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ORIGINAL RESEARCH

CHADS$_2$ score has a better predictive value than CHA$_2$DS$_2$-VASc score in elderly patients with atrial fibrillation

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Aim: The study aims to compare the ability of CHA$_2$DS$_2$-VASc (defined as congestive heart failure, hypertension, age $\geq$75 years [two scores], type 2 diabetes mellitus, previous stroke, transient ischemic attack, or thromboembolism [TE] [doubled], vascular disease, age 65–74 years, and sex category) and CHADS$_2$ (defined as congestive heart failure, hypertension, age $\geq$75 years, type 2 diabetes mellitus, previous stroke [doubled]) scores to predict the risk of ischemic stroke (IS) or TE among patients with nonvalvular atrial fibrillation (NVAF).

Methods: A total of 413 patients with NVAF aged $\geq$65 years, and not on oral anticoagulants for the previous 6 months, were enrolled in the study. The predictive value of the CHA$_2$DS$_2$-VASc and CHADS$_2$ scores for IS/TE events was evaluated by the Kaplan–Meier method.

Results: During a follow-up period of 1.99$\pm$1.29 years, 104 (25.2%) patients died and 59 (14.3%) patients developed IS/TE. The CHADS$_2$ score performed better than the CHA$_2$DS$_2$-VASc score in predicting IS/TE as assessed by c-indexes (0.647 vs 0.615, respectively; $P<0.05$). Non-CHADS$_2$ risk factors, such as vascular disease and female sex, were not found to be predictive of IS/TE (hazard ratio 1.518, 95% CI: 0.832–2.771; hazard ratio 1.067, 95% CI: 0.599–1.899, respectively). No differences in event rates were found in patients with the CHADS$_2$ scores of 1 and 2 (7.1% vs 7.8%). It was observed that patients with a CHADS$_2$ score of $\geq$3 were most in need of anticoagulation therapy.

Conclusion: In patients with NVAF aged $\geq$65 years, the CHADS$_2$ score was found to be significantly better in predicting IS/TE events when compared to the CHA$_2$DS$_2$-VASc score. Patients with a CHADS$_2$ score of $\geq$3 were associated with high risk of IS/TE events.

Keywords: NVAF, vascular disease, sex, elderly

Background

Atrial fibrillation (AF) is a common cardiac rhythm disorder, which is responsible for substantial morbidity and mortality. The prevalence of nonvalvular atrial fibrillation (NVAF) increases with advancing age and is considered to be an important risk factor for ischemic stroke (IS) and thromboembolism (TE).[1] Anticoagulation is the cornerstone for AF management. However, various studies have reported the underuse of oral anticoagulation (OAC) among elderly patients with NVAF,[2–4] and the situation is more grim in the People's Republic of China.[5]

Both CHADS$_2$ (defined as congestive heart failure, hypertension, age $\geq$75 years, type 2 diabetes mellitus [DM], previous stroke [doubled]) and CHA$_2$DS$_2$-VASc (defined as congestive heart failure, hypertension, age $\geq$75 years [two scores], type 2 diabetes mellitus, previous stroke, transient ischemic attack [TIA], or TE [doubled], vascular disease, age 65–74 years, and sex category) scores are well-validated tools for the

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estimation of stroke risk in patients with AF. CHA_2DS_2-VASc improves the precision of identifying "low-risk" patients.[6] Age is a very important factor of stroke, and it is unclear which score is better suited for use in elderly patients.[7] The goal of the present study was to compare the utility of CHA_2DS_2-VASc and $CHADS_2$ scores in predicting IS/TE for the patients with NVAF aged ≥65 years.

Methods

Ethical approval was obtained from the Hospital Ethical Committee of Beijing Friendship Hospital. A procedure-oriented informed consent form was signed by each patient. A retrospective study was conducted by collecting patient data available at Beijing Friendship Hospital for the period between January 1, 2011, and June 30, 2013. It was possible to retrieve the data pertaining to individual patients as all data at our hospital are linked to a unique, permanent, and personal registration number, which is assigned to every patient. Patients with NVAF aged ≥65 years, and not on OAC for the previous 6 months, were enrolled in the study. Diagnosis of AF was based on electrocardiography (12-lead electrocardiography) or 24-hour Holter monitoring. Patients with valvular AF, rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, and mitral valve repair and those receiving hemodialysis or on OAC were excluded from the study.

