

Using the CHA₂DS₂-VASc Score for Refining Stroke Risk Stratification in ‘Low-Risk’ Asian Patients With Atrial Fibrillation



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ABSTRACT

BACKGROUND A new scoring system, the anticoagulation and risk factors in atrial fibrillation (ATRIA) score, was proposed for risk stratification in patients with atrial fibrillation (AF). Whether the ATRIA scheme can adequately identify patients who are at low risk of ischemic stroke remains unknown.

OBJECTIVES The goal of the present study was to compare the performance of ATRIA to that of CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female) scores for stroke prediction.

METHODS This study used the National Health Insurance research database in Taiwan. A total of 186,570 AF patients without antithrombotic therapy were selected as the study cohort. The clinical endpoint was the occurrence of ischemic stroke.

RESULTS During the follow-up of 3.4 ± 3.7 years, 23,723 patients (12.7%) experienced ischemic stroke. The CHA₂DS₂-VASc score performed better than ATRIA score in predicting ischemic stroke as assessed by c-indexes (0.698 vs. 0.627, respectively; $p < 0.0001$). The CHA₂DS₂-VASc score also improved the net reclassification index by 11.7% compared with ATRIA score ($p < 0.0001$). Among 73,242 patients categorized as low-risk on the basis of an ATRIA score of 0 to 5, the CHA₂DS₂-VASc scores ranged from 0 to 7, and annual stroke rates ranged from 1.06% to 13.33% at 1-year follow-up and from 1.15% to 8.00% at 15-year follow-up. The c-index of CHA₂DS₂-VASc score (0.629) was significantly higher than that of the ATRIA score (0.593) in this “low-risk” category ($p < 0.0001$).

CONCLUSIONS Patients categorized as low-risk by use of the ATRIA score were not necessarily low-risk, and the annual stroke rates can be as high as 2.95% at 1-year follow-up and 2.84% at 15-year follow-up. In contrast, patients with a CHA₂DS₂-VASc score of 0 had a truly low risk of ischemic stroke, with an annual stroke rate of approximately 1%. (J Am Coll Cardiol 2014;64:1658-65) © 2014 by the American College of Cardiology Foundation.

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Atrial fibrillation (AF) is an important risk factor for ischemic stroke, and AF-related stroke has a worse prognosis and higher recurrence rate than non-AF-related stroke (1). Stroke prevention is the cornerstone for AF management, and effective stroke risk stratification is a key step. The current focus is the initial identification of “low risk” AF patients who do not need antithrombotic therapy, and, subsequent to this decision step, patients with stroke risk factor ≥ 1 can be offered effective stroke prevention, which is oral anticoagulation (OAC) (2).

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The congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack (TIA) (CHADS₂) score has been commonly used to guide antithrombotic therapies for AF patients since it was proposed and validated in 2001 (3). However, the annual stroke rate is still nearly 2% for patients with a CHADS₂ score of 0, and a considerable proportion of patients may be misclassified as “low risk” without taking OACs for stroke prevention, accordingly (4,5). In 2010, the congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female (CHA₂DS₂-VASc) score (6) was developed and was suggested to be better than the CHADS₂ score for identifying truly low-risk patients in several independent cohorts (4,7-10).

More recently, another new scoring system, the anticoagulation and risk factors in atrial fibrillation (ATRIA) score was proposed (11). This score includes renal dysfunction (estimated glomerular filtration rate [eGFR] < 45 ml/min or end-stage renal disease [ESRD]) and proteinuria in the model and requires different score weighting for primary and secondary prevention. Developers of the ATRIA scheme reported that the ATRIA score performed statistically better than the CHADS₂ and CHA₂DS₂-VASc scoring systems, although the differences in c-indexes were marginal with some overlap of the 95% confidence intervals (CI) (11). Also, the percentage of patients categorized as low-risk by ATRIA score was 46.7%, comparable to the percentage of low-risk patients stratified by CHADS₂ score (49.7%). The concern is raised as to whether the ATRIA score is able to identify patients with a truly low risk of ischemic stroke.

The goal of the present study was to compare the predictive accuracies of the CHA₂DS₂-VASc and ATRIA scores in predicting ischemic stroke in a contemporary unselected “real-world” cohort of nonanticoagulated AF patients from a nationwide cohort study. We also determined stroke rates in

patients classified as low-risk by the ATRIA scheme (score 0 to 5) and ascertained event rates in these patients in relation to the CHA₂DS₂-VASc score. We tested the hypothesis that the CHA₂DS₂-VASc score would be better in identifying truly low-risk patients than the ATRIA score.

