New score for predicting thromboembolic events in patients with atrial fibrillation using direct oral anticoagulants

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Determinants of thrombotic events remain uncertain in patients with atrial fibrillation treated with direct oral anticoagulants (DOACs). Our aim was to identify risk factors associated with thromboembolism in patients with at atrial fibrillation on DOACs and to construct and externally validate a predictive model that would provide a validated tool for clinical assessment of thromboembolism. In the development cohort, prediction model was built by logistic regression, the area under the curve (AUC), and Nomogram. External validation and calibration of the model using AUC and Hosmer–Lemeshow test. This national multicenter retrospective study included 3263 patients with atrial fibrillation treated with DOACs. The development cohort consisted of 2390 patients from three centers and the external validation cohort consisted of 873 patients from 13 centers. Multifactorial analysis showed that heavy drinking, hypertension, prior stroke/transient ischemic attack (TIA), cerebral infarction during hospitalization were independent risk factors for thromboembolism. The Alfalfa-TE risk score was constructed using these four factors (AUC = 0.84), and in the external validation cohort, the model showed good discriminatory power (AUC = 0.74) and good calibration (Hosmer–Lemeshow test *P* value of 0.649). Based on four factors, we derived and externally validated a predictive model for thromboembolism with DOACs in patients with atrial fibrillation (Alfalfa-TE risk score). The model has good predictive value and may be an effective tool to help reduce the occurrence of thromboembolism in patients with DOACs. *Blood Coagul Fibrinolysis* 34:530–537

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Introduction

Atrial fibrillation is a common arrhythmia that can lead to hemodynamic abnormalities and thromboembolic events, severely increasing the morbidity and mortality of stroke and other cardiovascular diseases [1]. Anticoagulants can be used for prevention and treatment of thrombotic events in atrial fibrillation [2]. Among them, oral anticoagulants are becoming more and more widely used because of their ease of administration, mainly including vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban. DOACs do not require regular monitoring, have few drug interactions, and low complexity of treatment management, making them convenient for patients and clinicians to use. Therefore, DOACs are gradually replacing VKAs as the drug of choice for anticoagulation in patients with atrial fibrillation [3–5].

In patients with atrial fibrillation, oral anticoagulation reduces the risks of ischemic stroke and systemic embolism in patients with atrial fibrillation by 60–70% [6]. In comparison to VKA, a retrospective study showed that the overall thrombosis rate and transient ischemic attack (TIA) rate after taking DOACs were 1.7 per 100 person-years and 1.3 per 100 person-years, respectively, significantly lower than the 3.2 per 100 person-years and 2.1 per

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100 person-years in the VKA group, but there was still a risk of thromboembolism [7]. Therefore, a scoring system that can reliably predict the risk of DOAC-induced thromboembolism is an essential tool for the clinician. In the past, attempts to identify independent risk factors for thromboembolism in patients with atrial fibrillation have produced a variety of scores, of which the more widely used and recommended by guidelines are the CHADS2 and CHA2DS2-VASc scores. However, most scoring scales including CHA2DS2-VASc are predictive models for thromboembolism because of warfarin use, and there are no risk models for thromboembolism in patients with atrial fibrillation using DOACs. In contrast, DOACs have different pharmacological–pharmacokinetic profiles and fewer drug interactions than warfarin, and DOACs are increasingly used for stroke prevention in atrial fibrillation, with a tendency to replace warfarin.

Therefore, we conducted a multicenter real-world study in China to identify factors associated with thromboembolism in patients with atrial fibrillation on DOACs, derive and externally validate a predictive model, and provide a validated tool for clinical assessment of thromboembolism.