The study consisted of baseline and follow-up periods. The date of the qualifying AF diagnosis made between January 1, 2011, and June 30, 2013, was designated as the index date. Data from the baseline period, which ended on the index date, were used to obtain information about each patient's medical history. Follow-up was performed by going through medical records available in the hospital database. Data from the follow-up period, which started from the day after the index date and ended on March 1, 2015, were used to assess the risk of IS/TE. All patients who were lost to follow-up and those who took OAC during the study period were excluded.

The primary end point was the development of IS or TE events (ie, TIA or peripheral embolism). The secondary end point was all-cause death.

IS was defined as a new, sudden focal neurological deficit resulting from a presumed cerebrovascular cause that persisted >24 hours and was not attributable to other identifiable causes, such as tumor and seizure. Events that involved symptoms that lasted <24 hours were considered as TIA. Brain imaging was sought in each case to distinguish hemorrhagic from IS. Peripheral artery embolism was defined as abrupt vascular insufficiency associated with clinical or radiographic evidence of peripheral arterial occlusion in the absence of other likely causes. Presence of vascular disease was identified from previous diagnoses, including myocardial infarction (MI), peripheral artery disease, and complex aortic plaque.

Data were expressed as mean ± SD. The analyses were performed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA), except net reclassification improvement (NRI), which was analyzed using SAS9.2. Mean values and proportions of variables were compared using unpaired Student's t-test, analysis of variance, and chi-square test. The IS/TE risk was assessed using Cox regression analysis. The cumulative incidence curve of IS/TE was plotted via the Kaplan–Meier method, with statistical significance examined using the log-rank test. We assessed the predictive accuracies of the $CHADS_2$ and CHA_2DS_2-VASc scores by calculating c-indices on the basis of receiver operating characteristic (ROC) curves and NRI. Areas under the ROC curves for these two scoring systems were compared using DeLong's test. Statistical significance was defined as a P-value of <0.05.

Results
Characteristics of patients

Baseline characteristics of the study population are listed in Table 1. The mean age of patients was 80.82±7.34 years, with 70.9% being male. The median score of CHA_2DS_2-VASc and $CHADS_2$ was 4.77 and 2.95, respectively. Hypertension was the most prevalent comorbidity and was noted in 77.5% of patients. A total of 36.8% had a history of previous stroke or TIA. During the follow-up period of 1.99±1.29 years, 104 (25.2%) patients died and 59 (14.3%) patients had an IS/TE event.

On the basis of the $CHADS_2$ score, 1.7%, 10.2%, and 86.3% of patients were classified as low risk (0 point), intermediate risk (1 point), and high risk (2–6 points), respectively.

Comparison between $CHADS_2$ and CHA_2DS_2-VASc scores

Both the $CHADS_2$ and CHA_2DS_2-VASc scores were the significant predictors of IS after adjusting for age and sex. Cox regression model improved from 1.286 (95% CI: 1.086–1.523) to 1.438 (95% CI: 1.187–1.743) when the $CHADS_2$ score was used for stroke risk categorization instead of the CHA_2DS_2-VASc score.

Of the components of $CHADS_2$ and CHA_2DS_2-VASc scores, cardiac failure and previous stroke/TIA were strongly associated with the primary end point (hazard ratio [HR] 2.253, 95% CI: 1.240–4.092; HR 2.555, 95% CI: 1.408–4.635, respectively). Age was also found to be associated with IS/TE

