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Original Article

$CHADS_2$ and CHA_2DS_2-VASc Scores Predict the Risk of Ischemic Stroke Outcome in Patients with Interatrial Block without Atrial Fibrillation

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***Aim*: To evaluate the role of $CHADS_2$ and CHA_2DS_2-VASc scores in predicting the risk of ischemic stroke or transient ischemic attack (TIA) outcomes in patients with interatrial block (IAB) without a history of atrial fibrillation (AF).**

***Methods*: A retrospective study was conducted, including 1,046 non-anticoagulated inpatients (612 males, 434 females; mean age: 63 ± 10 years) with IAB and without AF. IAB was defined as P-wave duration > 120 ms using a 12-lead electrocardiogram. $CHADS_2$ and CHA_2DS_2-VASc scores were retrospectively calculated. The primary outcomes evaluated were ischemic stroke or TIA.**

***Results*: During the mean follow-up period of 4.9 ± 0.7 years, 55 (5.3%) patients had an ischemic stroke or TIA. Receiver operating characteristic (ROC) curve analysis showed that the $CHADS_2$ score [area under the curve (AUC), 0.638; 95% confidence interval (CI), 0.562−0.715; P=0.001] and the CHA_2DS_2-VASc score (AUC, 0.671; 95% CI, 0.599−0.744; P<0.001) were predictive of ischemic strokes or TIA. Cut-off point analysis showed that a $CHADS_2$ score ≥ 3 (sensitivity=0.455 and specificity=0.747) and a CHA_2DS_2-VASc score ≥ 4 (sensitivity=0.564 and specificity=0.700) provided the highest predictive value for ischemic stroke or TIA. The multivariate Cox regression analysis showed that $CHADS_2$ [hazard ratio (HR), 1.442; 95% CI, 1.171−1.774; P=0.001] and CHA_2DS_2-VASc (HR, 1.420; 95% CI, 1.203−1.677; P<0.001) scores were independently associated with ischemic stroke or TIA following adjustment for smoking, left atrial diameter, antiplatelet agents, angiotensin inhibitors, and statins.**

***Conclusions*: $CHADS_2$ and CHA_2DS_2-VASc scores may be predictors of risk of ischemic stroke or TIA in patients with IAB without AF.**

Key words: $CHADS_2$, CHA_2DS_2-VASc, Interatrial block, Ischemic stroke, Transient ischemic attack

Introduction

Interatrial block (IAB) involves a conduction delay between the right and left atria and is manifested on a 12-lead electrocardiogram (ECG) by a P-wave duration of >120 ms[1]. A recent review of the prevalence of IAB has described this condition as being an underappreciated clinical "pandemic," particularly in the aging population[2]. IAB may be a preceding or causative risk factor for atrial arrhythmias, particularly atrial fibrillation (AF)[3-6], and can be associated with left atrial dilation[1], left atrial electromechanical dysfunction[7], and thromboembolic ischemic stroke[8-10]. Because of the association between IAB and increased risk of ischemic stroke, it has been suggested that these patients could benefit from anticoagulation therapy. However, since the IAB population may be heterogeneous in terms of their risk of developing ischemic stroke, an accurate, objective approach for evaluating the risk of ischemic stroke in these patients is urgently sought to allow physicians and patients to select and plan the most appropriate antithrombotic therapy.

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The $CHADS_2$ and CHA_2DS_2-VASc scores are currently the recommended clinical risk prediction tools used to evaluate the risk of thromboembolism in patients with non-valvular AF[11, 12]. Recently, $CHADS_2$ and CHA_2DS_2-VASc scores have also been reported to have a predictive role for outcomes in patients without known AF, including the risks of adverse clinical events in patients with pacemakers and sinus node dysfunction[13], new-onset peripheral arterial occlusive disease[14], incident AF[15, 16], ischemic stroke or TIA in patients with acute coronary syndrome[17], and ischemic stroke in hypertensive patients aged 65 years or older[18]. However, there is little information available regarding the predictive value of the $CHADS_2$ and CHA_2DS_2-VASc scores for ischemic stroke or TIA in IAB patients without known AF. The purpose of this retrospective study was to investigate the role of the $CHADS_2$ and CHA_2DS_2-VASc scores in predicting clinical outcomes including ischemic stroke or TIA in patients with IAB without a history of AF.