Methods

Study design

For this retrospective study, we analyzed the data of patients who had received DOACs from any of 16 medical centers (see supplementary material for information on the 16 medical centers and the distribution map of multicenter hospitals., http://links.lww.com/BCF/A169) in China during the period 1 January 2016 to 31 December 2020. The registration number of this study is ChiCTR2000031909, and the review committee waived the informed consent requirement for patients because of the retrospective nature of this study. The inclusion criteria for this study were as follows: age at least 18 years; diagnosis of atrial fibrillation; and treatment with DOACs. The exclusion criteria were as follows: patients with valvular atrial fibrillation; incomplete information that prevented subsequent analysis. As apixaban has no indication for atrial fibrillation in China, and edoxaban will only be available in China in 2019, the DOACs used in multicenter hospitals are rivaroxaban and dabigatran. A total of 3263 patients with nonvalvular atrial fibrillation treated with DOACs were eligible for this study after meeting the inclusion criteria.

Data collection

We collect data on each patient from the hospital's electronic database. Data were promptly clinically collated and recorded by specialized physicians, nurses, and pharmacists, including demographic information (age, gender, and BMI), lifestyle habits (smoking and alcohol consumption), concomitant diseases [hypertension, diabetes, heart failure, malignancy, coronary artery disease, gout, frailty, vascular disease, hepatic and renal insufficiency, previous stroke and transient ischemia attack (TIA), history of bleeding and anemia], co-medications [amiodarone, antiplatelet agents, NSAIDs, gastrointestinal protective agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), statins, β-blockers, digoxin, erythromycin, azole antifungals], and any thromboembolism occurring during hospitalization (cerebral infarction, TIA, DVT, pulmonary embolism [PE]). Clinically relevant events were obtained through follow-up. Selected patients were followed up by telephone to understand and record the occurrence of patient outcome indicators. Anemia was defined as hemoglobin less than 13 g/dl in men or hemoglobin less than 12 g/dl in women [8].

Follow-up and study endpoints

Follow-up was through outpatient visits or over the telephone. At each follow-up, information was collected on whether anticoagulation was being continued, dosage of the DOACs, other concurrent medications, comorbid diseases, thromboembolism site and date, and so on. Thromboembolic events were considered valid if they met the following criteria: sudden occlusion of an artery to a visceral organ or extremity documented by imaging, surgery, or pathology and not attributable to concomitant atherosclerosis or other cause. Follow-up visits and outcome adjudication were performed by local investigators, not in a blinded fashion. The date of first atrial fibrillation diagnosis was considered as the patient's index date. The follow-up period was defined from the index date until the discontinuation of index DOAC treatment, or the end date of study period (31 December 2019), which came first.

Statistical analysis

Clinicopathological variables associated with major bleeding were assessed a priori based on clinical importance, scientific knowledge, and predictors identified in previously published articles [9–13]. Continuous variables were presented as means ± standard deviation or medians, and categorical variables as percentages. *T* test was used for univariate analysis of continuous variables. Pearson chi-square test or Fisher exact test was used for categorical variables. Variables were considered to be potential risk factors if *P* values were less than 0.2 in an unadjusted univariate analysis. Variables significantly associated with thromboembolism (at $P < 0.20$) in univariate analysis were included in the multivariate binary logistics regression model, and those independently associated (at $P < 0.05$) with thromboembolism were used to construct the thromboembolism risk score. The area under the receiver operating characteristic curve (AUC) was used to evaluate the discriminatory power of the risk score. Normally, AUC at least 0.70 is usually considered sufficient to make clinically useful individual predictions [14]. Calibration power was

assessed by Hosmer–Lemeshow test ($P > 0.05$ indicates a good fit). Creating Nomogram models based on thromboembolism scores, Nomogram was a visual expression of a logistic regression model with a user-friendly interface, better accuracy, and easy-to-understand result, which was one of the most popular research directions [15]. The score corresponding to a 5% incidence of thromboembolism on the Nomogram was used as the high thromboembolism risk cut-off value. SPSS 25.0 (IBM Corp., Armonk, New York, USA) and R (version 4.2.0) were used for data analysis. A two-tailed P value of less than 0.05 indicated statistical significance.

