A simple and easily implemented risk model to predict 1-year ischemic stroke and systemic embolism in Chinese patients with atrial fibrillation

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Abstract

Background: Accurate prediction of ischemic stroke is required for deciding anticoagulation use in patients with atrial fibrillation (AF). Even though only 6% to 8% of AF patients die from stroke, about 90% are indicated for anticoagulants according to the current AF management guidelines. Therefore, we aimed to develop an accurate and easy-to-use new risk model for 1-year thromboembolic events (TEs) in Chinese AF patients.

Methods: From the prospective China Atrial Fibrillation Registry cohort study, we identified 6601 AF patients who were not treated with anticoagulation or ablation at baseline. We selected the most important variables by the extreme gradient boosting (XGBoost) algorithm and developed a simplified risk model for predicting 1-year TEs. The novel risk score was internally validated using bootstrapping with 1000 replicates and compared with the CHA_2DS_2-VA score (excluding female sex from the CHA_2DS_2-VASc score).

Results: Up to the follow-up of 1 year, 163 TEs (ischemic stroke or systemic embolism) occurred. Using the XGBoost algorithm, we selected the three most important variables (congestive heart failure or left ventricular dysfunction, age, and prior stroke, abbreviated as CAS model) to predict 1-year TE risk. We trained a multivariate Cox regression model and assigned point scores proportional to model coefficients. The CAS scheme classified 30.8% (2033/6601) of the patients as low risk for TE (CAS score = 0), with a corresponding 1-year TE risk of 0.81% (95% confidence interval [CI]: 0.41%–1.19%). In our cohort, the C-statistic of CAS model was 0.69 (95% CI: 0.65–0.73), higher than that of CHA_2DS_2-VA score (0.66, 95% CI: 0.62–0.70, $Z = 2.01$, $P = 0.045$). The overall net reclassification improvement from CHA_2DS_2-VA categories (low = 0/high ≥1) to CAS categories (low = 0/high ≥1) was 12.2% (95% CI: 8.7%–15.7%).

Conclusion: In Chinese AF patients, a novel and simple CAS risk model better predicted 1-year TEs than the widely-used CHA_2DS_2-VA risk score and identified a large proportion of patients with low risk of TEs, which could potentially improve anticoagulation decision-making.

Trial Registration: www.chictr.org.cn (Unique identifier No. ChiCTR-OCH-13003729).

Keywords: Atrial fibrillation; Stroke; Risk prediction; CHA2DS2-VA; CHA2DS2-VASc

Introduction

Stroke prevention with oral anticoagulants (OAC) is one of the most important therapeutic pillars in the management of atrial fibrillation (AF).[1] Bleeding is a major concern in patients using OAC, with patients on warfarin having an annual risk of 2%–5% and 0.5%–1.0% for major and fatal bleeding, respectively.[2] Although the bleeding risk is lower with non-vitamin K antagonist oral anticoagulants, it remains an important concern in high-risk patients.[3] Hence, there is a critical need for better balancing benefit

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001515

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Chinese Medical Journal 2021;134(19)
Received: 20-01-2021 **Edited by:** Jing Ni

and harm by targeting stroke prevention efforts more precisely.

Several stroke risk stratification schemes in AF patients have been developed.[4-8] The CHA_2DS_2-VASc score,[5] which assigns 1 point when a patient has a history of heart failure, hypertension, diabetes mellitus, vascular disease, is 65 to 74 years old or is female, and 2 points if the patient is 75 years and older, or if the patient has a history of prior stroke/transient ischemic attack, is the most commonly recommended scheme for assessing thromboembolic risk in patients with AF.[9,10] Patients except those classified as low-risk (with a CHA_2DS_2-VASc score of 0 in men and 1 in women) are all indicated for OAC. In previous study cohorts, the low-risk group based on CHA_2DS_2-VASc score only accounts for <10% of the AF population.[11] That is, >90% of the AF patients are indicated for anticoagulation therapy, which suggests that the risk stratification scheme is very limited in a clinical sense.

New techniques in data analysis provide the opportunity for increased prediction precision. Based on the China Atrial Fibrillation (China-AF) Registry study, we aimed to find out a higher proportion of patients who can safely avoid unnecessary anticoagulant therapy by developing a risk model using the state-of-the-art machine learning techniques.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Beijing Anzhen Hospital (No. D11110700300000). Written informed consent was obtained from all study participants.