Methods

Study Subjects

Our prospectively established database of ECG recordings of patients who were hospitalized in the Zhengzhou University People's Hospital for diagnosis and treatment between 1st March and 31st March 2010 were retrospectively reviewed. If patients underwent more than one ECG during the index hospitalization, only the first ECG recording was analyzed. We excluded from the analysis patients with a history of diagnosis of AF, patients who under anticoagulant therapy, patients with missing data for calculation of the $CHADS_2$ and CHA_2DS_2-VASc scores, and patients lost to follow-up. The study protocol was approved by the Local Institutional Review Board. The requirement for informed consent was waived because of the anonymous nature of the data.

Electrocardiogram Analysis

In all patients, interatrial conduction was assessed using a resting 12-lead ECG in sinus rhythm (high-pass filter 0.05Hz, low-pass filter 150 Hz, 25 mm/s, 10 mm/mv), which was previously described in detail[19]. Briefly, P-waves were manually measured using a caliper to identify the longest P-wave duration for all 12 ECG leads. At least three beats were measured on each ECG lead. The onset of the P-wave was the point of initial upward or downward deflection from the ECG baseline, and the P-wave endpoint was identified as the point where the waveform returned to the baseline. IAB was defined as a P-wave duration >120 ms on the 12-lead ECG[1]. The ECG analysis was independently performed by two observers who were blinded to the patient details, and any differences between the observers were resolved by consensus. The clinical records of all patients with IAB were then reviewed.

Calculation of the $CHADS_2$ and CHA_2DS_2-VASc Scores

The $CHADS_2$ score was calculated by assigning 1 point each for age >75 years, hypertension, diabetes mellitus, and congestive heart failure and 2 points for a previous stroke or TIA[11]. The CHA_2DS_2-VASc score was calculated for each patient by assigning 1 point each for age 65−74 years, hypertension, diabetes mellitus, congestive heart failure, vascular disease, and female sex and 2 points for a previous stroke or TIA and age ≥75 years[12]. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg or treatment with antihypertensive drugs. Congestive heart failure was considered present for patients with a history of heart failure or a measured left ventricular ejection fraction <0.35. Diabetes was defined as a fasting blood glucose level of >126 mg/dl or treatment with hypoglycemic agents.

Patient Follow-up

All patients included in the study were followed until March 1, 2015 or until the occurrence of an ischemic stroke or TIA. All study subjects were contacted by telephone every 6 months, and follow-up interviews were conducted with participants or their relatives or carers to identify any deaths or hospitalizations that occurred during the previous interval. For any reported event, medical records were retrieved and reviewed. Hemorrhagic stroke was defined as rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that was not caused by trauma[20]. Ischemic stroke was defined as central nervous system infarction of the brain due to ischemia, based on neuroimaging and/or clinical evidence of permanent injury[20]. Embolic stroke was identified based on the patient's clinical history and presentation (sudden onset, initial maximal symptoms, and/or subsequent rapid recovery among others), as well as the newly-evidenced lesion size, number, and anatomical cerebrovascular location[10, 21]. The diagnosis of TIA was made according to the World Health Organization (WHO) criteria[22], which include rapidly developing clinical signs of focal or global disturbance of cerebral function lasting less than 24 h, with no apparent non-vascular cause.

Table 1. Baseline characteristics of IAB patients with and without ischemic stroke or TIA.