Results

Patient characteristics

The flow chart of patient screening is shown in Fig. 1. This study included 3263 patients from 16 centers, of which 1686 (51.7%) patients were using rivaroxaban, 1577 (48.3%) were using dabigatran, and no patient was using apixabang and edoxaban. Over a mean follow-up period of 10 months, 40 thromboembolic events occurred in 2390 patients 1.67%) in the development cohort and 14 thromboembolic events occurred in 873 patients (1.6%) in the validation cohort. Mean age was higher in the thromboembolism group than in the non-thromboembolism group (64 vs. 63.1 years, $P = 0.639$). Table 1 shows the baseline characteristics of patients taking DOACs.

Development of the risk score

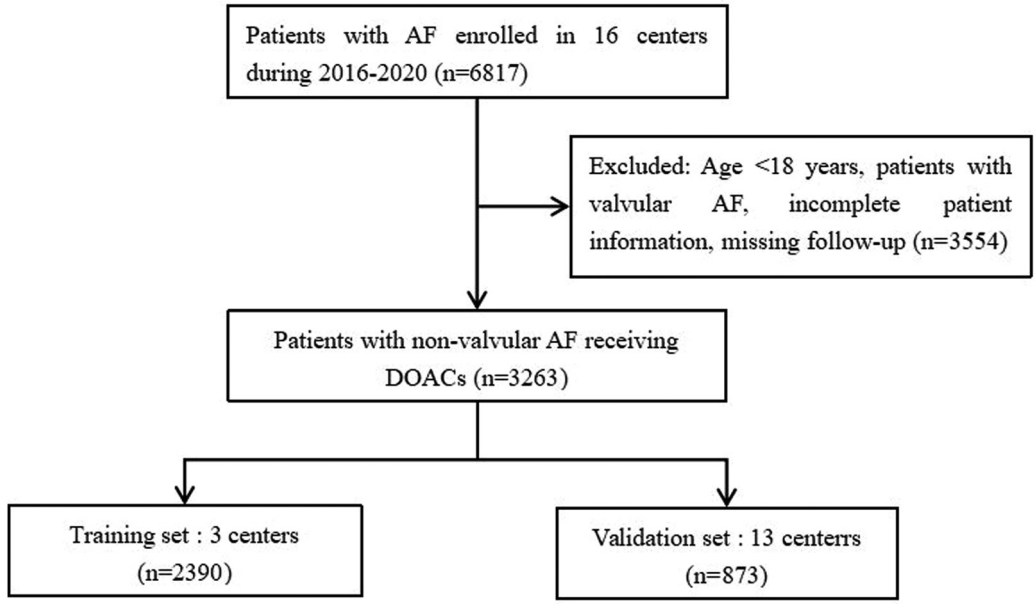
We included a total of 28 candidate predictors, and Table 1 shows the results of the univariate analysis. In univariate analysis, age 65–74 years ($P = 0.059$), age at least 75 years ($P = 0.053$), heavy drinking ($P < 0.001$), hypertension ($P < 0.001$), chronic liver disease ($P = 0.001$), vascular disease ($P = 0.001$), previous stroke/TIA ($P = 0.035$), radiofrequency ablation ($P = 0.027$), thrombolysis ($P = 0.01$), co-administration of digoxin ($P = 0.069$), intracranial hemorrhage during hospitalization ($P = 0.019$), cerebral infarction during hospitalization ($P = 0.001$), 12 factors with P less than 0.2, statistically significant and included in multifactorial analysis. In the multifactorial analysis, four factors were included in the final model, and Table 2 shows the results of the multifactorial analysis. Heavy drinking [odds ratio (OR) 17.256; 95% confidence interval (CI) 1.202–247.808), hypertension (OR 6.579, 95% CI 2.440–17.742), prior stroke/TIA (OR 7.796; 95% CI 1.703–35.690), cerebral infarction during hospitalization (OR 5.813; 95% CI 1.402–4.526) were associated with an increased risk of thromboembolism.

