Risks of Ischemic Stroke/Transient Ischemic Attack Based on CHA₂DS₂-VASc Scores in Non-Atrial Fibrillation Chinese Patients with Sinus Rhythm

A Large-Scale Observational Study Using Kailuan Cohort Data

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Summary

This study aims to evaluate the incidence of ischemic stroke or transient ischemic attack (TIA) based on CHA₂DS₂-VASc scores in non-AF Chinese patients with sinus rhythm.

We used health check-up data of 101,510 participants from the Kailuan Cohort Study. Participants' risk levels were defined by their CHA₂DS₂-VASc scores (range 0-3): Men with scores of 0, 1, or ≥ 2 and women with scores of 1, 2, or ≥ 3 were considered at low, intermediate, or high risk, respectively. Cox proportional hazards model was used to assess the association between the CHA₂DS₂-VASc-determined risk and the incidence of ischemic stroke/TIA.

The mean 7.5 year follow-up examination revealed 2968 ischemic strokes/TIA events. The incidence rates for ischemic stroke/TIA events in men and women were 3.8% and 1.5%, respectively. The incidence of ischemic stroke/TIA increased with elevated predicted risks based on CHA₂DS₂-VASc scores in men: 2.2% for low-risk, 4.1% for intermediate-risk, and 7.8% for high-risk groups ($P < 0.001$ for trend). The incidences of ischemic stroke/TIA also increased with elevated predicted risks in women: 0.8% for low-risk, 2.1% for intermediate-risk, and 5.0% for high-risk groups ($P < 0.001$ for trend). Compared with low-risk group, the crude hazard ratio (95% confidence interval) of ischemic stroke/TIA for men in moderate- and high-risk groups were 1.96 (1.79-2.14; $P < 0.001$) and 4.18 (3.81-4.57; $P < 0.001$). Similar findings were observed in women.

Risks of ischemic stroke/TIA events was high, particularly among those with high CHA₂DS₂-VASc scores. (Int Heart J 2021; 62: 312-319)

Key words: Cardiovascular disease, Arrhythmia, Risk model, Prediction

Ischemic stroke is one of the serious medical conditions with a greater risk for recurrent cardiovascular events. Currently, it is one of the top leading causes of death in China,¹⁾ which calls for greater attention for an early risk assessment and stratification. Although atrial fibrillation (AF) is an independent risk factor for ischemic stroke and the commonest arrhythmia observed in health-care facilities, earlier evidence emphasized that non-AF patients can also be predisposed to transient ischemic stroke.²⁾

Recently, the CHA₂DS₂-VASc score, which extended from the CHADS₂ score by adding three score elements for ages 65-74 years, vascular disease, and gender, has received renewed interest. Particularly, the CHA₂DS₂-VASc score has been incorporated by the European Society of

Cardiology in its 2016 guideline, for predicting the risk of ischemic stroke in patients with non-valvular AF.^{3,4)} Additionally, previous studies support the hypothesis that the utilization of CHA₂DS₂-VASc scoring criteria was able to improve the prediction of thromboembolism in patients with hypertension and sinus rhythm⁵⁾ and heart failure and sinus rhythm⁶⁾ and in those with an implantable monitoring device and sinus rhythm.⁷⁾ Given that the data of thromboembolism may be superior to that of ischemic stroke/transient ischemic attack (TIA), it is highly important to consider the prediction power of CHA₂DS₂-VASc score for ischemic stroke/TIA to review the prediction capacity of CHA₂DS₂-VASc score in non-AF patients.

Although the CHA₂DS₂-VASc score has been widely used to evaluate the risk of ischemic stroke/TIA in pa-

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Figure 1. Flow chart of the study participants.

tients with AF, according to CHA₂DS₂-Vasc scores in China, there has been limited evidence on the ischemic stroke/TIA in non-AF patients with sinus rhythm. In the extension of this, the concept of searching for ischemic stroke/TIA regardless of AF existence has emerged. Thus, the purpose of the present large-scale observational study using data from the Kailuan Cohort Study (KCS) was to evaluate the incidence of ischemic stroke/TIA according to CHA₂DS₂-VASc scores in Chinese patients with sinus rhythm who were free from AF.