Parameters	Stroke or TIA (n=55)	No-Stroke or TIA (n=991)	P-value
Age, years	66 ± 10	63 ± 10	0.054
Age ≥ 75	18 (32.7%)	198 (20.0%)	0.023
Age 65−74	8 (14.5%)	104 (10.5%)	0.344
Female, n (%)	27 (49.1%)	407 (41.1%)	0.240
Congestive heart failure, n (%)	8 (14.5%)	118 (11.9%)	0.558
Hypertension, n (%)	36 (65.5%)	526 (53.1%)	0.073
Diabetes mellitus, n (%)	33 (60.0%)	429 (43.3%)	0.015
Previous stroke or TIA, n (%)	20 (36.4%)	237 (23.9%)	0.037
Coronary artery disease, n (%)	21 (38.2%)	278 (28.1%)	0.106
PCI during index admission, n (%)	9 (16.4%)	110 (11.1%)	0.767
CABG during index admission, n (%)	3 (5.6%)	39 (3.9%)	0.576
Current Smoker (%)	17 (30.9%)	227 (22.9%)	0.172
LVEF, %	58.3 ± 13.6	60.2 ± 11.3	0.064
LA diameter, mm	38.4 ± 4.6	36.9 ± 4.4	0.013
Medication Use			
Antiplatelet Agent, n (%)	26 (47.3%)	320 (32.3%)	0.022
β-blockers, n (%)	29 (52.7%)	415 (41.9%)	0.113
Angiotensin inhibitors, n (%)	18 (32.7%)	285 (28.8%)	0.528
Statins, n (%)	28 (50.9%)	445 (44.9%)	0.384
Antiarrhythmics, n (%)	7 (12.7%)	90 (9.1%)	0.364
$CHADS_2$ score	2.5 ± 1.4	1.8 ± 1.3	< 0.001
0	3 (5.5%)	158 (15.9%)	
1	13 (23.6%)	299 (30.2%)	
2	14 (25.5%)	283 (28.6%)	
≥ 3	25 (45.5%)	252 (25.4%)	
CHA_2DS_2-VASc score	3.8 ± 1.8	2.7 ± 1.7	< 0.001
0	1 (1.8%)	102 (10.3%)	
1	5 (9.1%)	165 (16.6%)	
2	8 (14.5%)	206 (20.8%)	
3	10 (18.2%)	221 (22.3%)	
≥ 4	31 (56.4%)	297 (30.0%)	

TIA, transient ischemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; LA, left atrial.

Statistical Analysis

Data analysis was performed using SPSS software version 17.0. Continuous data are presented as the mean ± standard deviation. Univariate analysis to assess the predictive value of clinical variables on ischemic stroke or TIA was performed using the unpaired independent-samples t-test for continuous variables and the χ^2 test and Fisher's exact test, if necessary, for categorical variables. The cumulative event incidence rates were calculated for the $CHADS_2$ and CHA_2DS_2-VASc scores. A Kaplan−Meier estimation with a log-rank test was performed for unadjusted analysis of the association between increased $CHADS_2$ and CHA_2DS_2-VASc scores and the risk of ischemic stroke or TIA. Receiver operating characteristic (ROC) curves were constructed to test the ability of the $CHADS_2$ and CHA_2DS_2-VASc scores to predict ischemic stroke or TIA and to identify optimal cut-off values. A Cox regression analysis was performed to assess the ability of the $CHADS_2$ and CHA_2DS_2-VASc scores to predict the incidence of ischemic stroke or TIA, following multivariate adjustment. Based on clinical validity and the review of the previous literature, an adjustment was added for five covariates: current smoking[23], left atrial (LA) diameter[24-27], use of antiplatelet agents[28], use of angiotensin inhibitors[29, 30], and used of statins[31]. All probability values were two-sided, and a P-value of < 0.05 was considered to be significant.