METHODS

This study used the National Health Insurance (NHI) research database released by the Taiwan National Health Research Institutes. The NHI system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. The NHI research database consists of detailed health care data from > 23 million enrollees, representing $> 99\%$ of Taiwan’s population. In this cohort dataset, the patients’ original identification numbers were encrypted to protect their privacy, using a consistent encrypting procedure so that it was feasible to link and continuously follow all of the claims belonging to the same patient within the NHI database. The large sample size of this database

ABBREVIATIONS AND ACRONYMS

- AF** = atrial fibrillation
- ATRIA** = anticoagulation and risk factors in atrial fibrillation
- CI** = confidence interval
- CHA₂DS₂-VASc** = congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female
- eGFR** = estimated glomerular filtration rate
- ESRD** = end-stage renal disease
- NHI** = National Health Insurance
- NRI** = net reclassification index
- OAC** = oral anticoagulation
- ROC** = receiver operating characteristic curve
- TIA** = transient ischemic attack

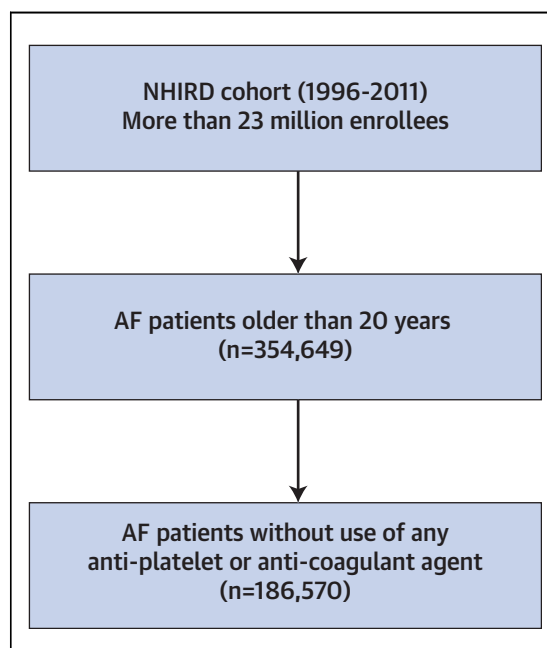


FIGURE 1 Flowchart of Study Cohort Enrollment

From January 1, 1996, to December 31, 2011, a total of 186,570 AF patients who were not receiving oral anticoagulants or antiplatelet agents were enrolled in this study. AF = atrial fibrillation; NHIRD = National Health Insurance Research Database.

provided a good opportunity to study the risk of ischemic stroke in AF patients stratified by CHA₂DS₂-VASc and ATRIA scores.

STUDY COHORT. From January 1, 1996, to December 31, 2011, a total of 354,649 AF patients aged 20 years and older were identified from the NHI research database as the study population. AF was diagnosed using International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) codes (427.31). To ensure diagnostic accuracy, we defined patients with AF only when it was a discharge diagnosis or confirmed more than twice in the outpatient department. Patients who received treatments with warfarin or any antiplatelet agent, including aspirin, clopidogrel, dipyridamole, and ticlopidine, were excluded from the study population. A total of 186,570 patients were finally enrolled in the study cohort. A flowchart of the enrollment of the study cohort is shown in [Figure 1](#).

CALCULATION OF SCORE AND DEFINITION OF CLINICAL ENDPOINT. The CHA₂DS₂-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, history of hypertension,

diabetes, recent cardiac failure, vascular disease (myocardial infarction or peripheral artery disease), and female sex, and 2 points each for a history of a stroke, TIA, or age ≥75 years (6). The ATRIA score was calculated for patients with a history of stroke by assigning 9 points for age ≥85 years, 7 points for age between 65 and 84 years, or 8 points for age <65 years and 1 point each for history of diabetes, congestive heart failure, hypertension, proteinuria, eGFR <45 ml/min or ESRD, and female sex (11). For patients without prior stroke, the ATRIA score was calculated by assigning 6 points for age ≥85 years, 5 points for age between 75 and 84 years, 3 points for age between 65 and 74 years, and 1 point each for history of diabetes, congestive heart failure, hypertension, proteinuria, eGFR <45 ml/min or ESRD, and female sex (11). On the basis of the ATRIA score, the study cohort was stratified into low (0 to 5 points), moderate (6 points), and high (7 to 15 points) risk categories (11). The ICD-9-CM codes used to identify risk factor components of the scoring schemes are shown in [Online Table 1](#).