Methods

Study participants: The data that support the findings of this study are available from the corresponding author upon reasonable request. This observational study was based on health check-ups of the workers of a coal company from the Kailuan community in Tangshan City, Hebei Province of China. A brief description of KCS has previously been described elsewhere.⁸⁾ Altogether, 101,510 (81,110 men and 20,400 women, aged 18-98 years) individuals who belonged to the company during the study period (January 2008 and December 2016) and who had no definitive diagnoses of atrial flutter or AF (International Classification of Diseases, Tenth Revision [ICD-10]: I48) were extracted. A total of 99,386 participants were included in the data analysis after excluding those who were in AF at baseline ($n = 407$), had incomplete electrocardiogram (ECG) data ($n = 955$), died before ischemic stroke/TIA ($n = 655$), and had severe arrhythmias such as supraventricular tachycardia, atrial flutter, or frequent ventricular premature contractions ($n = 107$). The flow diagram describes the selection of the study participants (Figure 1). The Ethics Committee of Kailuan General Hospital approved the present study, and all the participants provided written informed consent. The study protocol con-

forms to the guidelines of the Helsinki Declaration II.

Data collection: A self-administered questionnaire was distributed during each health check-ups to collect data on demography, anthropometry, lifestyle, past medical history, clinical history of cardiovascular disease (CVD), medication use, and CVD risk factors. ECG data were detected either by 12-lead ECG or Holter reports. To avoid bias, participants who did not show sinus arrhythmia in the ECG but had a history of arrhythmia based on clinical records were excluded.

Follow-up and outcomes: Participants were followed from the first visit to the last visit during the study period (December 31, 2016) for the occurrence of ischemic stroke/TIA. The occurrences of ischemic stroke/TIA were retrieved and ascertained from the medical records. Individuals who died or moved out of the coal company because of a job change during the follow-up were censored. We defined outcomes as admission to a hospital because of ischemic stroke/TIA. Ischemic stroke was defined as any neurologic deficit lasting for > 24 hours confirmed by the help of magnetic resonance imaging (MRI) or computed tomography (CT) or a persistent focal neurological deficit lasting longer than 24 hours regardless of MRI or CT findings. TIA was defined as a sudden onset, temporary neurologic deficit presumably due to reduced blood flow in a particular cerebral artery lasting for ≤ 24 hours with a complete resolution of the neurologic deficit but with no signs of cerebral infarction on brain imaging. Of note, all patients who fulfill the criteria of stroke/TIA with comorbidity of AF were excluded during the outcomes assessment with the intention to avoid bias associated with AF, considering that AF is an independent risk factor for ischemic stroke and is being reported to strongly associate with CHA₂DS₂-VASc score previously.

Definition of explanatory variables: The CHA₂DS₂-VASc score included the patient's age and sex, the pres-

ence of congestive heart failure (CHF), hypertension (HTN), diabetes mellitus (DM), history of ischemic stroke/TIA, and/or vascular disease. Participants were divided into two groups by sex. CHF is defined as per the New York Heart Association classification of grades II to IV (clinical heart failure with mild to severe symptoms or with moderate-severe clinical evidence of LV dysfunction) in the past 6 months. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured from the upper right arm thrice after 30 minutes in the seated position, and the average of these three readings was recorded as the SBP and DBP values. HTN is defined as SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg, a self-reported history of hypertension or history of current antihypertensive use. DM was defined as fasting blood glucose (FBG) $\geq$ 7 mmol/L or self-reported use of glucose-lowering drugs. Vascular disease was defined as any previous myocardial infarction or peripheral vascular disease. The estimated glomerular filtration rate (eGFR) was calculated using a chronic kidney disease epidemiology collaborative equation.⁹⁾ Smoking and drinking status were self-reported and classified as never smokers/drinkers, past smokers/drinkers, or current smokers/drinkers based on the claims data or a disease history according to questionnaires administered at the health check-ups. Finally, we calculated the CHA₂DS₂-VASc score. A CHA₂DS₂-VASc score of 0 in men or 1 in women classified them as at low risk; 1 in men or 2 in women as at intermediate risk; and $\geq$ 2 in men or $\geq$ 3 in women as at high risk.¹⁰⁾