Table 1 Baseline characteristics of patients with AF by CHADS$_2$ scores

Variable	Total (n=413)	CHADS$_2$ score 0 (n=7)	CHADS$_2$ score 1 (n=42)	CHADS$_2$ score ≥2 (n=364)	P-value
Age (years), mean ± standard deviation	80.82±7.34	68.29±2.81	73.90±7.46[a]	81.87±6.71[a]	0.000
Components of CHA$_2$DS$_2$-VASc, n (%)					
Cardiac failure	99 (24.0)	0 (0)	2 (4.8)[a]	97 (26.7)[a,b]	0.015
Hypertension	320 (77.5)	0 (0)	20 (47.6)[a]	300 (82.4)[a,b]	0.000
≥75 years	343 (83.1)	0 (0)	15 (35.7)[a]	328 (90.1)[a,b]	0.000
DM	149 (36.1)	0 (0)	5 (11.9)[a]	144 (39.6)[a,b]	0.000
Previous stroke/TIA	152 (36.8)	0 (0)	0 (0)[a]	152 (41.8)[a,b]	0.000
Vascular disease	221 (53.5)	1 (14.3)	18 (42.9)[a]	202 (55.5)[a]	0.033
65–74 years	70 (16.9)	7 (100)	27 (64.3)[a]	36 (9.9)[a,b]	0.000
Sex category (female)	119 (28.8)	1 (14.3)	19 (45.2)[a]	99 (27.2)[a,b]	0.035
Antiplatelet	282 (68.3)	5 (71.4)	30 (71.4)	247 (67.9)	0.630
CHA$_2$DS$_2$-VASc, n (%)					
1	5 (1.4)	5 (71.4)	0 (0)	0 (0)	
2	13 (3.1)	2 (28.6)	11 (26.2)	0 (0)	
3	77 (18.6)	0 (0)	25 (59.5)	52 (14.3)	
4	96 (23.2)	0 (0)	6 (14.3)	90 (24.7)	
5	79 (19.1)	0 (0)	0 (0)	79 (21.7)	
6	88 (21.3)	0 (0)	0 (0)	88 (24.2)	
7	40 (9.7)	0 (0)	0 (0)	40 (11.0)	
8	14 (3.4)	0 (0)	0 (0)	14 (3.8)	
9	1 (0.2)	0 (0)	0 (0)	1 (0.3)	

Notes: CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, type 2 DM, previous stroke (doubled); CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 years (two scores), type 2 DM, previous stroke, TIA, or TE (doubled), vascular disease, age 65–74 years, and sex category. [a]Compared to patients with CHADS$_2$ score 0, $P<0.05$. [b]CHA$_2$DS$_2$-VASc score ≥2 compared to patients with CHA$_2$DS$_2$-VASc score 1, $P<0.05$.
Abbreviations: DM, diabetes mellitus; TE, thromboembolism; TIA, transient ischemic attack.

during follow-up. However, hypertension, DM, vascular disease, and female sex were not found to be predictive of IS/TE (Tables 2 and 3). Among patients with the vascular disease, peripheral arterial disease significantly increased the risk of stroke by 2.71-fold. Previous MI was not a significant predictor of IS/TE.

Figure 1 shows the ROC curves of CHADS$_2$ and CHA$_2$DS$_2$-VASc scores in predicting IS/TE. The c-indices on the basis of area under the ROC curves for the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were 0.647 (95% CI: 0.599–0.693) and 0.615 (95% CI: 0.566–0.662), respectively. The difference was statistically significant in favor of the CHADS$_2$ score (DeLong's test, P-value =0.0498–0.05, NRI =0.237). The cut-off value of CHADS$_2$ score was 2.5, with a specificity of 0.537 and a sensitivity of 0.780.

CHADS$_2$ score of ≥3 identified a true high-risk cohort

The Kaplan–Meier curve of freedom from IS is shown in Figure 2. Patients with a CHADS$_2$ score of 0 had no stroke

Table 2 IS/TE risk of CHADS$_2$ components from Cox regression analyses

Variables	IS/TE risk	
	HR (95% CI)	P-value
Cardiac failure	2.253 (1.240–4.092)	0.008
Hypertension	1.033 (0.537–1.989)	0.922
Age	1.038 (1.000–1.076)	0.047
DM	1.419 (0.801–2.517)	0.231
Previous stroke/TIA	2.555 (1.408–4.635)	0.002
CHADS$_2$ score	1.438 (1.187–1.743)	0.000

Note: CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, type 2 DM, previous stroke (doubled).
Abbreviations: DM, diabetes mellitus; HR, hazard ratio; IS, ischemic stroke; TE, thromboembolism; TIA, transient ischemic attack; CI, confidence interval.