The clinical endpoint was the occurrence of ischemic stroke with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in the NHI research database was validated previously (12).

STATISTICAL ANALYSIS. Data are mean values ± SD for normally distributed continuous variables and proportions for categorical variables. Differences between continuous values were assessed using an unpaired 2-tailed Student *t*-test for normally distributed variables and Mann-Whitney rank-sum test for skewed variables. Differences among nominal variables were compared by chi-square test. Ischemic stroke risk was assessed using Cox regression analysis. The cumulative incidence curve of ischemic stroke was plotted via the Kaplan-Meier method, with statistical significance examined by the log-rank test. We assessed the predictive accuracies of the ATRIA and CHA₂DS₂-VASc scores by calculating c-indexes on the basis of receiver operating characteristic (ROC) curves. Areas under the ROC curves for these two scoring systems were compared using DeLong's test. The net reclassification index (NRI) comparing the ATRIA and CHA₂DS₂-VASc scores was also calculated. Statistical significance was defined as a *p* value of <0.05.

RESULTS

Baseline characteristics of the study cohort are shown in [Table 1](#). The mean age of patients was 72.0 ± 13.9 years, and 54.0% were male. The median values

TABLE 1 Baseline Characteristics of AF Patients by ATRIA Score

Variable	Total N = 186,570	ATRIA Score 0-5 n = 73,242 (39.3%)	ATRIA Score 6 n = 19,952 (10.7%)	ATRIA Score 7-15 n = 93,376 (50.0%)
Age, yrs	72.0 ± 13.9	60.3 ± 12.7	76.7 ± 6.6	80.2 ± 8.5
Components of the CHA ₂ DS ₂ -VASc score				
Congestive heart failure	72,220 (38.7)	15,690 (21.4)	6,352 (31.8)	50,178 (53.7)
Hypertension	117,285 (62.9)	30,071 (41.1)	11,330 (56.8)	75,884 (81.3)
Age ≥75 yrs	93,980 (50.4)	5,068 (6.9)	12,819 (64.3)	76,093 (81.5)
Diabetes mellitus	50,180 (26.9)	10,961 (15.0)	4,325 (21.7)	34,894 (37.4)
Previous stroke/TIA	38,223 (20.5)	0 (0.0)	0 (0.0)	38,223 (40.9)
Vascular diseases	28,509 (15.3)	9,292 (12.7)	2,740 (13.7)	16,477 (17.7)
Age ≥65 yrs	46,868 (25.1)	26,551 (36.3)	6,928 (34.7)	13,389 (14.3)
Sex category (female)	85,862 (46.0)	25,347 (34.6)	7,968 (39.9)	52,547 (56.3)
CHA ₂ DS ₂ -VASc score				
0	9,416 (5.1)	9,416 (12.9)	0 (0.0)	0 (0.0)
1	19,325 (10.4)	19,325 (26.4)	0 (0.0)	0 (0.0)
2	26,096 (14.0)	22,993 (31.4)	2,187 (11.0)	916 (1.0)
3	31,272 (16.8)	14,185 (19.4)	9,185 (46.0)	7,902 (8.5)
4	31,512 (16.9)	5,003 (6.8)	5,014 (25.1)	21,495 (23.0)
5	27,295 (14.6)	1,840 (2.5)	2,490 (12.5)	22,965 (24.6)
6	20,860 (11.2)	458 (0.6)	846 (4.2)	19,556 (20.9)
7	13,585 (7.3)	22 (0.0)	230 (1.2)	13,333 (14.3)
8	5,970 (3.2)	0 (0.0)	0 (0.0)	5,970 (6.4)
9	1,239 (0.7)	0 (0.0)	0 (0.0)	1,239 (1.3)

Values are n (%) or mean ± SD.
AF = atrial fibrillation; ATRIA = anticoagulation and risk factors in atrial fibrillation; CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female; TIA = transient ischemic attack.

(interquartile range) of the CHA₂DS₂-VASc and ATRIA scores were 4 (2 to 5) and 7 (4 to 9), respectively. Hypertension was the most prevalent comorbidity and was noted in 62.9% of patients. On the basis of the ATRIA score, there were 39.3%, 10.7%, and 50.1% of patients who were classified as low-risk (0 to 5 points), moderate-risk (6 points), and high-risk (7 to 15 points) groups, respectively.