The Nomogram (Fig. 2) was also constructed based on the beta regression coefficients in multivariate analysis and scored for the four factors (Table 2), with a total score at least 88 considered as high thromboembolism risk. Based on the Nomogram, the score greater than 88 corresponds to a 1-year risk of thromboembolism greater than 5%.

Validation of the Alfalfa-TE risk score

The thromboembolism risk score – which we named the Alfalfa-TE score ('Alfalfa' is the name of our team,

Fig. 1



Flowchart of patient screening.

Table 1 Baseline clinical characteristics of patients

Characteristics	No event ($N=2350$)	Any thromboembolism ($N=40$)	P values
Age (mean ± SD)	63.1 ± 12.1	64.0 ± 8.0	0.639
Age categories (years)			
<65 [*n* (%)]	1181 (50.2)	19 (47.5)	0.73
65–74 [*n* (%)]	783 (33.3)	19 (47.5)	0.059
≥75 [*n* (%)]	386 (16.4)	2 (5.0)	0.053
Gender, male [*n* (%)]	1396 (59.4)	24 (60.0)	0.939
Smoking [*n* (%)]	35 (87.5)	1926 (82.0)	0.365
Heavy drinking [*n* (%)]	23 (1.0%)	5 (12.5)	$P<0.001$
Hypertension [*n* (%)]	1260 (53.6)	26 (65.0)	$P<0.001$
Diabetes mellitus [*n* (%)]	600 (25.5)	8 (20.0)	0.426
Chronic liver disease [*n* (%)]	48 (2.0)	4 (10.0)	0.001
Vascular disease (CAD, MI, PAD) [*n* (%)]	152 (6.5)	8 (20.0)	0.001
Heart failure [*n* (%)]	142 (6.0)	1 (2.5)	0.349
COPD [*n* (%)]	31 (1.3)	1 (2.5)	0.519
Anemia [*n* (%)]	626 (26.6)	14 (35)	0.236
History of stroke or TIA [*n* (%)]	50 (21.2)	3 (7.5)	0.035
Radiofrequency ablation [*n* (%)]	2000 (85.1)	29 (72.5)	0.027
Thrombolysis [*n* (%)	399 (17.0)	13 (32.5)	0.01
INR ≤2 [*n* (%)]	2301 (98.0)	40 (100.0)	0.356
BMI ≥30 [*n* (%)]	198 (8.4)	3 (7.5)	0.834
Drug combination			
Statins [*n* (%)]	1289 (54.9)	21 (52.5)	0.767
Antiplatelet drugs [*n* (%)]	657 (28.0)	9 (22.5)	0.445
CCB [*n* (%)]	815 (34.7)	16 (40.0)	0.484
ACEI [*n* (%)]	648 (27.6)	8 (20.0)	0.287
ARB [*n* (%)]	617 (26.3)	9 (22.5)	0.592
β-blocker [*n* (%)	1678 (71.4)	26 (65.0)	0.375
Digoxin [*n* (%)]	277 (11.8)	1 (2.5)	0.069
PPI/H2 antagonists [*n* (%)]	1609 (68.5)	23 (57.5)	0.139
Bleeding or thromboembolism events hospitalization			
Intracranial hemorrhage [*n* (%)]	214 (9.1)	8 (20.0)	0.019
Cerebral infarction [*n* (%)]	261 (11.1)	11 (27.5)	0.001

ACEI, angiotensin-converting enzyme inhibitor; anemia, defined as a hemoglobin concentration of less than 13 g/dl in men or less than 12 g/dl in females; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral arterial disease; PPI, proton pump inhibitors; TIA, transient ischemic attack.