Table 3 IS/TE risk of CHA$_2$DS$_2$-VASc components from Cox regression analyses

Variables	IS/TE risk	
	HR (95% CI)	P-value
Cardiac failure	2.253 (1.240–4.092)	0.008
Hypertension	1.033 (0.537–1.989)	0.922
Age	1.038 (1.000–1.076)	0.047
DM	1.419 (0.801–2.517)	0.231
Previous stroke/TIA	2.555 (1.408–4.635)	0.002
Vascular disease	1.518 (0.832–2.771)	0.174
Previous MI	0.598 (0.323–1.108)	0.102
PAD	2.717 (1.395–5.294)	0.003
Female	1.067 (0.599–1.899)	0.826
CHA$_2$DS$_2$-VASc score	1.286 (1.086–1.523)	0.004

Note: CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 years (two scores), type 2 DM, previous stroke, TIA, or TE (doubled), vascular disease, age 65–74 years, and sex category.
Abbreviations: DM, diabetes mellitus; HR, hazard ratio; IS, ischemic stroke; MI, myocardial infarction; PAD, peripheral artery disease; TE, thromboembolism; TIA, transient ischemic attack; CI, confidence interval.
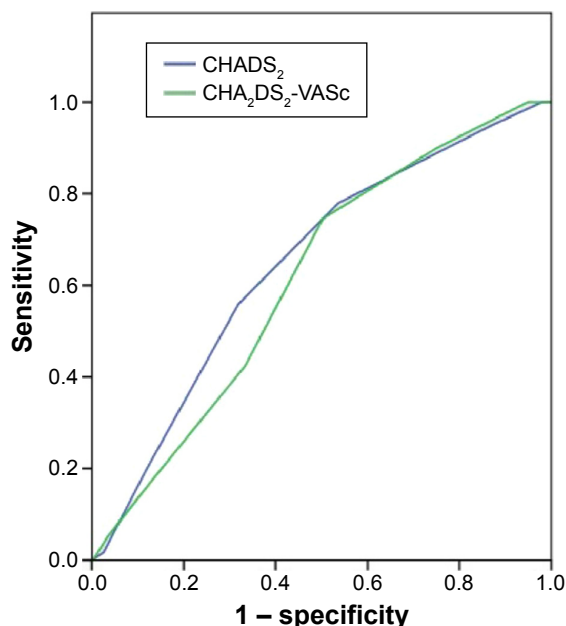
Figure 1 ROC curves of CHADS$_2$ and CHA$_2$DS$_2$-VASc scores in predicting IS/TE.
Notes: CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, type 2 DM, previous stroke (doubled); CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 years (two scores), type 2 DM, previous stroke, TIA, or TE (doubled), vascular disease, age 65–74 years, and sex category.
Abbreviations: DM, diabetes mellitus; IS, ischemic stroke; ROC, receiver operating characteristic; TE, thromboembolism; TIA, transient ischemic attack.

event. Patients with a CHADS$_2$ score of 2 had a similar event rate to those with a CHADS$_2$ score of 1 during the follow-up period (7.1% vs 7.8%; *P*=0.887). Compared with a CHADS$_2$ score of 1, patients with a CHADS$_2$ score of 3, 4, 5, or 6 had a higher event rate (14.4%, 23.1%, 24.4%, and 10%, respectively).
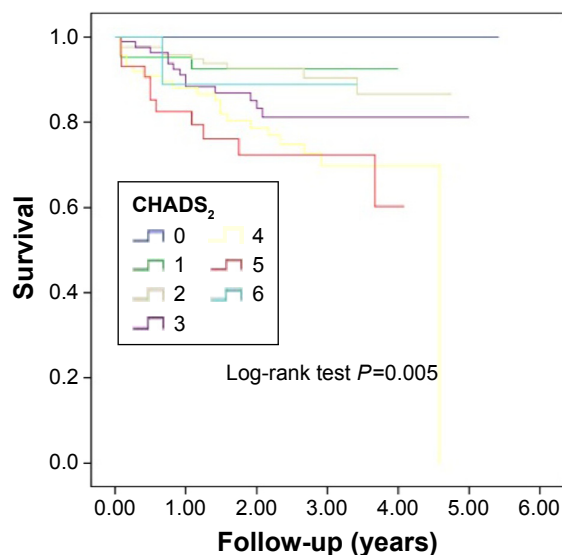

Figure 2 The Kaplan–Meier curve of freedom from ischemic stroke by CHADS$_2$ score.
Note: CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, type 2 DM, previous stroke (doubled).
Abbreviation: DM, diabetes mellitus.