During the follow-up of 3.4 ± 3.7 years, 23,723 patients (12.7%) experienced ischemic stroke. Both the ATRIA and CHA₂DS₂-VASc scores were significant predictors of ischemic stroke, with a hazard ratio of 1.093 (95% CI: 1.089 to 1.098) and 1.153 (95% CI: 1.146 to 1.161) per 1 increment of the ATRIA and CHA₂DS₂-VASc scores, respectively.

Figure 2 shows the ROC curves of ATRIA and CHA₂DS₂-VASc scores in predicting ischemic stroke. The c-indexes on the basis of areas under the ROC curves for the ATRIA and CHA₂DS₂-VASc scores in predicting ischemic stroke were 0.627 (95% CI: 0.620 to 0.635) and 0.698 (95% CI: 0.691 to 0.705), respectively. The difference was statistically significant in favor of the CHA₂DS₂-VASc score (DeLong test, p < 0.0001). The CHA₂DS₂-VASc score also improved the NRI by 11.7% (95% CI: 9.9% to 13.6%) compared with the ATRIA score (p < 0.0001).

RISK OF ISCHEMIC STROKE FOR PATIENTS WITH AN ATRIA SCORE OF 0-5. Among 73,242 patients with an ATRIA score of 0 to 5, the stroke rate was 2.95 per 100 person-years at 1-year follow-up, 2.75 per 100 person-years at 5-year follow-up, 2.80 per 100 person-years at 10-year follow-up, and 2.84 per 100 person-years at 15-year follow-up (**Table 2**). For 10,039 patients with an ATRIA score of 0, the annual event rates at 1-year, 5-year, 10-year, and 15-year follow-up examinations were 1.28, 1.36, 1.31, and 1.32 per 100 person-years, respectively.

LOW-RISK PATIENTS WITH AN ATRIA SCORE OF 0 TO 5, SUBSTRATIFIED BY CHA₂DS₂-VASc SCORES.

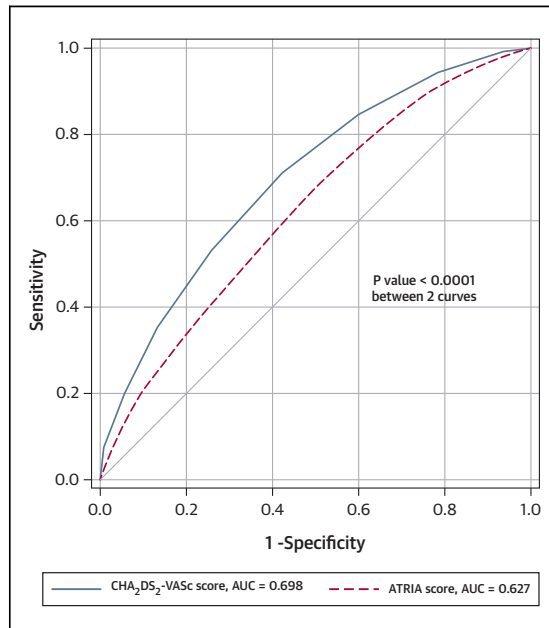


FIGURE 2 ROC Curves of CHA₂DS₂-VASc and ATRIA Scores in Predicting Ischemic Stroke

The c-indexes on the basis of AUCs for the CHA₂DS₂-VASc and ATRIA scores in predicting ischemic stroke were 0.698 and 0.627, respectively (DeLong test, p < 0.0001). ATRIA = anti-coagulation and risk factors in atrial fibrillation; AUC = area under the curve; CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74, female; ROC = receiver operating characteristic.

Among patients with an ATRIA score of 0 to 5, the CHA₂DS₂-VASc scores of these subjects ranged from 0 to 7. Kaplan-Meier estimates of the probability of remaining free of ischemic stroke according to the CHA₂DS₂-VASc score are illustrated in **Figure 3**.

Even for patients categorized as low risk using the ATRIA score, there was a graded increase in the stroke rate when subdivided by CHA₂DS₂-VASc scores.