Statistical analyses: Continuous variables were expressed as mean $\pm$ standard deviation, and categorical variables were expressed as percentages. The demographic and clinical variables were compared using Student's *t*-test or Chi-squared test. Incidence rates were obtained by extracting all ischemic stroke/TIA during a 7.5 year follow-up period divided by the total number of participants in a particular CHA₂DS₂-VASc score. Kaplan-Meier survival curves were performed to study the differences in survival as stratified by baseline CHA₂DS₂-VASc score. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) and confidence interval (CI) for incident ischemic stroke/TIA events. The model was adjusted for age, body mass index, SBP, low-density lipoprotein cholesterol, FBG, serum uric acid, eGFR, recent smoking, recent alcohol use, and physical activity. Receiver-operating characteristic curve analysis was applied to analyze the performance of CHA₂DS₂-VASc score in ischemic stroke/TIA prediction. The C-Statistic (area under the curve) was presented as a unified estimate of sensitivity and specificity. All data were analyzed via SAS software. All statistical tests are two-sided, and *P* < 0.05 was considered statistically significant.

Results

Descriptive analysis: After a mean follow-up duration of 63.4 ± 10.7 months, a total of 99,386 participants (79,195 men and 20,191 women) were included in the final analysis. In total, 2,968 of the 3,277 (3.3%) participants who had ischemic stroke/TIA were men, which accounted for 90.6% of the ischemic stroke/TIA population. The mean

(SD) ages of ischemic stroke/TIA patients were 61.0 ± 10.1 , and 60.0 ± 8.9 , respectively. Among men, 710 participants had vascular disease, 318 participants were diagnosed with heart failure, and 1,430 participants had a history of ischemic stroke/TIA. Among female participants, the numbers of people with a history of vascular disease, heart failure, and previous ischemic stroke/TIA were 98, 39, and 234, respectively. Table I shows the comparison of the baseline characteristics of men and women participants. Participants with ischemic stroke /TIA were older and had a higher proportion of HTN, DM, CHF, vascular disease, and previous history of ischemic stroke/TIA (*P* < 0.001). The participants with ischemic stroke/TIA were more frequently treated with antihypertensive drugs and anti-diabetic drugs.

Distribution of the CHA₂DS₂-VASc scores: During the mean 7.5 year follow-up, 3,277 ischemic stroke/TIA events were observed. Most men and women had CHA₂DS₂-VASc scores of $\leq$ 3. The incidence rate and incidence density of ischemic stroke/TIA were increased with heightened CHA₂DS₂-VASc risk. For instance, the incidence of ischemic stroke/TIA ranged from 2.2% in men with a CHA₂DS₂-VASc score of 1 to 13.9% in those men with a score of 6. Additionally, the incidence of ischemic stroke/TIA increased from 0.8% to 20.5% for women who scored 1 and 6, respectively. Table II shows the incidence rate and incidence density of ischemic stroke/TIA according to CHA₂DS₂-VASc scores. Men and women with CHA₂DS₂-VASc scores of 6 had the highest incidence density of ischemic stroke/TIA (25.5 and 32.8 per 1000 person-years for men and women, respectively). In men, the incidence rates of ischemic stroke/TIA increased with an elevation of predicted risks based on CHA₂DS₂-VASc scores: 2.2% for low-risk, 4.1% for intermediate-risk, and 7.8% for high-risk groups (*P* < 0.001 for trend). Moreover, the incidence rate of ischemic stroke/TIA in women increased with elevated predicted risks based on CHA₂DS₂-VASc scores: 0.8% for low-risk, 2.1% intermediate-risk, and 5.0% high-risk groups (*P* < 0.001 for trend).