Using a CHADS$_2$ score of 1 as the reference in the Cox regression analysis model, the HRs associated with the CHADS$_2$ scores of 2, 3, 4, 5, and 6 were 1.09, 2.02, 3.32, 3.42, and 1.40, respectively (Figure 3). The event rates with the CHADS$_2$ scores of 1, 2, 3, 4, 5, and 6 were 7.14%, 7.81%, 14.44%, 23.08%, 20%, and 10%, respectively. These findings indicated that a CHADS$_2$ score of 2 had a similar event rate to a CHADS$_2$ score of 1, and CHADS$_2$ score ≥3 identified a cohort with a true high risk. The HR of the group with a CHADS$_2$ score of 6 was 1.40, perhaps because of its small size.

Discussion

CHA$_2$DS$_2$-VASc is reported to be better than the CHADS$_2$ score in identifying the true low-risk patients.[8–12] However, for the regions and population where OAC is frequently underused, it is more important to identify the true high-risk patients. The underuse of OAC among elderly patients with NVAF has been confirmed in different settings.[2–4] One of the most important reasons is that the treating physicians are not sure about which scoring system to follow to determine which patient requires the OAC the most. Therefore, it is necessary to compare the predictive value of two scores, CHA$_2$DS$_2$-VASc and CHADS$_2$, in predicting IS among patients diagnosed with NVAF aged ≥65 years, and to find patients with a true high risk.

In the present study, we only included patients aged 65 years or older. This implies that every patient was added at least 1 point by the CHA$_2$DS$_2$-VASc system, and that both CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were useful parameters for predicting adverse events in patients with NVAF aged ≥65 years. However, the CHADS$_2$ score was found to be more appropriate for patients aged ≥65 years for the categorization of stroke risk when compared with the CHA$_2$DS$_2$-VASc score. A CHADS$_2$ score of ≥3 identified patients with a true high risk. Consistent with the findings of our study, Friberg et al[13] found that the risk of IS in patients with a CHA$_2$DS$_2$-VASc score of 1 seemed to be lower than previously reported (0.1%–0.7%).

In the present study, cardiac failure, age, and history of previous stroke were found to be the independent predictors of IS/TE. Although vascular disease and female sex were not associated with IS/TE risk, both are the additional "non-CHADS$_2$" risk factors that are incorporated into the CHA$_2$DS$_2$-VASc score as per 2012 European Society of Cardiology guidelines.[14]

Several studies have been conducted to assess the impact of atherosclerotic vascular disease on stroke in patients with AF. Peripheral arterial disease significantly increased
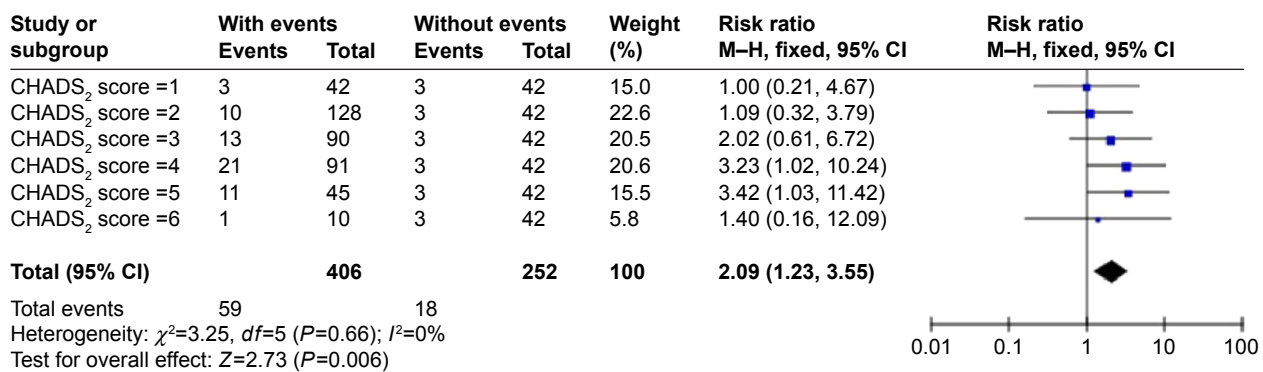
Study or subgroup	With events Events	Total	Without events Events	Total	Weight (%)	Risk ratio M–H, fixed, 95% CI	Risk ratio M–H, fixed, 95% CI
CHADS$_2$ score =1	3	42	3	42	15.0	1.00 (0.21, 4.67)	
CHADS$_2$ score =2	10	128	3	42	22.6	1.09 (0.32, 3.79)	
CHADS$_2$ score =3	13	90	3	42	20.5	2.02 (0.61, 6.72)	
CHADS$_2$ score =4	21	91	3	42	20.6	3.23 (1.02, 10.24)	
CHADS$_2$ score =5	11	45	3	42	15.5	3.42 (1.03, 11.42)	
CHADS$_2$ score =6	1	10	3	42	5.8	1.40 (0.16, 12.09)	
Total (95% CI)		**406**		**252**	**100**	**2.09 (1.23, 3.55)**	
Total events	59		18				