TABLE 2 Event Rate of Ischemic Stroke Per 100 Person-Years in AF Patients With an ATRIA Score of 0-5

ATRIA Score	1-Year Follow-Up			5-Year Follow-Up			10-Year Follow-Up			15-Year Follow-Up		
	Person-Years	No. of Events	Stroke Rate	Person-Years	No. of Events	Stroke Rate	Person-Years	No. of Events	Stroke Rate	Person-Years	No. of Events	Stroke Rate
0	8,115	104	1.28	36,958	501	1.36	57,095	748	1.31	63,118	834	1.32
1	13,670	226	1.65	54,513	873	1.60	81,861	1,389	1.70	89,763	1,573	1.75
2	8,415	262	3.11	32,045	805	2.51	46,262	1,177	2.54	49,572	1,294	2.61
3	8,230	270	3.28	30,513	982	3.22	43,290	1,456	3.36	46,260	1,584	3.42
4	10,343	394	3.81	37,773	1,402	3.71	53,410	2,089	3.91	57,115	2,266	3.97
5	14,313	603	4.20	46,377	1,994	4.30	62,607	2,798	4.47	65,619	2,998	4.57
Total patients	63,086	1,859	2.95	238,179	6,557	2.75	344,525	9,657	2.80	371,447	10,549	2.84

Abbreviations as in **Table 1**.

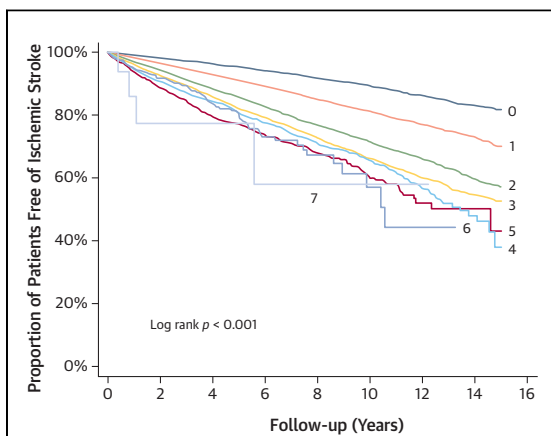


FIGURE 3 Kaplan-Meier Survival Curves in Patients With an ATRIA Score of 0 to 5 Stratified on the Basis of Their CHA₂DS₂-VASc Scores (15-Year Follow-Up)

Among 73,242 patients with an ATRIA score of 0 to 5, the rate of ischemic stroke differed significantly among patients with CHA₂DS₂-VASc scores of 0 to 7. Abbreviation as in Figure 2.

The rate of ischemic stroke ranged from 1.06 to 13.33 per 100 persons-years at 1-year follow-up; 1.00 to 7.50 per 100 person-years at 5-year follow-up; 1.09 to 8.33 per 100 person-years at 10-year follow-up; and 1.15 to 8.00 per 100 person-years at 15-year follow-up (Table 3). A CHA₂DS₂-VASc score of 0 identified a truly low-risk cohort with annual event rates at 1-, 5-, 10-, and 15-year follow-up examinations of 1.06, 1.00, 1.09, and 1.15 per 100 person-years, respectively.

Using a CHA₂DS₂-VASc score of 0 as the reference in Cox regression analysis models, the hazard ratios at 1-year follow-up associated with CHA₂DS₂-VASc scores of 1, 2, 3, 4, 5, 6, and 7 were 1.62, 2.99, 3.93, 5.45, 6.21, 5.20, and 12.15, respectively (Table 4, Central Illustration). The hazard ratios in predicting

ischemic stroke at 5-, 10-, and 15-year follow-up examinations associated with CHA₂DS₂-VASc scores are also shown in Table 4 and the Central Illustration.

In this “low-risk” subgroup using the ATRIA score, the c-index for CHA₂DS₂-VASc in predicting ischemic stroke (0.629, 95% CI: 0.616 to 0.641) was significantly higher than that of the ATRIA score (0.593, 95% CI: 0.587 to 0.598; DeLong test, *p* < 0.001). The CHA₂DS₂-VASc score also improved the NRI by 9.2% compared with the ATRIA score (*p* < 0.0001).

DISCUSSION

In this nationwide cohort study, we demonstrated that the CHA₂DS₂-VASc scoring system performed better than the ATRIA scoring system in predicting ischemic stroke among nonanticoagulated AF patients, as assessed by c-indexes and NRI. Even in patients categorized as “low-risk” using an ATRIA score of 0 to 5, the CHA₂DS₂-VASc score could further refine stroke risk stratification, with improved prediction for ischemic stroke on the basis of c-indexes. A CHA₂DS₂-VASc score of 0 could clearly identify truly low-risk subjects, whereas those defined using the ATRIA score were not actually low-risk patients, with 1-year event rates ranging from 1.06 (CHA₂DS₂-VASc score = 0) to 13.33 (CHA₂DS₂-VASc score = 7).