Incidences and HRs for ischemic stroke/TIA according to the CHA₂DS₂-VASc risk groups: Elevated CHA₂DS₂-VASc scores were significantly associated with ischemic stroke/TIA. Table III shows incidences and HRs for ischemic stroke/TIA according to the CHA₂DS₂-VASc risk groups. Compared with low-risk group, the crude HR (95% CI) of ischemic stroke/TIA for men in moderate- and high-risk groups were 1.96 (1.79-2.14; *P* < 0.001) and 4.18 (3.81-4.57; *P* < 0.001). Similar findings were observed in women. The linear association of the CHA₂DS₂-VASc risk group with ischemic stroke/TIA remained significant even after adjusting for potential confounding factors (all *P* < 0.001 for trend). Similarly, the incidences and risk of ischemic stroke/TIA increased with an elevation of predicted risks based on CHA₂DS₂-VASc scores across the different age groups in men and women (Figure 2).

Among the factors that make up the CHA₂DS₂-VASc score, prior history of ischemic stroke/TIA accounts for the highest risk for ischemic stroke/TIA, followed by hypertension, diabetes, and age $\geq$ 75 years. The HRs (95%

Table I. Baseline Clinical Characteristics of the Participants

	Men				Women			
	Total	Ischemic stroke/TIA	No ischemic stroke/TIA	P-value	Total	Ischemic stroke/TIA	No ischemic stroke/TIA	P-value
Number, <i>n</i> (%)	79,195	2,968 (3.75%)	76,227 (96.25%)	< 0.001	20,191	309 (1.53%)	19,882 (98.47%)	< 0.001
Age, years	54.5 ± 12.8	61.0 ± 10.1	54.2 ± 12.8	< 0.001	50.8 ± 11.5	60.0 ± 8.9	50.6 ± 11.5	< 0.001
BMI (kg/m ²)	25.0 ± 3.3	25.6 ± 3.4	25.0 ± 3.3	< 0.001	24.6 ± 3.7	26.3 ± 3.5	24.6 ± 3.7	< 0.001
SBP (mmHg)	133.7 ± 20.2	146.6 ± 22.1	133.2 ± 20.0	< 0.001	124.3 ± 21.0	139.6 ± 22.3	124.1 ± 20.9	< 0.001
DBP (mmHg)	85.9 ± 11.4	90.8 ± 12.7	85.7 ± 11.3	< 0.001	79.8 ± 11.0	85.1 ± 12.7	79.7 ± 10.9	< 0.001
TC (mmol/L)	5.1 ± 1.4	5.2 ± 1.7	5.1 ± 1.4	< 0.001	5.1 ± 1.8	5.4 ± 1.1	5.1 ± 1.8	< 0.001
LDL-C (mmol/L)	2.6 ± 1.2	2.7 ± 1.0	2.6 ± 1.2	0.003	2.7 ± 1.1	2.8 ± 1.0	2.7 ± 1.1	0.006
FBG (mmol/L)	5.7 ± 1.8	6.3 ± 2.4	5.7 ± 1.8	< 0.001	5.5 ± 1.7	6.7 ± 2.9	5.5 ± 1.7	< 0.001
SUA (mg/dL)	295.7 ± 84.3	300.4 ± 89.8	295.5 ± 84.0	0.010	247.7 ± 68.8	262.0 ± 77.7	247.5 ± 68.6	0.001
eGFR (mL/minute/1.73 m ²)	89.9 ± 25.7	84.6 ± 23.3	90.1 ± 25.8	< 0.001	86.0 ± 23.0	79.0 ± 20.3	86.2 ± 23.0	< 0.001