Study population

The China-AF Registry is a prospective, multicenter, and ongoing study of AF patients in Beijing, China. The rationale and design of the study were previously published.[12] From August 2011 to December 2017, a total of 23,108 patients were recruited from outpatient clinics and cardiac wards of 31 tertiary and non-tertiary hospitals located in Beijing. In this analysis, we excluded patients who received OAC treatment ($n = 15,667$) or underwent catheter ablation at baseline ($n = 330$), and patients without follow-up information ($n = 510$). Finally, 6601 AF patients were included in this study [Supplementary Figure 1, http://links.lww.com/CM9/A550].

Data collection and follow-up

Data on the patient's demographic characteristics, lifestyle factors, medical history, and treatment were collected at baseline. Each patient was followed up every 6 months at outpatient clinic or by telephone contact. Major adverse events, including death, non-fatal stroke, hospitalization, and major bleeding, were collected at each time of follow-up. As female sex was not considered as a risk factor for stroke by current AF guidelines,[9,10,13] a sexless CHA_2DS_2-VASc score, abbreviated as CHA_2DS_2-VA score, was calculated by excluding female sex from the CHA_2DS_2-VASc score. Person-time was censored at the time of OAC initiation, catheter ablation, first ischemic stroke or systemic embolism, death, or 1 year after enrollment.

Outcome assessment

The primary outcome was the time to the first occurrence of a thromboembolic event (TE), including ischemic stroke and systemic embolism, whichever came first. The transient ischemic attack was not included in the outcome events because it was notoriously difficult to diagnose. Patient-reported TEs were adjudicated by two independent neurologists separately. Disagreements on the diagnosis were resolved by discussion or a third neurologist.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as counts and percentages. The methodology of model derivation and validation in our analysis was shown in Supplementary Figure 2, http://links.lww.com/CM9/A550.

Model derivation

A total of 44 variables [Supplementary Table 1, http://links.lww.com/CM9/A550] were included as candidate predictors. The extreme gradient boosting (XGBoost), a state-of-the-art machine learning technique that assembles weak prediction models (typically decision trees) into a stronger classifier,[14] was used to select important features, and the result was validated by ten-fold cross-validation to reduce overfitting. The XGBoost algorithm can handle missing data automatically and estimate the relative contribution of each variable, thereby allowing feature importance ranking and feature selection. We constructed a Cox proportional hazards model based on the selected variables by the XGBoost model. The risk score was derived from coefficients of the three variables in the Cox regression model.

Model validation

The novel risk score was internally validated using bootstrapping with 1000 replicates.[15] We assessed the model's discrimination ability using the C-statistics (area under the receiver operating characteristic curve) and compared the C-statistics of our model with that of the CHA_2DS_2-VA score. We also calculated the net reclassification improvement (NRI) based on our risk prediction model as compared with the CHA_2DS_2-VA score.

This report followed the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement.[16] All statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). All P values were two-tailed, and P value < 0.05 was considered statistically significant.

Table 1: Demographics and baseline characteristics in the China-AF cohorts ($n = 6601$).

Variables	Statistics
Age	67.12 ± 12.92
Female	2762/6601 (41.8)
BMI, kg/m^2	25.11 ± 3.64
SBP, mmHg	129.15 ± 18.31
Heart rate, beats/min	81.42 ± 21.68
eGFR <60 mL·min^{-1}·1.73 m^{-2}	979/4808 (20.4)
FBG, mmol/L	6.07 ± 1.92
LDL-C, mmol/L	2.54 ± 0.85
TC, mmol/L	4.32 ± 1.04
TG, mmol/L	1.44 ± 1.04
Hemoglobin, g/L	135.45 ± 19.66
Anteroposterior left atrial diameter, mm	40.60 ± 7.40
Left ventricular posterior wall, mm	9.42 ± 1.46
LVEF	
<40%	248/4759 (5.2)
40%–54%	742/4759 (15.6)
≥55%	3769/4759 (79.2)
Current smoker	778/6491 (12.0)
Current drinker	763/6494 (11.7)
AF type, persistent or permanent	2081/6555 (31.7)
Heart failure	1759/6601 (26.6)
Hypertension	4315/6601 (65.4)
Diabetes mellitus	1698/6601 (25.7)
Ischemic stroke	912/6601 (13.8)
Vascular disease	1395/6601 (21.1)
Previous bleeding	348/6601 (5.3)
Antiplatelets	4465/5696 (78.4)
Statins	2640/6566 (40.2)
Education, completed high school	1703/5836 (29.2)
Health insurance	6138/6532 (94.0)

Data are shown as mean ± standard deviation or *n*/*N* (%). AF: Atrial fibrillation; BMI: Body mass index; China-AF: China atrial fibrillation; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; SBP: Systolic blood pressure; TC: Total cholesterol; TG: Total triglyceride.