representing happiness and luck). Figure 3 shows the receiver operating characteristic (ROC) curve of the Alfalfa-TE score with an AUC value of 0.84, which has a strong predictive power. Figure 4 shows the ROC curve of the external validation cohort with an AUC value of 0.74 (95% CI 0.615–0.862). In addition, the Hosmer–Lemeshow test showed that the model had good calibration performance ($P=0.696$). After fitting the ROC curves (Fig. 5), the predictive power of the three scores, from largest to smallest, were Alfalfa-TE score (AUC = 0.739, 95% CI 0.623–0.855), CHA2DS2-VASc (AUC = 0.683, 95% CI 0.534–0.832), CHADS2 (AUC = 0.662, 95% CI 0.512–0.813). Comparison of the above three atrial fibrillation thromboembolism prediction models with our Alfalfa-TE score revealed that our model had the highest AUC value, indicating a relatively good possible predictive ability for the Chinese population.

Examples

A male patient, 70 years old, with a hypertension and heavy drinking, is taking dabigatran and has had no thromboembolism events during the follow-up period. Total score = 100 (heavy drinking) + 66.2 (hypertension) = 166.2 points. Therefore, this patient had a total score of 166.2, which is less than 88 and belongs to the high-risk group for thromboembolism.

Discussion

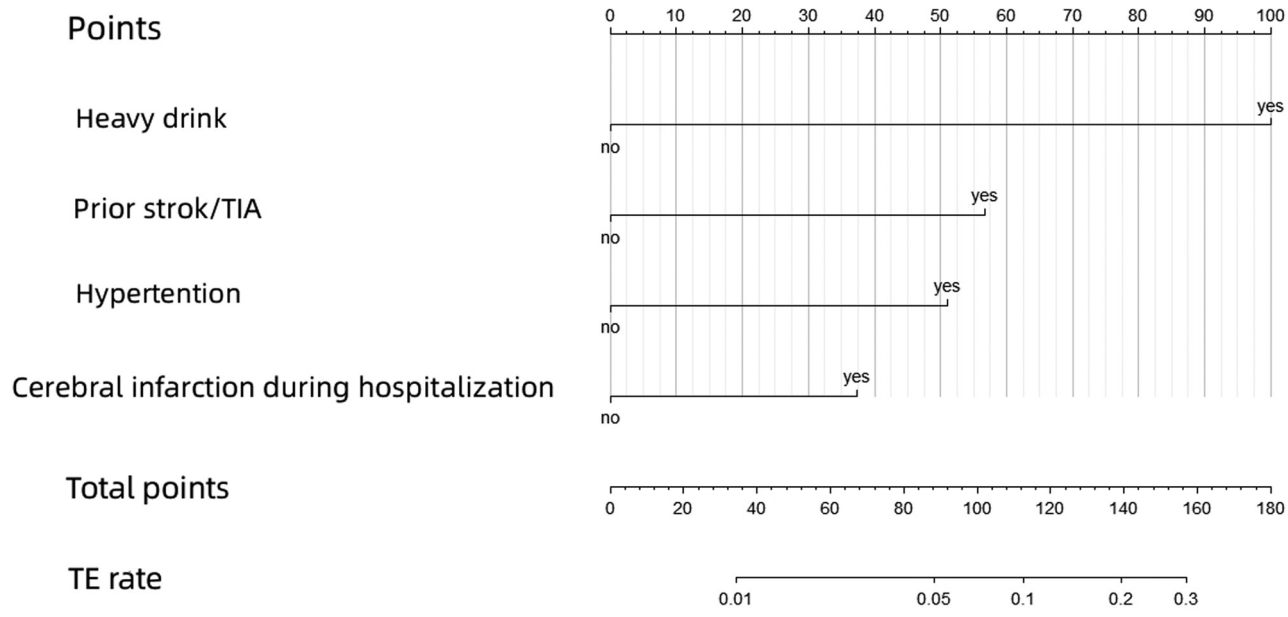
In the present study, we evaluated 28 candidate predictors and identified 4 independent factors associated with thromboembolism. Heavy drinking, hypertension, prior stroke/TIA, cerebral infarction during hospitalization increased the risk of any thromboembolism, which is consistent with SPAF investigators [16], Eighth ACCP guidelines (2008) [17], CHA2DS2-VASc [1] and ATRIA [18] thromboembolism risk score. A study by Paciaroni