Hypertension, <i>n</i> (%)	29,482 (37.2%)	1,579 (53.2%)	27,903 (36.6%)	< 0.001	5,498 (27.2%)	161 (52.1%)	5,337 (26.8%)	< 0.001
Diabetes, <i>n</i> (%)	6,816 (8.6%)	476 (16.0%)	6,340 (8.3%)	< 0.001	1,548 (7.7%)	78 (7.7%)	1,470 (7.4%)	< 0.001
Hyperlipidemia, <i>n</i> (%)	4,134 (5.2%)	213 (7.2%)	3,921 (5.1%)	< 0.001	1,156 (5.7%)	30 (9.7%)	1,126 (5.7%)	0.002
Current smoker, <i>n</i> (%)	25,034 (31.6%)	850 (28.6%)	24,184 (31.7%)	< 0.001	189 (0.9%)	9 (2.9%)	180 (0.9%)	< 0.001
Alcohol use, <i>n</i> (%)	14,750 (18.6%)	541 (18.2%)	14,209 (18.6%)	0.571	61 (0.3%)	3 (1.0%)	58 (0.3%)	0.031
Physical activity, <i>n</i> (%)	11,337 (14.3%)	494 (16.6%)	10,843 (14.2%)	< 0.001	3,210 (15.9%)	64 (20.7%)	3,146 (15.8%)	0.020
Anti-hypertensive drugs use, <i>n</i> (%)	6,061 (7.7%)	466 (15.7%)	5,595 (7.3%)	< 0.001	2,118 (10.5%)	81 (26.2%)	2,037 (10.2%)	< 0.001
Anti-diabetic drugs use, <i>n</i> (%)	2,824 (3.6%)	236 (8.0%)	2,588 (3.4%)	< 0.001	938 (4.6%)	54 (17.5%)	884 (4.4%)	< 0.001
Follow-up time (years)	7.5 ± 1.5	4.2 ± 2.4	7.6 ± 1.3	< 0.001	7.7 ± 0.9	4.1 ± 2.3	7.8 ± 0.8	< 0.001
CHA ₂ DS ₂ -VASc mean	0.7 ± 0.9	1.2 ± 1.1	0.7 ± 0.9	< 0.001	1.5 ± 0.8	2.2 ± 1.2	1.5 ± 0.8	< 0.001

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; FBG, fasting blood glucose; SUA, serum uric acid; and eGFR, glomerular filtration rate.

Table II. Distribution of the CHA₂DS₂-VASc Scores and Incidences of Ischemic Stroke/TIA

Score	Men				Women			
	Number	Ischemic stroke/TIA	Incidence (%)	Incidence density (per 1000 person-years)	Number	Ischemic stroke/TIA	Incidence (%)	Incidence density (per 1000 person-years)
0	39,630	873	2.2	2.84	/	/	/	/
1	26,920	1,112	4.1	5.51	13,262	103	0.8	1.00
2	9,449	638	6.8	9.83	4,912	105	2.1	2.81
3	2,318	222	9.6	14.67	1,478	59	4.0	5.40
4	651	90	13.8	22.33	380	24	6.3	8.93
5	187	28	15.0	25.21	113	10	8.8	12.71
6	36	5	13.9	25.48	39	8	20.5	32.77
7	4	0	0	0	7	0	0	0
Total	79,195	2,968	3.7	4.54	20,191	309	1.5	2.00

CI) associated with prior ischemic stroke/TIA, hypertension, diabetes, and age ≥ 75 years for the risk of ischemic stroke/TIA were 2.76 (2.35-3.24), 2.43 (2.16-2.72), 1.90 (1.70-2.13), and 1.77 (1.37-2.28), respectively. Table IV shows the crude and adjusted HR (95% CI) for each component of CHA₂DS₂-VASc scores.

