipidemia	147 (33.5)	72 (30.9)	75 (36.4)	0.258
CHF	114 (26)	55 (26.7)	59 (25.3)	0.743
PAD	40 (9.1)	18 (7.7)	22 (10.7)	0.283
CAD	85 (19.4)	43 (18.5)	42 (20.4)	0.609
Previous stroke	71 (16.2)	50 (21.5)	21 (10.2)	0.001*
Stroke severity[a]	6 [3–16]	14 [5–20]	3 [1–6]	<0.001*
$CHADS_2$[a]	2 [2–3]	3 [2–3]	2 [1–3]	0.012*
CHA_2DS_2-VASc[a]	4 [3–5]	4 [4–5.5]	4 [3–5]	0.001*
Pretreatments[b]				0.011*
None	158 (36)	81 (34.8)	77 (37.4)	
Antiplatelets	162 (36.9)	101 (43.3)	61 (29.6)	
SubTh-OAC	62 (14.1)	28 (12.0)	34 (16.5)	
Th-OAC	57 (13)	23 (9.9)	34 (16.5)	

Age is presented as mean value ± standard deviation. Values in parentheses are percentages

CHF congestive heart failure, *PAD* peripheral arterial disease, CAD, coronary artery disease, *SubTh-OAC* subtherapeutic-oral anticoagulation, *Th-OAC* Therapeutic-oral anticoagulation

* Indicates a statistically significant result

[a] Stroke severity represented as NIHSS value, $CHADS_2$ and CHA_2DS_2-VASc are expressed as median values and quartile values q1–q3 in brackets

[b] Pretreatment of all patients

Table 4 Logistic regression model including variables selected from univariate analysis, after removing stroke severity

Multivariate analysis	OR (95% CI)	*p*
CHA_2DS_2-VASc	1.29 (1.12–1.49)	0.001*
Current smoking	0.74 (0.34–1.57)	0.428
Antithrombotic pre-treatment		
Therapeutic anticoagulation	0.45 (0.23–0.86)	0.016*
Subtherapeutic anticoagulation	0.59 (0.32–1.11)	0.100
Antiplatelets	1.18 (0.73–1.90)	0.485

* Indicates a statistically significant result

outcome. This finding could help physicians to choose a more intensive treatment in patients with a recent diagnosis of AF, especially in those with a good quality of life, to avoid further disability and dependency.

Antithrombotic pretreatment

In our series, which excluded previously disabled patients, most cases with previous known AF ($n = 282$) had high CHA_2DS_2-VASc scores and yet only 41.8% were using oral anticoagulation at the time of the stroke and only 20.2% had appropriate INR levels. Up to 17.7% were not receiving any antithrombotic medication.

Our results agree with previous studies that reported a low proportion of anticoagulation use in patients with a stroke due to AF [6, 19].

A low rate of intervention by the treating physicians, the need to monitor INR, the narrow therapeutic margin, the related drug and lifestyle limitations, and the overall fear of major bleeding could be among the reasons for the extensive underuse of oral anticoagulation therapy in our population [19].

Antithrombotic treatment was not associated with stroke prognosis in the multivariate model. However, after removing initial severity from the analysis, Th-OAC was independently associated with better outcome. This beneficial role reflects its protective effect with respect to the severity of the initial stroke. These findings concur with previous studies that have found a lower stroke severity and mortality in AF patients with therapeutic levels of

anticoagulation, compared with subtherapeutic levels or antiplatelet treatment [6, 18, 27].

Limitations

Some limitations of our study must be mentioned. First, it has the shortcomings of a retrospective study design, but on a prospective identification of consecutive stroke patients. Second, we perform a standardised outcome assessment at 90 days after stroke onset. This analysis does not provide information about long-term functional status.

Conclusions

A high CHA_2DS_2-VASc score reflects an increased risk of IS with poor short-term outcome. Despite the high proportion of CHA_2DS_2-VASc score ≥ 2 at the time of the stroke, patients had been undertreated with oral anticoagulation.

Finally, in patients with AF, the CHA_2DS_2-VASc score is not only useful to stratify the risk of embolic events but also patient prognosis after an IS. This offers to all physicians a robust tool in our efforts to be more proactive in the primary prevention of stroke and other embolic events.

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Conflict of interest None.

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