Results

Patient characteristics

We included 6601 AF patients who were not on OAC at baseline in this analysis. The baseline characteristics of the patients were shown in Table 1. During the 1-year follow-up, 163 TEs (147 ischemic strokes and 16 systemic embolisms) occurred.

Derivation of the CAS risk score

The ten most important variables measured by the XGBoost importance score were shown in Figure 1. The top three most important variables were prior stroke, age, and history of heart failure or left ventricular ejection fraction (LVEF) <55%. These three variables accounted for 73.1% of the prognostic information provided by all clinical variables. The other variables did not add significant incremental information to the prediction model [Supplementary Figure 3, http://links.lww.com/CM9/A550]. Of note, hypertension, diabetes mellitus, and vascular disease were not among the top ten most important variables, neither were their combinations.

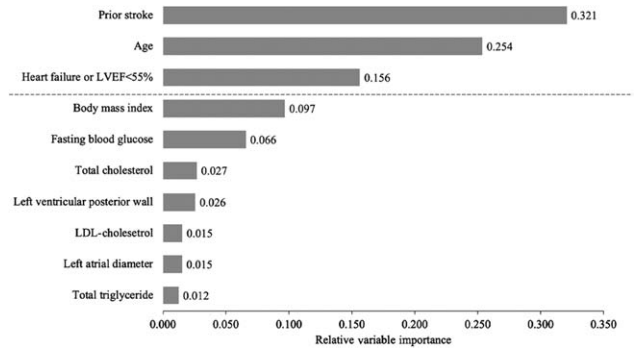

Figure 1: Top ten variables selected using the extreme gradient boosting (XGBoost) and the corresponding variable importance score. Candidate variables are listed in Supplementary Table 1, http://links.lww.com/CM9/A550. LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction.

We developed a novel stroke risk model with the three selected variables (congestive heart failure or LVEF <55%, age, and prior stroke, abbreviated as CAS model). According to the coefficients in the Cox regression model, we assigned 1 point for patients with congestive heart failure or LVEF <55%, and age >65 years, and 2 points for those with a prior stroke [Table 2]. The scores corresponding to these three variables were added together to obtain the CAS score to predict the patient's 1-year stroke risk.

Validation of the CAS risk score

The CAS risk score of 0 classified 30.8% (2033/6601) of the patients as low-risk group, whereas the CHA_2DS_2-VA risk score of 0 classified 15.2% (1002/6601) of the patients as low-risk group. The 1-year risk for TEs and the estimated 95% confidence interval (CI) by 1000 bootstrap replicates in patients with CAS risk score of 0 were 0.81% (95% CI: 0.41%–1.19%), as compared with 1.01% (95% CI: 0.36%–1.64%) in patients with CHA_2DS_2-VA score of 0 [Table 3]. The Kaplan-Meier curves for survival free from TEs by CAS and CHA_2DS_2-VA risk groups during follow-up were shown in Figure 2.

Comparison of the CAS and CHA_2DS_2-VA risk scores

The C-statistic of CAS model was 0.69 (95% CI: 0.65–0.73), significantly higher than that of CHA_2DS_2-VA score (0.66, 95% CI: 0.62–0.70, $Z = 2.01$, $P = 0.045$) [Figure 3]. We defined the CAS score of 0 as low-risk group and CAS score ≥1 as high-risk group. The NRI was 12.2% (95% CI: 8.7%–15.7%) when CHA_2DS_2-VA score ≥1 was categorized as high-risk group.

When classifying a specific proportion of cases as high-risk patients, the CAS score consistently identified a higher proportion of patients who will actually experience TEs than the CHA_2DS_2-VA risk score in our cohort [Supplementary Table 2, http://links.lww.com/CM9/A550]. In

Table 2: Regression coefficients and derived score for the CAS stroke risk score.

