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Derivation of a simple clinical model to categorize the probability of acute myocardial infarction in patients with atrial fibrillation

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Abstract. – OBJECTIVE: Atrial fibrillation (AF) is independently associated with a higher risk of acute myocardial infarction (AMI). The occurrence of AMI in AF patients may lead to dismal prognosis. Risk assessment is a fundamental component of prevention for AMI.

PATIENTS AND METHODS: 2419 consecutive patients with nonvalvular AF were enrolled in this retrospective study. A logistic regression analysis was performed on clinical variables to create a simple clinical prediction rule. The following nine variables and assigned scores (in brackets) were included in the prediction rule: age ≥65 years (1.0), heart failure (1.0), hypertension (1.0), diabetes mellitus (1.0), hyperlipidemia (0.5), history of stroke/TIA (0.5), vascular disease (1.0), current smoking (0.5), and resting heart rate >90 beats/min (1.0). Patients were considered to have a low probability if the score was ≤2.5, moderate if the score was 3.0 to 4.0, and high if the score was ≥4.5. The AMI unlikely was assigned to patients with scores <3.5 and AMI likely if the score was ≥3.5. To evaluate the score, we included an external validation cohort of 1810 nonvalvular AF patients from the Cardiology Center, Shandong Provincial Hospital affiliated to Shandong University, Jinan, China.

RESULTS: The score showed a good ability in discriminating AF patients experiencing AMI both in the internal derivation cohort, with a c-index of 0.80 [95% Confidence Interval (CI) 0.77-0.83, $p<0.001$] and in the external validation cohort (c-index 0.73, 95% CI 0.69-0.77, $p<0.001$). Our scoring system offered significantly better predictive performance than the CHA_2DS_2-VASc score (c-index 0.80 *vs* 0.71, $p<0.001$).

CONCLUSIONS: Our scoring system is a simple and accurate way of predicting the risk of AMI in AF patients. Therefore, more accurate targeting of preventive therapy will be allowed.

Key Words:
Atrial fibrillation, Myocardial infarction, Risk score, CHA_2DS_2-VASc.

Introduction

Atrial fibrillation (AF), present in over 33 million individuals around the world, increases mortality and morbidity and impairs quality of life[1,2]. AF is characterized by a constellation of atherosclerotic risk factors and by systemic signs of atherosclerosis, such as aortic plaque[3], increased intima-media thickness[4], and low ankle-brachial index[5]. When AF occurs, it creates and sustains an inflammatory and prothrombotic environment[6], which can increase the risk of acute myocardial infarction (AMI). Besides, AF may cause direct thromboembolization from the left atrium into the coronary arteries and increase the risk of AMI[7]. Moreover, Sandoval et al[8] suggested that episodes of AF with high ventricular rates could promote imbalance between demand and blood supply, and are usually associated with non-ST elevation MI. Left ventricular hypertrophy, which is commonly encountered in AF patients, further increases the risk and extent of supply-demand mismatch in rapid AF. These findings suggest that AF could be a risk factor for AMI. A growing body of evidence from population studies supports this assertion by revealing that AF is independently associated with an increased risk of AMI despite the anticoagulant treatment[9-13]. The annual rate of AMI in observational studies of AF patients ranges from 0.4% to 2.5%. Higher rates

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were reported in AF patients with stable coronary artery disease (CAD) (11.5%/year), vascular disease (4.47%/year), heart failure (2.9%/year), or those undergoing coronary artery intervention (6.3%/year)[14].

The occurrence of AMI in AF patients may lead to dismal prognosis. Marijon et al[15] in the contemporary anticoagulated AF population showed that cardiac deaths accounted for a vast majority of deaths (37.4%) rather than stroke (9.8%)[15]. In addition, the concomitance of AMI and AF requires careful consideration of antithrombotic therapy, balancing bleeding risk, stroke risk, in-stent thrombosis or reinfarction risk. The optimal antithrombotic treatment remains uncertain for primary protection against MI[16]. Co-prescription of antiplatelet treatment with anticoagulant increases the absolute risk of major bleeding. Besides, major bleeding is associated with an increased risk of death up to 5 times following an acute coronary syndrome[17]. As such, the identification of AF patients at higher risk of AMI requiring strict clinical monitoring and intervention on modifiable cardio-metabolic risk factors is of particular relevance. However, the clinical and laboratory predictors and a reliable clinical risk stratification scheme for AMI in AF patients are still undefined.