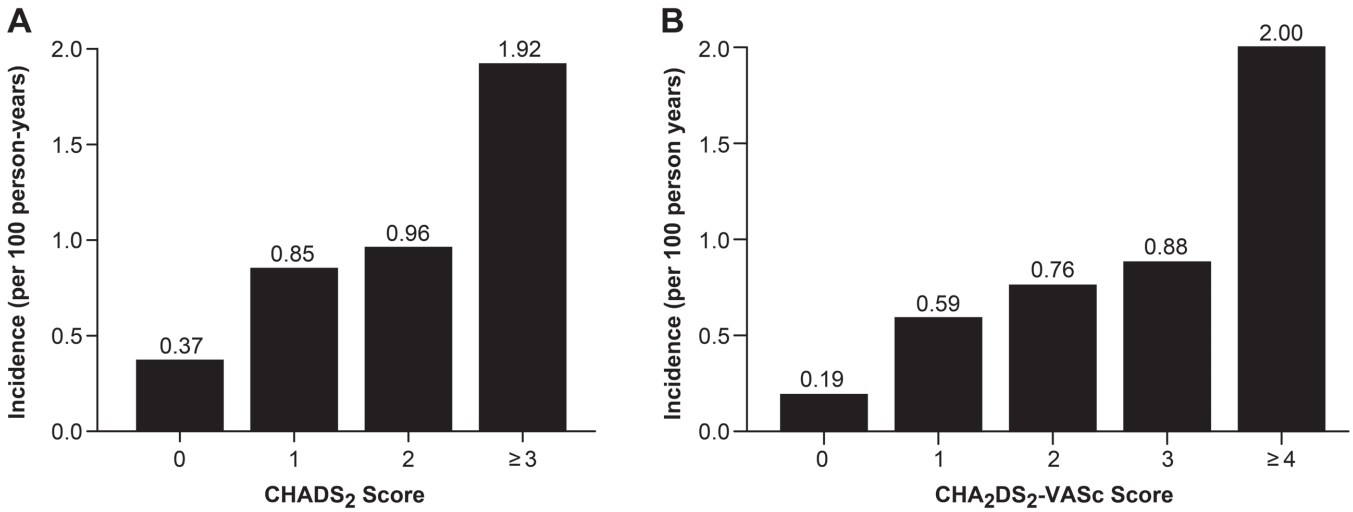

Fig. 1. Incidence of ischemic stroke or TIA based on the $CHADS_2$ (A) and CHA_2DS_2-VASc (B) scores

Results

We analyzed the ECG recordings during sinus rhythm of a total of 3,487 patients between March 1, 2010 and March 31, 2010. IAB was detected in 38.2% (1,332/3,487) of these patients. On the basis of review of the clinical records of the patients with IAB, 1,084 patients were initially enrolled, and 248 patients were excluded. Of the 1,084 patients, 1,046 (612 males, 434 females; mean age: 63 ± 10 years) completed follow-up (96.5%) and were included in the final study sample.

The mean follow-up period was 4.9 ± 0.7 years, during which 8 (0.8%) patients without baseline AF were subsequently diagnosed with hemorrhagic stroke and 55 (5.3%) were diagnosed with ischemic stroke or TIA, including 29 (52.7%) patients with a probable embolic stroke, 20 (36.4%) with a probable thrombotic stroke, and 6 (10.9%) with TIA. The baseline clinical characteristics of IAB patients with and without ischemic stroke or TIA are shown in **Table 1**. Ischemic stroke or TIA during follow-up was reported significantly more often in patients above the age of 75 ($P=0.023$), patients with diabetes mellitus ($P=0.015$), and patients with a previous recorded stroke or TIA ($P=0.037$). More patients with ischemic stroke or TIA were receiving antiplatelet agents compared with those without ischemic stroke or TIA. Patients with ischemic stroke or TIA had larger LA diameters and higher $CHADS_2$ ($P<0.001$) and CHA_2DS_2-VASc ($P<0.001$) scores than those without ischemic stroke or TIA.

The incidence of ischemic stroke or TIA increased with an increased $CHADS_2$ score. For $CHADS_2$ scores of 0, 1, 2, and ≥3, the event incidences were 0.37, 0.85, 0.96, and 1.92 per 100 person-years, respectively (**Fig. 1A**). ROC curve analysis showed that the $CHADS_2$ score [area under the curve (AUC), 0.638; 95% confidence interval (CI), 0.562−0.715; $P=0.001$] was a significant predictor of ischemic stroke or TIA (**Fig. 2A**). Cut-off point analysis showed that a $CHADS_2$ score ≥3 gave the highest predictive value for ischemic stroke or TIA (sensitivity=0.455 and specificity=0.747). The incidence of ischemic stroke or TIA was significantly higher in patients with $CHADS_2$ score ≥3 compared with those with a $CHADS_2$ score <3 (the log-rank test, $P=0.001$) (**Fig. 3A**).