Variable	Beta	HR (95% CI)	*Z* scores	*P* values	Derived scores
Congestive heart failure or left ventricular dysfunction (LVEF <55%)	0.48	1.62 (1.18–2.23)	2.99	0.003	1
Age >65 years	0.75	2.12 (1.42–3.16)	3.67	<0.001	1
Prior stroke	0.91	2.48 (1.77–3.48)	5.25	<0.001	2

CI: Confidence interval; HR: Hazard ratio; LVEF: Left ventricular ejection fraction.

Table 3: Distribution of patients and event rates with 95% CI using bootstrap ($n = 1000$) for the CAS and CHA_2DS_2-VA scores in the China-AF cohort.

Risk class	Proportion in the study population ($n = 6601$)	Event rates (95% CI)
CAS score		
0	30.8% (2033)	0.81% (0.41%–1.19%)
1	39.1% (2581)	2.33% (1.78%–3.02%)
≥2	30.1% (1987)	5.51% (4.47%–6.71%)
CHA_2DS_2-VA score		
0	15.2% (1002)	1.01% (0.36%–1.64%)
1	19.1% (1262)	1.24% (0.53%–1.91%)
≥2	65.7% (4337)	3.67% (3.08%–4.27%)

AF: Atrial fibrillation; CAS: Congestive heart failure or left ventricular dysfunction, age, and prior stroke; China-AF: China atrial fibrillation; CI: Confidence interval.

addition, to prevent a specific proportion of patients who will eventually experience TEs by treating them with OAC therapy, the CAS score consistently classified a lower proportion of patients than the CHA_2DS_2-VA risk score [Supplementary Table 3, http://links.lww.com/CM9/A550].

Discussion

Based on a large prospective cohort of anticoagulation-naive Chinese AF patients, we have developed and validated a simplified CAS risk model for predicting TEs in AF patients. The CAS stroke score can be easily implemented in clinical practice, only encompassing three variables (congestive heart failure or LVEF <55%, age >65 years, and prior stroke). It has good discrimination in predicting 1-year TE risk when compared with the guideline-recommended CHA_2DS_2-VASc score.

Prior stroke, older age, and heart failure were the dominant predictors in our CAS risk model. This is in line with the other stroke prediction schemes.[4-7] Previous studies showed that heart failure or left ventricular dysfunction was a powerful driver of stroke risk even in young AF patients.[17-19] Heart failure is associated with a hypercoagulable state, which facilitates thrombus formation and cerebral embolism.[20,21] Female sex was not an independent risk factor for thromboembolism in our previous report.[13] Hypertension, diabetes mellitus, and vascular disease or their combinations did not add significant incremental information to the risk score. In the CHA_2DS_2-VASc score, all these factors are assigned one score despite their limited contribution to the risk of stroke. Several prior studies reported that vascular disease was not associated with increased stroke risk.[5,6,22] Other studies reported that blood pressure and glycemic control appeared to be more important than a history of hypertension or diabetes in predicting thromboembolism risk in patients with AF.[23,24] These findings were also supported by studies reporting that well-controlled risk factors were associated with improved clinical outcomes in AF patients.[25] Other clinical risk factors, such as obstructive sleep apnea, may also affect the stroke risk in patients with AF.[26] However, we did not collect the data at baseline.

The advantage of CAS risk score is the ability to identify as high as 30% of patients with true low risk of stroke. By only anticoagulating 70% of patients in the AF population, we can capture 90% of those who will experience thromboembolism if left untreated. The CAS scheme yielded a C-index of 0.69, outperforming the current guideline-recommended CHA_2DS_2-VASc score in discrimination and stratification. Another advantage of CAS risk scheme is that it clearly separates the AF patients into low-risk and high-risk groups, which facilitates clinical decision making. With a CAS score of 0, the risk of thromboembolism is even lower than those who have a CHA_2DS_2-VA score of 0 (0.81% [0.41%–1.19%] *vs.* 1.01% [0.36%–1.64%]). This means a more precise targeting of high-risk patients. The CAS model was derived to predict 1-year stroke risk. Dynamic (annually) evaluation of the AF patients to adequately identify incident stroke risk factors was recommended by current guidelines, as changes of risk factors may have a great impact on the risk of stroke.[27,28]