Stroke risk scoring schemes were initially developed with the goal of helping physicians to select patients who should receive OACs after considering the net clinical benefit, balancing stroke reduction against major bleeding, particularly with an “inconvenient” drug, warfarin (13). The CHADS₂ score was a popular scoring system in the past 10 years because of its simplicity in identifying “high-risk” patients. However, the annual stroke rate was still nearly 2% for patients with a CHADS₂ score of 0, suggesting that the CHADS₂ score was inadequate in identifying

TABLE 3 Event Rate of Ischemic Stroke Per 100 Person-Years in AF Patients With an ATRIA Score of 0-5 Substratified by CHA₂DS₂-VASc Scores

ATRIA Score Substratified	1-Year Follow-Up			5-Year Follow-Up			10-Year Follow-Up			15-Year Follow-Up		
	Person-Years	No. of Events	Stroke Rate	Person-Years	No. of Events	Stroke Rate	Person-Years	No. of Events	Stroke Rate	Person-Years	No. of Events	Stroke Rate
CHA ₂ DS ₂ -VASc = 0	8,511	90	1.06	34,710	341	1.00	53,486	584	1.09	59,194	683	1.15
CHA ₂ DS ₂ -VASc = 1	17,136	294	1.72	67,518	1,274	1.89	101,103	2,044	2.02	110,854	2,312	2.09
CHA ₂ DS ₂ -VASc = 2	19,453	617	3.17	71,918	2,246	3.12	102,566	3,354	3.27	109,810	3,659	3.33
CHA ₂ DS ₂ -VASc = 3	12,089	504	4.17	44,216	1,752	3.96	61,620	2,473	4.01	65,050	2,636	4.05
CHA ₂ DS ₂ -VASc = 4	4,020	233	5.80	13,616	614	4.51	17,795	786	4.42	18,374	830	4.52
CHA ₂ DS ₂ -VASc = 5	1,500	99	6.60	4,966	275	5.54	6,463	343	5.31	6,655	354	5.32
CHA ₂ DS ₂ -VASc = 6	362	20	5.52	1,195	52	4.35	1,444	69	4.78	1,460	71	4.86
CHA ₂ DS ₂ -VASc = 7	15	2	13.33	40	3	7.50	48	4	8.33	50	4	8.00
Total patients	63,086	1,859	2.95	238,179	6,557	2.75	344,525	9,657	2.80	371,447	10,549	2.84

Abbreviations as in Table 1.

truly low-risk patients; indeed, among patients with a low-risk CHADS₂ (score = 0), the stroke rate can be as high as 3.2%/year when substratified by the CHA₂DS₂-VASc score (4).

The introduction of new OACs has changed the landscape for stroke prevention in AF, given their relative efficacy, safety, and convenience (14,15). The use of new OACs may lower the threshold for initiating OAC for AF patients, as the tipping point threshold has shifted toward initiating OACs at a stroke rate of approximately 1%/year (16), given the positive net clinical benefit of new OACs, even in patients with a CHA₂DS₂-VASc score of 1 (17). Well-controlled warfarin therapy with a high time in the therapeutic range (>70%) has also been associated with low rates of stroke and bleeding (18-20).

More recently, the focus has shifted toward initially identifying patients who are truly at low risk for ischemic stroke, in whom no antithrombotic therapy is recommended (2,21). The CHA₂DS₂-VASc score has been shown in multiple cohorts to be the best for identifying truly low-risk patients, even in those with a CHADS₂ score of 0 (4,8). Indeed, the risk of ischemic stroke for AF patients with a CHA₂DS₂-VASc score of 0 was even as low as that of non-AF patients (10).

In the present study, we found that patients categorized as low-risk on the basis of their ATRIA scores were not actually at low risk, with an annual ischemic stroke rate of 2.95% at 1-year follow-up, which was even higher than the rate of life-threatening bleeding with dabigatran use in the RE-LY study (Randomized Evaluation of Long Term Anticoagulant Therapy With Dabigatran Etexilate) (1.22%/year for dabigatran 110 mg; 1.45%/year for dabigatran 150 mg) (14). Thus, if we used the ATRIA score to guide decisions for OAC therapy, a considerable number of patients who could benefit from new OACs or well-controlled warfarin therapy (with high time in therapeutic range) would be denied treatment. Moreover, among low-risk patients with an ATRIA score of 0 to 5, the CHA₂DS₂-VASc score could range from 0 to 7, and these patients had stroke rates as high as 13.3 per 100 person-years (1-year follow-up). For patients with an ATRIA score of 0, the annual risk of ischemic stroke was 1.28%, which was higher than that of patients with a CHA₂DS₂-VASc score of 0 (1.06%; 1-year follow-up). Accordingly, the CHA₂DS₂-VASc score may perform better than the ATRIA score in identifying truly low-risk patients.