Table 2 thromboembolism risk with a multifactorial analysis

Variables	*B*	OR (95% CI)	*P* value	Points
Heavy drinking	2.848	17.256 (1.202–247.808)	0.036	100
Hypertension	1.884	6.579 (2.440–17.742)	<0.001	66.2
Prior stroke/TIA	2.054	7.796 (1.703–35.690)	0.008	72.1
Cerebral infarction during hospitalization	1.760	5.813 (1.402–4.526)	0.043	61.8

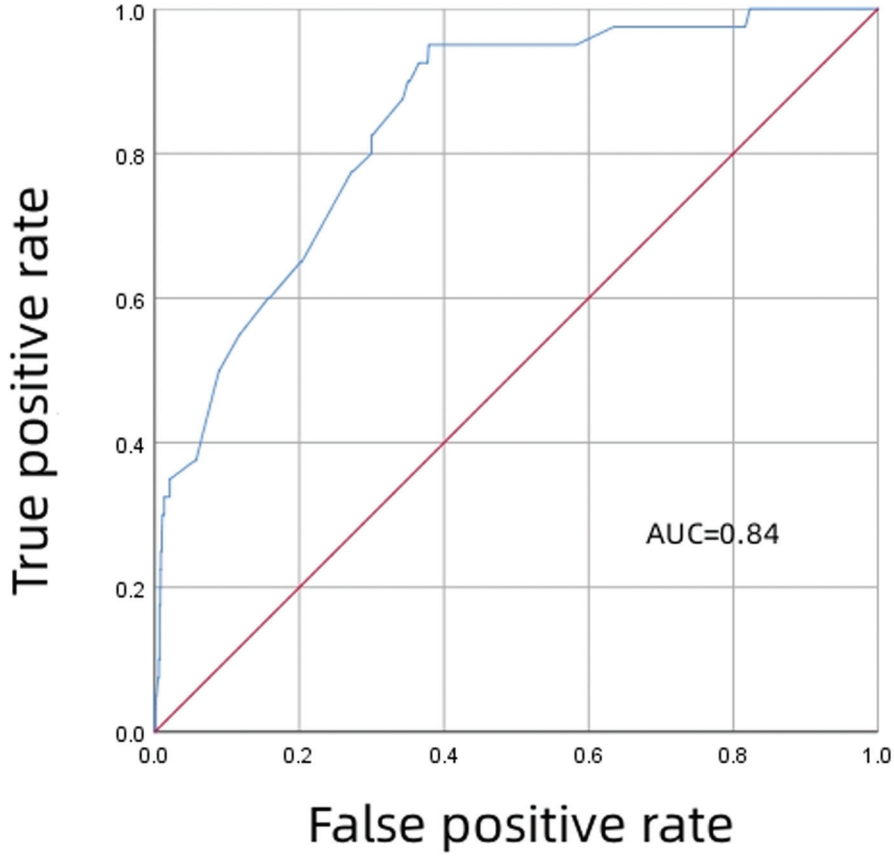
CI, confidence interval; OR, odds ratio.