This study has several limitations. First, the CAS risk prediction scheme was derived and internally validated in a Chinese AF patient cohort. Therefore, external validations with other datasets are warranted to generalize our findings. Nonetheless, the relative simplicity of our model may prevent the risk of over-fitting from external validation. Second, the calibration of our model was not assessed with a split-sample approach due to the limited size of cases. However, we used 1000 bootstrap replicates to estimate the 95% CI of event rate. Finally, we did not incorporate biomarkers, left atrial morphology and function, AF burden, or other clinical factors in our risk prediction model. These factors may be useful for incremental risk prediction, as suggested by other studies.[29-31]

The CAS model outperformed the current widely-used CHA_2DS_2-VA score, especially in identifying a large proportion of patients with low risk for thromboembolism. The model can be easily applied as a risk stratification

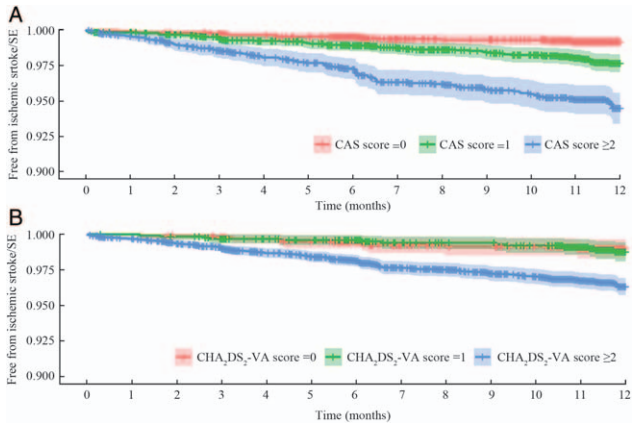

Figure 2: Survival free from ischemic stroke/SE by CAS and CHA_2DS_2-VA stroke risk groups. (A) CAS risk score and (B) CHA_2DS_2-VA risk score. CAS: Congestive heart failure or left ventricular dysfunction, age, and prior stroke; SE: Systemic embolism.

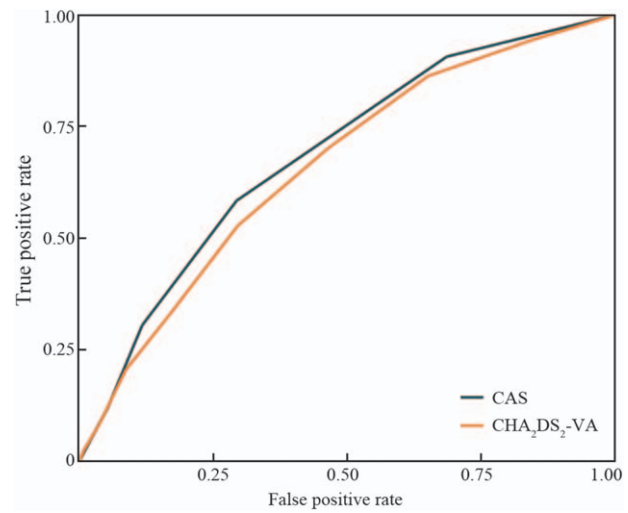

Figure 3: Receiver operating characteristic curves of the CAS and CHA_2DS_2-VA risk score. CAS: Congestive heart failure or left ventricular dysfunction, age, and prior stroke.

tool to inform clinical decision-making on anticoagulant use.

Funding

This work was supported by the National Key Research and Development Program of China (Nos. 2017YFC 0908803, 2018YFC1312501, and 2020YFC2004803) and a grant from the Beijing Municipal Commission of Science and Technology (No. D171100006817001). The construction of the China Atrial Fibrillation Registry was also supported by grants from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, and Bayer.

Conflicts of interest

Dr. Jian-Zeng Dong received honoraria from Johnson & Johnson for giving lectures. Dr. Chang-Sheng Ma received honoraria from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, and Bayer for giving lectures. The other authors report no conflicts of interest.

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How to cite this article: Jiang C, Chen TG, Du X, Li X, He L, Lai YW, Xia SJ, Liu R, Hu YY, Li YX, Jiang CX, Liu N, Tang RB, Bai R, Sang CH, Long DY, Xie GT, Dong JZ, Ma CS. A simple and easily implemented risk model to predict 1-year ischemic stroke and systemic embolism in Chinese patients with atrial fibrillation. Chin Med J 2021;134:2293–2298. doi: 10.1097/CM9.0000000000001515