The risk of ischemic stroke/TIA and predictive ability of the CHA₂DS₂-VASc scores: The ischemic stroke/TIA gradually increased across ascending categories of CHA₂DS₂-VASc scores. The CHA₂DS₂-VASc scores pre-

dicted the ischemic stroke/TIA with the Kaplan-Meier curves displaying a decreased survival probability for patients who scored high CHA₂DS₂-VASc scores (Figure 3). The prediction analyses of ischemic stroke/TIA events based on CHA₂DS₂-VASc scores yielded an area under the curve (AUC) of 0.64 and 0.69 for men and women with sinus rhythm, respectively (Figure 4).

Table III. Incidence, Crude, and Adjusted Hazard Ratios for Ischemic Stroke/TIA According to the CHA₂DS₂-VASc Risk Groups

Gender/risk groups	Number of ischemic stroke/TIA	Incidence rate (%)	Crude HR (95% CI)	<i>P</i> for Trend	Adjusted HR (95% CI)	<i>P</i> for trend
Men						
Low (0)	873	2.2	1	< 0.001	1	< 0.001
Intermediate (1)	1,112	4.1	1.96 (1.79–2.14) ***		2.01 (1.72–2.34) ***	
High (≥ 2)	983	7.8	4.18 (3.81–4.57) ***		2.74 (2.28–3.29) ***	
Women						
Low (1)	103	0.8	1	< 0.001	1	< 0.001
Intermediate (2)	105	2.1	2.85 (2.17–3.74) ***		2.16 (1.40–3.35) ***	
High (≥ 3)	101	5.0	7.05 (5.35–9.28) ***		3.46 (2.04–5.85) ***	

CHA₂DS₂-VASc scores are interpreted as follows: low risk was 0 in men and 1 in women; intermediate risk was 1 in men and 2 in women; high risk was ≥ 2 in men and ≥ 3 in women. The model was adjusted for age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, fasting blood glucose, serum uric acid, glomerular filtration rate, current smoking, recent alcohol use, and physical activity.

P* < 0.05; *P* < 0.01; ****P* < 0.001.

Figure 2. Comparison of ischemic stroke/TIA risk among the different risk groups stratified by age and gender. Adjusted hazard ratio and 95% CI for ischemic stroke/TIA for men aged 18–45 years (A), 45–65 years (B), and ≥ 65 years (C). Adjusted hazard ratio and 95% CI for ischemic stroke/TIA for women aged 18–45 years (D), 45–65 years (E), and ≥ 65 years (F).

Discussion

This large-scale observational study in China comprehensively evaluated the natural history of individuals with sinus rhythm who were not on AF. Among them, the incidences of ischemic stroke/TIA for men and women were 3.7% and 1.5%, respectively. The risks of ischemic stroke/TIA events increased with elevation of the CHA₂DS₂-VASc score. The highest risks were observed for the high-risk group with CHA₂DS₂-VASc scores of ≥ 3 for men and women.

Previous studies have similarly explored the use of CHA₂DS₂-VASc score for risk stratification of ischemic stroke in non-AF populations. The CHA₂DS₂-VASc score has been used to predict ischemic stroke in sinus rhythm

with post-myocardial infarction,¹¹⁾ diabetes,¹²⁾ and post-coronary artery bypass grafting.¹³⁾ Additionally, another study explored the predictive effect of CHA₂DS₂-VASc score on ischemic stroke, major bleeding, and death in patients with heart failure with reduced ejection fraction.¹⁴⁾ According to a prior study, the incidence of ischemic stroke among AF patients without anticoagulation for the entire cohort following the CHA₂DS₂-VASc score have been reported at 0.44% to 4.0% for overall,¹⁵⁾ 0% to 0.95% for low-risk patients,¹⁰⁾ 0.10% to 6.6% for intermediate-risk patients,^{10,16)} and 2.4% to 6.2% for high-risk patients.¹⁷⁾ Evidence from prior studies, however, was mainly derived from Western populations, with only limited evidence from a Chinese population. The result of the present study showed that heightened CHA₂DS₂-VASc