Heterogeneity: χ^2=3.25, df=5 (P=0.66); I^2=0%
Test for overall effect: Z=2.73 (P=0.006)

0.01 0.1 1 10 100

Figure 3 Risk of IS/TE based on CHADS$_2$ scores.
Note: CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, type 2 DM, previous stroke (doubled).
Abbreviations: DM, diabetes mellitus; IS, ischemic stroke; TE, thromboembolism; M–H, Mantel–Haenszel test.

the risk of stroke in all observational studies with the reported risk ranging from 1.3-fold to 2.5-fold.[15,16] Complex aortic plaque in the descending aorta has also been reported as a significant risk factor.[17–19] However, there is no conclusive evidence that previous MI is a predictor of IS.[20] In our study, vascular disease included previous MI and peripheral arterial disease. We found peripheral arterial disease to significantly increase the risk of stroke by 2.71-fold. Previous MI was not a significant predictor of IS/TE, which is consistent with the findings of Lin et al.[21]

Though female sex is another "non-CHADS$_2$" risk factor and has been reported to be associated with IS/TE in patients with AF,[22,23] the said association is considered as controversial. Various studies have reported that female sex is associated with an increased risk of stroke in only those patients with AF aged ≥75 years, whereas female patients aged <65 years without other risk factors do not require anticoagulation therapy.[24,25] Moreover, most of the clinical trials supporting female sex as a risk factor are from the western countries. However, studies conducted in the eastern countries have not reported similar results.[26] It has been reported that female sex increases the risk for their comorbidities, such as heart and renal failures.[22] In our study, which enrolled patients aged ≥65 years, there was no significant difference in the rate of hypertension, previous stroke/TIA, DM, and CHF in females when compared with males (73.4% vs 75.5%, 39.1% vs 37.7%, 37.5% vs 34.3%, and 23% vs 22.5%, respectively). In addition, the rate of IS/TE in females was not found to be significantly different from males (13.4% vs 14.6%; P>0.05). Therefore, in-line with other studies, the findings of our study indicate that female sex need not be considered when deciding on the antithrombotic therapy.[27]

In our study, the cut-off value for a very high risk of stroke when using the CHADS$_2$ score was 3, which was determined by ROC curve analysis. In fact, the event rates during the

follow-up period among patients with the CHADS$_2$ scores of 1 and 2 were almost the same (7%), thus indicating intermediate risk in the CHADS$_2$ score of 1. Both the CHADS$_2$ scores of 1 and 2 need OAC.

It is important to note the limitations of our study. Being a retrospective analysis, follow-up was performed by assessing medical records available in the hospital database only, hence some clinically relevant events may have been missed. The study had a limited number of patients, especially in the group of CHADS$_2$ scores 0 and 9. The HR associated with a CHADS$_2$ score of 6 (relative risk [RR] =1.4 [95% CI {0.16–12.09}]) is considerably lower than that with a CHADS$_2$ score of RR =5 (3.42, 95% CI [1.03–12.42]). for the size of sample. We will enlarge the sample in the future.

Conclusion

For patients with NVAF aged 65 years or older, both vascular disease and female sex were not the predictors of IS/TE risk. The use of the CHADS$_2$ score significantly improves the classification of patients with AF at high risk of stroke compared with the CHA$_2$DS$_2$-VASc score. Thus, future large-scale studies involving multiple centers are needed to further corroborate our findings.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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