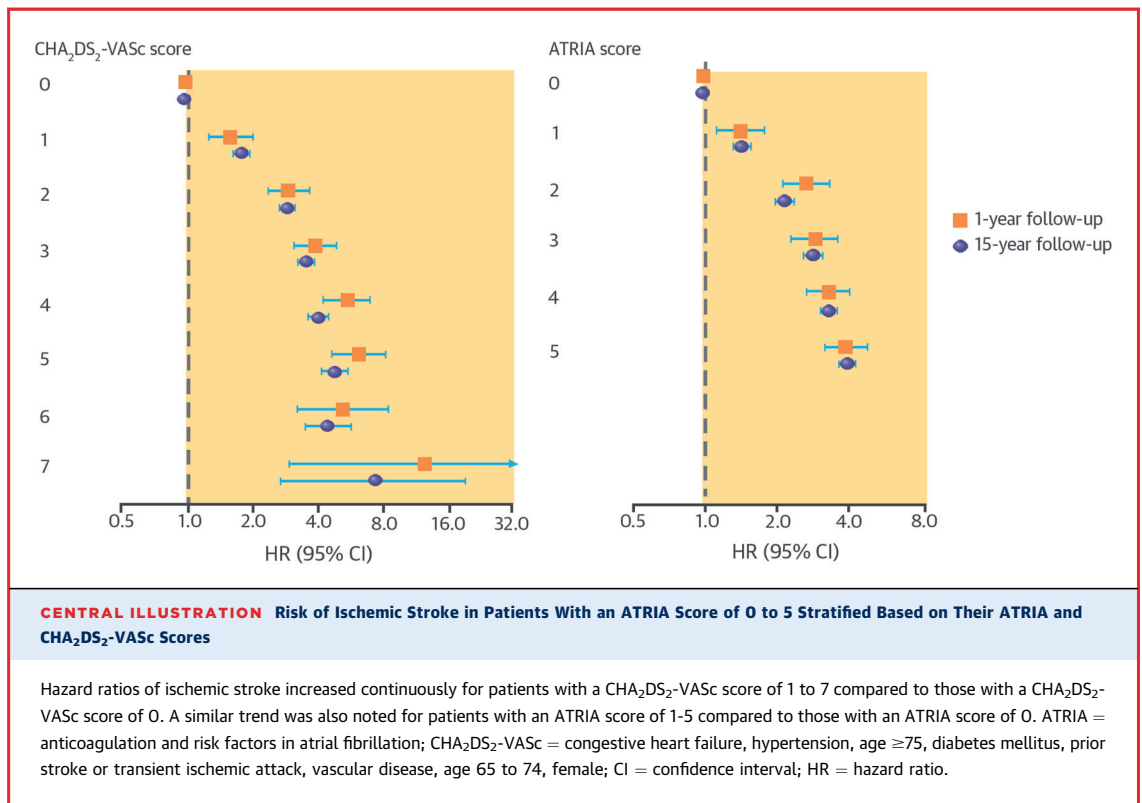
Compared with the CHA₂DS₂-VASc score, the ATRIA score includes renal dysfunction (eGFR <45 ml/min or ESRD) and proteinuria instead of vascular diseases in the scoring system. Whether renal dysfunction is an

TABLE 4 Risk of Ischemic Stroke in Patients with an ATRIA Score of 0 to 5, Stratified on the Basis of Their CHA₂DS₂-VASc Scores