Fig. 2



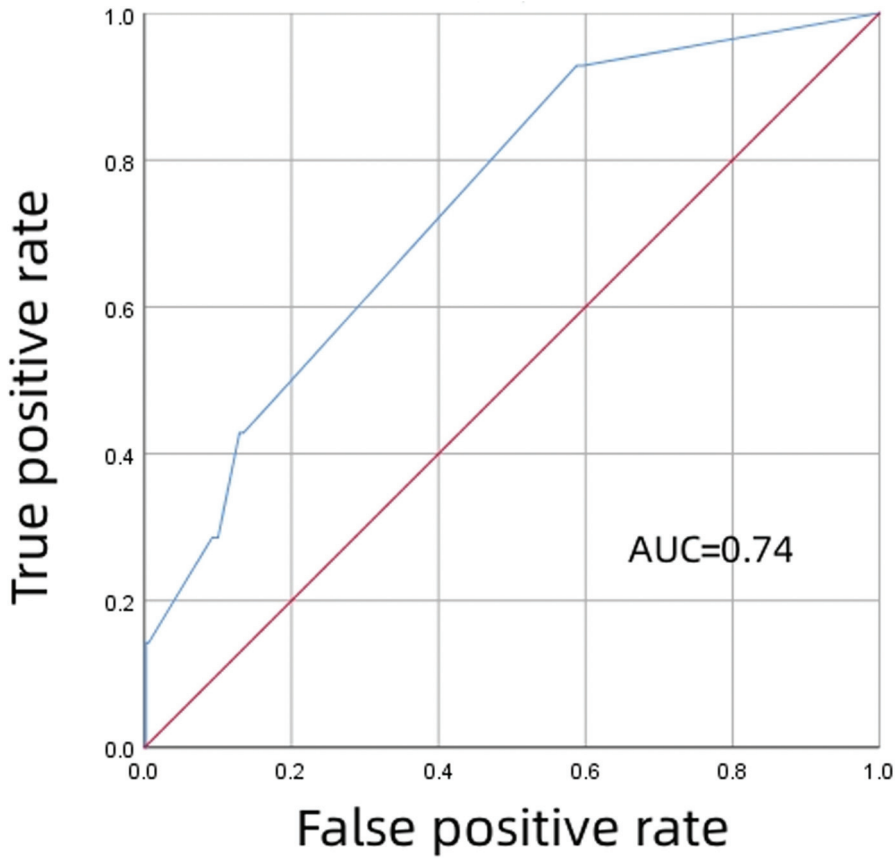
Nomogram for predicting the risk of thromboembolism in the development cohort.

Fig. 3



The receiver operating characteristic curve of the development cohort.

Fig. 4

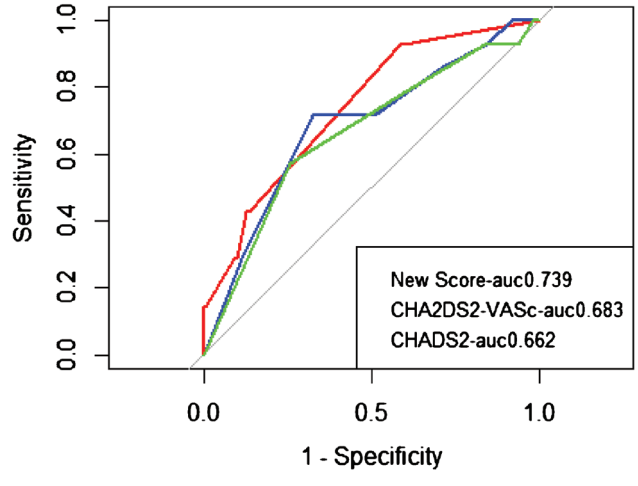


The receiver operating characteristic curve of the validation cohort.

et al. [19] showed that recurrent thromboembolic events in patients with atrial fibrillation who suffered an acute stroke while on treatment with DOACs were associated with hypertension. Carlisle *et al.* [20] also found that hypertension (hazard ratio 1.50; 95% CI 1.09–2.06; $P = 0$ 0.01) was significantly associated with thromboembolic events in a multivariate Cox proportional risk analysis of 18 955 atrial fibrillation patients taking DOACs in the ORBIT-AF I and II registries. Therefore, several studies have shown that hypertension is a likely risk factor for thrombosis, suggesting that strict blood pressure control is warranted in patients with atrial fibrillation on DOACs.