Table IV. Crude and Adjusted HR (95% CI) for Each Component of CHA₂DS₂-VASc Scores

	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Heart failure	2.41 (1.53, 3.78)	< 0.001	1.66 (0.96, 2.86)	< 0.001
Hypertension	2.13 (1.98, 2.30)	< 0.001	2.43 (2.16, 2.72)	< 0.001
Age > 75 years	2.22 (1.91, 2.59)	< 0.001	1.77 (1.37, 2.28)	< 0.001
Diabetes	2.326 (2.10, 2.57)	< 0.001	1.90 (1.70, 2.13)	< 0.001
Prior ischemic stroke/TIA	5.27 (4.56, 6.10)	< 0.001	2.76 (2.35, 3.24)	< 0.001
Vascular disease	2.50 (1.90, 3.30)	< 0.001	1.63 (1.22, 2.17)	< 0.001
Sex category (female)	2.52 (2.21, 2.87)	< 0.001	1.61 (1.37, 1.90)	< 0.001

Crude model: Unadjusted model, Adjusted model: The model was adjusted for age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, fasting blood glucose, serum uric acid, glomerular filtration rate, current smoking, recent alcohol use, and physical activity.

Figure 3. Cumulative event-free rate of ischemic stroke/TIA stratified by CHA₂DS₂-VASc in 2,968 men (A) and 309 women (B) with sinus rhythm enrolled in the Kailuan Cohort Registry.

score was associated with an increased risk of ischemic stroke/TIA in participants with sinus rhythm in the Chinese population.

In the present study, we showed that the CHA₂DS₂-VASc score has a good performance to predict the risk of ischemic stroke/TIA outcomes in patients with sinus rhythm. The risk prediction of CHA₂DS₂-VASc score for ischemic stroke/TIA among Chinese patients with sinus rhythm seems compatible with previous studies that showed similar prediction capacity in Chinese patients with AF who were not on anticoagulants. Chan, *et al.*¹⁸⁾ used the CHA₂DS₂-VASc score to predict adverse vascular function, ischemic stroke, and cardiovascular death in high-risk patients (those with prior coronary artery disease or ischemic stroke or DM) without AF. Additionally, Chan, *et al.* reported that the CHA₂DS₂-VASc score had good predictive power for ischemic stroke (C-statistic of 0.68), indicating that CHA₂DS₂-VASc scores were predictors for ischemic stroke.

Evidence from prior studies reported that patients with established AF are at high risk for ischemic stroke events and mortality. The elements that make up the CHA₂DS₂-VASc score are risk factors for AF and ischemic stroke. Although AF and ischemic stroke share common risk factors, the CHA₂DS₂-VASc score has been reported as an efficient scheme in predicting the risk of ischemic stroke in AF patients. There is a significant variation of the underlying risk of ischemic stroke in patients

without AF. For instance, heart failure is a known risk factor for ischemic stroke in people without AF.¹⁹⁾ Other risks of ischemic stroke during heart failure include hemodynamic changes caused by decreased ejection fraction during heart failure, blood coagulation activation, decreased fibrinolytic activity, and endothelium dysfunction. Additionally, inflammation plays an essential role in heart failure.²⁰⁾ Reportedly, left ventricular thrombosis due to insufficient ejection and hypercoagulability during heart failure can cause ischemic stroke.²¹⁾ The combination of vascular endothelial injury, inflammation, the formation of atherosclerotic plaques and narrowing of blood vessels, and shedding of atherosclerotic plaques could increase the incidence of ischemic stroke events.^{22,23)} The empirical use of direct oral anticoagulant for high-risk patients with sinus rhythm may not be entirely effective.^{24,25)} The occurrence of such a gap in the effectiveness of anticoagulants may contribute to the lack of early prediction and could be an explanation for the relatively high risk of ischemic stroke. Thus, the application of the CHA₂DS₂-VASc score in sinus rhythm can be meaningful because the new onset of AF increases in patients with high CHA₂DS₂-VASc scores.