Similarly, there was an ascending pattern of the incidence of ischemic stroke or TIA with increasing CHA_2DS_2-VASc scores: for a CHA_2DS_2-VASc score of 0, 1, 2, 3, and ≥4, the event incidences were 0.19, 0.59, 0.76, 0.88, and 2.0 per 100 person-years, respectively (**Fig. 1B**). ROC curve analysis showed that the CHA_2DS_2-VASc score (AUC, 0.671; 95% CI, 0.599−0.744; $P<0.001$) (**Fig. 2B**) was also a significant predictor of ischemic stroke or TIA. The optimal cut-off point for a CHA_2DS_2-VASc score displaying the best predictive value was ≥4 (sensitivity=0.564 and specificity=0.700). The incidence of ischemic stroke or TIA was significantly higher in patients with a CHA_2DS_2-VASc score ≥4 than in those with a CHA_2DS_2-VASc score <4 (the log-rank test, $P<0.001$) (**Fig. 3B**).

The multivariate Cox regression analysis showed that the $CHADS_2$ score [hazard ratio (HR), 1.442; 95% CI, 1.171−1.774; $P=0.001$] was independently associated with ischemic stroke or TIA following adjustment for smoking, LA diameter, antiplatelet agents, angiotensin inhibitors, and statins in model 1 (**Table 2**). The CHA_2DS_2-VASc score (HR, 1.420; 95% CI, 1.203−1.677; $P<0.001$) was also an inde-