In the present study, we found that heavy drink was a risk factor for thromboembolism in atrial fibrillation patients taking DOACs, and the mainstream score for predicting thromboembolism did not incorporate this risk factor. Studies by Johansson *et al.* [21] and Zöller *et al.* [22] also found heavy alcohol consumption was associated with an increased risk of first venous thromboembolism (VTE) in men. This may be because of the fact that alcohol causes atherosclerosis to clog blood vessels, forming plaque in

Fig. 5



The receiver operating characteristic curves for validation of three scores.

the arteries and leading to blood viscosity, thus making it more likely that a thrombotic event will occur. Therefore, this suggests that our abstinence from alcohol would be well placed to prevent any thrombotic events in patients with atrial fibrillation taking DOACs.

In our study, prior stroke/TIA significantly increased the risk of thromboembolism. This is consistent with most mainstream scores-R2CHADS2 [23], CHA2DS2-VASc, ATRIA. A simple CAS model developed by the team of Jiang *et al.* [24] to predict the occurrence of thromboembolism in the Chinese population also included previous stroke as an important risk factor. This is because the obstruction or rupture of cerebral blood vessels in patients with stroke/TIA makes it more likely that cerebral blood circulation will be impaired or brain tissue will be damaged, greatly increasing the occurrence of ischemic events. Patients with a prior history of stroke/TIA require special attention for thrombosis prevention when taking DOACs. We also found that cerebral infarction during hospitalization significantly increased the risk of thromboembolism, suggesting that we need to invest more effort in preventing cerebral infarction during hospitalization.

This model did not include risk factors for aging, unlike mainstream models, probably because the study population in our model was essentially elderly, whereas other studies' population are a much wider distribution of patient ages. However, this does not ignore the significant effect of old age on the risk of thromboembolism, and a meta-analysis by Marzona *et al.* [25] showed that increasing age significantly increases the risk of thromboembolism, especially for the female population.

Several strengths of the current study are worth mentioning. First, we are a multicenter study, with development and validation cohort from different centers. Second, thromboembolism outcomes are followed up directly with each patient by phone by our team, and the one-on-one communication makes the data more reliable. The patients included in this study were taking DOACs (and not the population that included warfarin). To our knowledge, this is the first risk score specifically designed to predict thromboembolism because of DOACs. Compared with other thromboembolism scores such as CHA2DS2-VASc and ATRIA, the Alfalfa-TE score is simple in structure and easy to use in clinical practice.

There are several potential limitations to this study. First, the forecasting model was developed and externally validated in China, which leads to the potential problem that it is unclear whether the model is applicable to other countries and regions. In addition, over two-thirds of patients had received radiofrequency ablation and the proportion of patients treated this way is not the same in other clinical realities. Secondly, we do not have a validation committee of events, which may have uncertainty about the determination of the end point. Thirdly, effect of time on the occurrence of bleeding events was not explored in this study, which deserves further exploration in future studies. Finally, it is worth collecting patients taking apixaban and edoxaban to verify the score.

Conclusion

For the Chinese population, the Alfalfa-TE risk score (heavy drink, hypertension, history of previous stroke/TIA and cerebral infarction during hospitalization) may be an effective tool to help reduce the occurrence of thromboembolism in patients with atrial fibrillation using DOACs, but the availability of this model still needs to be validated on a large scale.

Acknowledgements

Ethical approval: the review committee waived the informed consent requirement for patients because of the retrospective nature of this study.

Authors' contributions: all authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by F.M., J.C., S.C. The first draft of the manuscript was written by F.M., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability statement: the original contributions presented in the study are included in the article/supplementary material, http://links.lww.com/BCF/A169, further inquiries can be directed to the corresponding author/s.

Conflicts of interest

There are no conflicts of interest.

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