It is well documented that those patients with cardiovascular comorbidity, at the moment of the appearance of new AF, are at high risk for ischemic stroke/TIA. In the present study, among the factors that make up the CHA₂DS₂-VASc score, prior history of ischemic stroke/

Figure 4. Prediction analyses of ischemic stroke/TIA events based on CHA₂DS₂-VASc scores.

TIA, hypertension, and diabetes consecutively carry a significant HR for ischemic stroke/TIA risk. Despite that age ≥ 75 years was significantly associated with the risk of ischemic stroke/TIA, it carried a lower risk compared with the aforementioned variables. This can be explained by the fact that the population in the present study comprises oilfield employees, of whom the majority of them were younger than 75 years old. Although how to detect AF in the high-risk populations is a critical challenge and, so far, it still requires an in-depth investigation, continuous follow-up for those patients with sinus rhythm with known risk factors such as a prior history of ischemic stroke/TIA, hypertension, and diabetes is of high importance.

Earlier evidence consistently reported that males have an increased incidence of ischemic stroke/TIA, whereas females have an increased incidence of AF. Our study also replicated similar findings that a substantial number of ischemic stroke/TIA events occurred in men. As such researchers could use a modification of the CHA₂DS₂-VASc score where the male gender would be scored instead of the female gender. Such a modified CHA₂DS₂-VASc score might be a better predictor of non-AF ischemic stroke/TIA risk. At the same time, it will not only eliminate the need to subtract 1 point for females, but it will resolve the dilemma of scoring the CHA₂DS₂-VASc score in both AF and non-AF ischemic stroke/TIA.

Limitation: The main strength of this prospective cohort study is that it includes a large sample size of 99,386 cases, with a wide range of age (between 18 and 98 years), and the long follow-up and the rigorous assessment of outcome events from the general database of Kailuan Group's medical insurance, which covers various industries in Tangshan City. However, the present study has certain limitations. First, the data were collected from the ECG measurements and Holter reports, which were performed only once; thus, it may inevitably underesti-

mate arrhythmia incidence. The study would have benefited from the use of long-duration monitoring of cardiac rhythm, particularly among patients with increased risk of AF. Second, complete control of reporting bias is difficult because women may have underreported their ischemic stroke/TIA symptoms and may not have visited for medical care. However, we double-checked the KCS data, and we find out that, by far, coal companies enrolled more men than women, which contributed to a large incidence of ischemic stroke/TIA (90%) in men. Third, the result of this large-scale observational study is limited to ischemic stroke/TIA; thus, this study did not evaluate the incidence of total bleeding events of different anatomical locations. Fourth, all the participants were from the northern region of China, and a sample of coal company employees in a Chinese city does not represent the demographic of the rest of the world. This limits us to generalize the results at an international level. Hence, the results of this study may require replication for consistency from other parts of the country or other regions of the world. Fifth, our study did not consider adjustment for the use of antithrombotic agents in the multivariable model. We recommend further study to consider the influence of antithrombotic agents for the risk of stroke/TIA in the non-AF population with sinus rhythm.

Conclusion

To conclude, the risks of ischemic stroke/TIA events were high among Chinese patients with sinus rhythm who were free of AF, particularly among those with high CHA₂DS₂-VASc scores. Optimal management strategies, including blood pressure monitoring, modification of lifestyles, and glucose-lowering therapy are required for these high-risk patients with sinus rhythm. Further studies are needed to evaluate an early risk assessment and early intervention in high-risk populations for improving the risk of ischemic stroke/TIA among patients with established sinus rhythm.

Disclosure

Conflicts of interest: The authors declare that they have no conflict of interest.

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