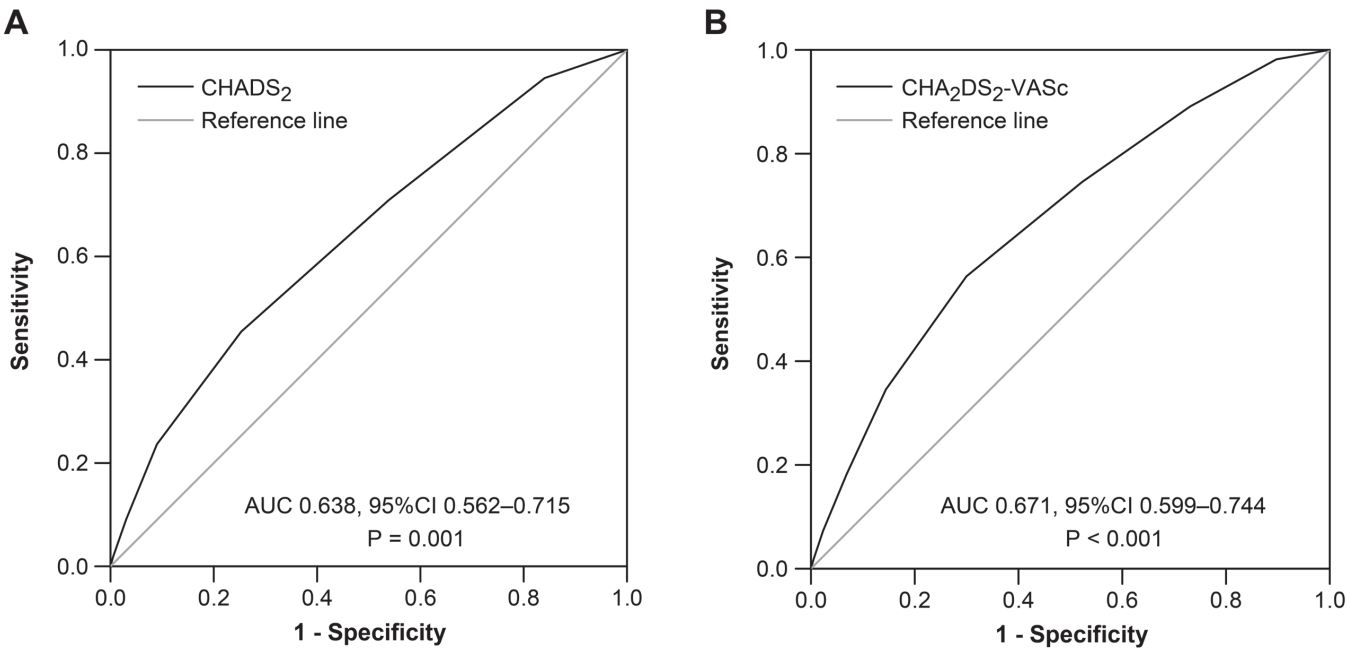

Fig. 2. Receiver operating characteristic (ROC) curves for the $CHADS_2$ (A) and CHA_2DS_2-VASc (B) scores for prediction of ischemic stroke or TIA

pendent predictor of ischemic stroke or TIA following adjustment for the same potential clinical confounders in model 2 (**Table 2**). In addition, the multivariate analysis showed that the LA diameter was also independently associated with ischemic stroke or TIA in model 1 (HR, 1.067; 95% CI, 1.006−1.133; P=0.032) and model 2 (HR, 1.065; 95% CI, 1.004−1.131; P=0.037) (**Table 2**).

In 18.6% (195/1046) of patients, there was an incidental finding of AF at the hospital discharge diagnosis. To determine whether the predictive abilities of the $CHADS_2$ and CHA_2DS_2-VASc scores for ischemic stroke or TIA were mediated by incidental AF, the ROC curve analysis was repeated after excluding patients who developed AF during follow-up. However, excluding these patients from the analysis had no impact on the predictive ability of these risk-scoring methods for ischemic stroke or TIA ($CHADS_2$: AUC, 0.643; 95% CI, 0.555−0.730; P=0.002, and CHA_2DS_2-VASc: AUC, 0.673; 95% CI, 0.589−0.757; P<0.001). The ROC curve analysis was also performed to evaluate the utility of these scores for prediction of new-onset AF. The analysis showed that the $CHADS_2$ score (AUC, 0.578; 95% CI, 0.533−0.622; P=0.001) and the CHA_2DS_2-VASc score (AUC, 0.623; 95% CI, 0.583−0.662; P<0.001) were both predictive of new-onset AF.

Discussion

The main findings presented in this study are as follows: (1) $CHADS_2$ and CHA_2DS_2-VASc scores may be used to predict ischemic stroke or TIA in patients with IAB without a history of AF and (2) $CHADS_2$ scores ≥3 and CHA_2DS_2-VASc scores ≥4 displayed the highest predictive value for ischemic stroke or TIA.

It was previously reported that IAB is a common but poorly recognized condition in the hospital inpatient population[2, 32-34] and that patients with IAB have an increased risk of ischemic stroke[8-10]. Ischemic stroke is a major cause of premature death and disability and can occur without any warning symptoms[20, 22, 35, 36]. Hence, it is crucial to identify IAB patients who are at high risk of ischemic stroke.

In the present study, we sought to investigate the role of the $CHADS_2$ and CHA_2DS_2-VASc scores in predicting ischemic stroke or TIA in patients with IAB without a history of AF. The ROC curve analysis showed that $CHADS_2$ and CHA_2DS_2-VASc scores were both predictive of ischemic strokes or TIA, and multivariate analysis showed that $CHADS_2$ and CHA_2DS_2-VASc were independently associated with ischemic stroke or TIA. Several potential mechanisms may explain these findings. First, the various components of the $CHADS_2$ and CHA_2DS_2-VASc scoring systems may include independent risk factors for ischemic stroke. In 1997, Dries and colleagues reported