CHA ₂ DS ₂ -VASc Score	No. of Events	Person-Years	HR	95% CI	p Value
1-yr follow-up					
0	90	8,511	-	-	-
1	294	17,136	1.62	1.28-2.05	<0.001
2	617	19,453	2.99	2.40-3.73	<0.001
3	504	12,089	3.93	3.14-4.92	<0.001
4	233	4,020	5.45	4.27-6.95	<0.001
5	99	1,500	6.21	4.67-8.26	<0.001
6	20	362	5.20	3.20-8.44	<0.001
7	2	15	12.15	3.00-49.31	0.001
5-yr follow-up					
0	341	34,710	-	-	-
1	1,274	67,518	1.92	1.70-2.16	<0.001
2	2,246	71,918	3.18	2.83-3.56	<0.001
3	1,752	44,216	4.03	3.59-4.52	<0.001
4	614	13,616	4.58	4.01-5.23	<0.001
5	275	4,966	5.63	4.80-6.59	<0.001
6	52	1,195	4.42	3.30-5.92	<0.001
7	3	40	7.53	2.43-23.34	0.001
10-yr follow-up					
0	584	53,486	-	-	-
1	2,044	101,103	1.86	1.69-2.04	<0.001
2	3,354	102,566	3.02	2.76-3.29	<0.001
3	2,473	61,620	3.71	3.39-4.06	<0.001
4	786	17,795	4.11	3.69-4.57	<0.001
5	343	6,463	4.94	4.32-5.65	<0.001
6	69	1,444	4.48	3.49-5.76	<0.001
7	4	48	7.77	2.91-20.77	<0.001
15-yr follow-up					
0	683	59,194	-	-	-
1	2,312	110,854	1.82	1.67-1.98	<0.001
2	3,659	109,810	2.94	2.71-3.19	<0.001
3	2,636	65,050	3.60	3.31-3.91	<0.001
4	830	18,374	4.06	3.67-4.50	<0.001
5	354	6,655	4.79	4.21-5.45	<0.001
6	71	1,460	4.44	3.48-5.67	<0.001
7	4	50	7.16	2.68-19.14	<0.001

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

important risk factor with an additive role that improves risk stratification scores in AF has been the subject of some attention. In the analysis of ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) trial cohort, reduced creatinine clearance was an independent predictor of stroke and systemic embolism. In that anticoagulated trial cohort that selected only high-risk AF patients for study and excluded those with severe renal failure, a risk model including creatinine clearance could improve NRI by 6.2% compared with CHA₂DS₂-VASc and by 8.2% compared with CHADS₂ (22). Subsequent studies with a broader range of AF stroke risk and renal dysfunction



have not confirmed an additive impact of renal impairment to stroke prediction using the CHA₂DS₂-VASc or CHADS₂ score (23-25). The ATRIA score assigns 1 point for ESRD patients, and because new OACs are contraindicated in patients with severe renal dysfunction, use of the ATRIA score to determine the strategy of stroke prevention in the era of new OACs may perhaps be suboptimal. Another unique characteristic of the ATRIA scheme was that it calculated scores for patients with or without prior stroke by using different rules (i.e., different weighting for risk), and the inconvenient calculation process may prohibit its widespread acceptance.

STUDY LIMITATIONS. Our study is the first population-based investigation comparing the performances of ATRIA and CHA₂DS₂-VASc scores for stroke prediction in nonanticoagulated AF patients. The strength of our study is the use of a nationwide dataset, which enrolled a large sample of subjects. However, some limitations are still evident. First, precise data about eGFR were not recorded in this registry database. Thus, we used the diagnosis of chronic kidney disease to represent eGFR of <45 ml/min for calculation of the ATRIA score. Because the diagnosis of chronic kidney disease in our database may not be adequately sensitive, a significant number of individuals with reduced eGFR could be missed

and were potentially misclassified by ATRIA score as low-risk patients. Second, the types of AF (paroxysmal or nonparoxysmal) were not available from this nationwide dataset. Because the risk of stroke does not differ between patients with paroxysmal and those with nonparoxysmal AF (26), the type of AF would not confound the findings of this study. Third, because the present study enrolled only Asian patients, whether the results can be extrapolated to non-Asian population remains uncertain.

CONCLUSIONS

In this real-world nationwide AF cohort study, we demonstrated that the CHA₂DS₂-VASc score performs better than the ATRIA scoring system in predicting ischemic stroke. Importantly, patients categorized as “low-risk” using the ATRIA score were not necessarily at low risk, and annual stroke rates can be as high as 2.95% at 1-year follow-up and 2.84% at 15-year follow-up. In contrast, patients with a CHA₂DS₂-VASc score of 0 had a truly low risk of ischemic stroke.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The CHA₂DS₂-VASc score performed better than the ATRIA score in predicting ischemic stroke in AF patients, as assessed by the c-statistic and net reclassification index.

COMPETENCY IN PATIENT CARE: The CHA₂DS₂-VASc score may be used for stroke risk stratification in Asian patients with atrial fibrillation.

TRANSLATIONAL OUTLOOK: Additional research is needed to determine whether incorporation of additional risk factors, including validated biomarkers, could further refine clinical risk stratification for patients with atrial fibrillation.

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KEY WORDS ATRIA score, atrial fibrillation, CHA₂DS₂-VASc score, ischemic stroke

APPENDIX For a supplemental table, please see the online version of this article.