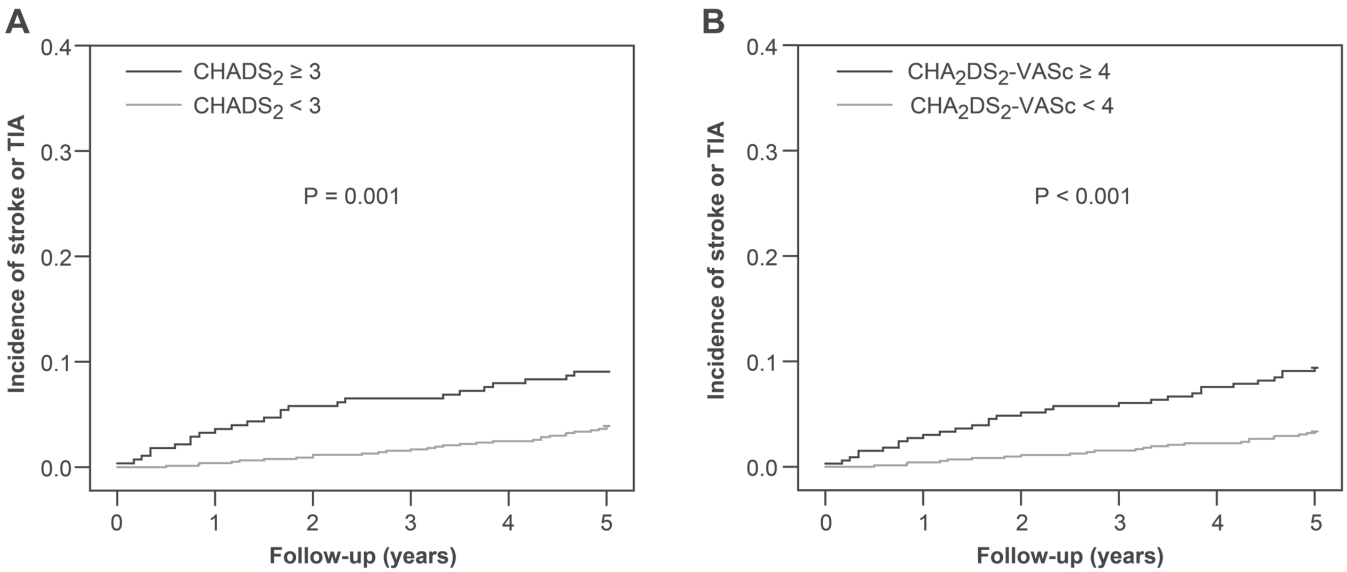

Fig. 3. Kaplan–Meier curves showing the incidence of ischemic stroke or TIA stratified by $CHADS_2$ and CHA_2DS_2-VASc scores; A: Patients with a $CHADS_2$ score ≥ 3 had a higher incidence of ischemic stroke or TIA than those with a $CHADS_2$ score < 3 (P = 0.001). B: Patients with a CHA_2DS_2-VASc score ≥ 4 had a higher incidence of ischemic stroke or TIA than those with a CHA_2DS_2-VASc score < 4 (P < 0.001).

that patients with heart failure are at a risk of embolism due to ventricular thrombi, even in sinus rhythm[37]. In 2007, Ariyarajah and colleagues found that there was direct and significant correlation between hypertension and embolic stroke[10]. Furthermore, a recent study found that diabetes mellitus and dyslipidemia, along with hypertension and smoking, are the leading risk factors for the occurrence of ischemic stroke[38]. In addition, patients with high $CHADS_2$ and CHA_2DS_2-VASc scores may have a higher risk of developing AF. In a study by Mitchell and colleagues[17], the $CHADS_2$ and CHA_2DS_2-VASc scores were predictive for subsequent hospital discharge with a diagnosis of AF in acute coronary syndrome. In 2013, Chao and colleagues[39] also reported that the incidence of AF progressively increased when patients had more complicated systemic diseases, as indicated by a high $CHADS_2$ score; this is in agreement with the finding of Tischer and colleagues that the prevalence of AF increases with increasing $CHADS_2$ and CHA_2DS_2-VASc scores[40]. These studies support the finding that higher $CHADS_2$ and CHA_2DS_2-VASc scores can identify patients who are more likely to develop asymptomatic AF. Finally, the various components of the $CHADS_2$ and CHA_2DS_2-VASc scores may directly contribute to LA remodeling, a process characterized by atrial dilatation and mechanical dysfunction[41]; this may lead to blood stasis and an increased thromboembolic risk, regardless of the cardiac rhythm.

One of the findings of the present study was that there were patients without baseline AF who were subsequently diagnosed with AF. Exclusion of these patients from the analysis did not change the predictive ability of the risk-scoring methods to predict ischemic stroke or TIA. This suggests that $CHADS_2$ and CHA_2DS_2-VASc scores can predict ischemic stroke or TIA in patients with IAB but no history of AF, regardless of the incidental finding of AF during follow-up. In agreement with these findings, IAB has previously been reported to be associated with the subsequent development of AF[3-6]. Also, our study found that $CHADS_2$ and CHA_2DS_2-VASc scores were both predictive of new-onset AF, which is in accordance with the findings of a recent study by Mitchell and colleagues[17].

In the present study, patients in the stroke or TIA group had larger LA diameters than those in the no-stroke or TIA group. This may be because patients in the stroke or TIA group had higher $CHADS_2$ or CHA_2DS_2-VASc scores, which are associated with LA enlargement[42, 43]. In addition to the $CHADS_2$ and CHA_2DS_2-VASc scores, the LA diameter was also found to be independently associated with ischemic stroke or TIA in the multivariate analysis. This is supported by the findings of previous studies[24-27], which showed that LA enlargement may be a risk factor for ischemic stroke. In addition, more patients in the stroke or TIA group were receiving antiplatelet agents compared with the no-stroke or TIA group. There are

Table 2. Risk of ischemic stroke or TIA using multivariate analysis.

	HR (95%CI)	*P*-values
Model 1		
Smoking	1.719 (0.967-3.056)	0.065
LA diameter	1.067 (1.006-1.133)	0.032
Antiplatelet Agent	1.696 (0.618-4.654)	0.305
Angiotensin inhibitors	0.886 (0.503-1.560)	0.675
Statins	0.703 (0.256-1.930)	0.494
$CHADS_2$ score	1.416 (1.147-1.749)	0.001
Model 2		
Smoking	1.792 (1.008-3.185)	0.047
LA diameter	1.065 (1.004-1.131)	0.037
Antiplatelet Agent	1.381 (0.507-3.762)	0.528
Angiotensin inhibitors	0.887 (0.504-1.562)	0.679
Statins	0.676 (0.253-1.808)	0.436
CHA_2DS_2-VASc score	1.402 (1.184-1.661)	<0.001

HR, hazard ratio; CI, confidence interval. For other abbreviations, see Table 1.

two potential explanations for this finding. First, patients in the stroke or TIA group had a higher prevalence of previous stroke or TIA, for which antiplatelet therapy is recommended by the stroke prevention guidelines[44, 45], than those in the no-stroke or TIA group. Second, patients in the stroke or TIA group had higher $CHADS_2$ and CHA_2DS_2-VASc scores, indicating more atherosclerotic risk factors; thus, these patients may have had a higher prevalence of antiplatelet agent use.

There were several limitations to this study. Ischemic stroke and TIA were analyzed in a global manner, and no distinction was made between the various causes of these conditions (embolic, atherothrombotic, etc.). As we excluded patients previously diagnosed with AF at baseline ECG from this study, it is possible that individuals with asymptomatic paroxysmal AF who were in sinus rhythm at the time of the baseline ECG could have been misclassified as non-AF participants and included in the analysis. It is also possible that AF was under-diagnosed, as it was identified using hospital discharge data. However, since AF is asymptomatic in some patients, only continuous ECG monitoring would have correctly classified all patients. Additionally, because this study did not evaluate the prognostic performance of the $CHADS_2$ and CHA_2DS_2-VASc scores for predicting the risk of ischemic stroke in patients without IAB, it was difficult to determine whether the utility of these scores for predicting the risk of ischemic stroke was specific for patients with IAB; thus, further studies are needed. Finally, prescription data obtained during follow-up was unavailable, which may have affected the accuracy of the predictive models.

In conclusion, the $CHADS_2$ and CHA_2DS_2-VASc scores may be predictors of the risk of ischemic stroke or TIA in patients with IAB without AF.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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