The CHA_2DS_2-VASc score consists of congestive cardiac failure, hypertension, age ≥75 years, diabetes mellitus (DM), previous stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, and sex category. The score has been recommended for the assessment of thromboembolic risk and antithrombotic therapy guide of AF14[14,18]. However, it has recently been used to predict not only stroke but also various cardiovascular diseases beyond the original AF field[19-22]. For example, several studies[20,21] have demonstrated an association between the CHA_2DS_2-VASc score and mortality in patients with acute coronary syndrome, regardless of the presence of AF. Furthermore, Cetin et al[22] suggested that the CHA_2DS_2-VASc score was independently correlated with the severity of coronary artery disease. The CHA_2DS_2-VASc scoring scheme includes similar risk factors for the development of AMI and provides a fast and simple method for physicians in risk evaluation requiring no calculators or computers. The present retrospective cohort work aimed to verify the value of the CHA_2DS_2-VASc score as a risk assessment tool for AMI in patients with AF. In addition, we screened out and combined factors into an explicit clinical model to increase the likelihood of determining AMI risk.

Patients and Methods

Study Population

This retrospective study enrolled 2419 consecutive patients with paroxysmal, persistent, or permanent nonvalvular AF lasting at least 1 year before the baseline evaluation admitted to Qilu Hospital of Shandong University between January 2010 and December 2015. AF was diagnosed using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31) based on electrocardiography (12-lead electrocardiography). All the patients enrolled were in presence of AF rhythm at the time of admission. Patients with valvular AF, rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, and mitral valve repair were excluded from the study. AMI, comprised of ST-segment elevation MI and non- ST-segment elevation MI, was diagnosed using the ICD-9-CM codes (410.xx). To be eligible for our research, the AMI was diagnosed at the time of admission and validated by the discharge diagnosis. Of the 2419 AF patients enrolled, 215 were diagnosed with AMI. Ethical approval was obtained from the Hospital Ethical Committee of Qilu Hospital of Shandong University and Shandong Provincial Hospital affiliated to Shandong University.

Data Collection

Each patient's chart was reviewed in detail to gather data on symptoms, medications, cardiovascular disease risk factors, previous cardiovascular events, smoking status, admission heart rate (HR), results of routine biochemical tests, and other systemic diseases. It was possible to retrieve the data pertaining to individual patients since all data are linked to a unique, permanent, and personal registration number, which is assigned to every patient. The data collection was performed by the same researchers after standard training. Data were evaluated independently by two individuals before entering the information into the electronic database. The pre-admission CHA_2DS_2-VASc score was calculated for each patient. Chronic heart failure was defined as presence of signs and symptoms typical of heart failure confirmed with reduced left ventricular ejection fraction (<40%). Hypertension was defined as measurements of systolic and diastolic blood pressure ≥140/90 mmHg or chronic treatment with antihypertensive medications. Type 2 diabetes mellitus (DM) was defined as a previous diagnosis and/or fasting blood glucose ≥126 mg/dl or using anti-diabetic drugs. Vascular disease was defined as a his-

tory of MI, peripheral arterial disease, or complex aortic plaques. A serum total cholesterol concentration ≥220 mg/dl, low-density lipoprotein cholesterol ≥140 mg/dl, or the usage of lipid- lowering medications was defined as hyperlipidemia. Cigarette smoking was defined as smoking >10 cigarettes a day for at least 1 year without a quit attempt. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. All patients provided a written informed consent, and the study was conducted according to principles of the Declaration of Helsinki.

Statistical Analysis

Continuous variables were reported as mean ± SD if normally distributed and as median (interquartile range, IQR), if non-normally distributed. Numeric categorical variables are expressed as number (percent). Comparisons of continuous variables among groups were performed by the Student's *t*-test or Mann-Whitney U test, as appropriate. Comparisons of categorical variables were assessed by the chi-square or Fisher's exact test. Univariable logistic regression analysis was used to calculate the effects of multiple variables on AMI. Potential risk markers were eliminated using stepwise multivariate logistic regression analysis. For each significant variable, a regression coefficient was obtained. The points for the clinical prediction rule were assigned by doubling the value of the regression coefficients from the stepwise logistic regression and rounding to the nearest 0.5. We then created cut points to classify patients as having a low, moderate, and high probability of AMI. In addition, we sought to determine a score to be designated AMI likely or unlikely. We, then, compared the performance of our scoring system with that of the logistic regression model and CHA_2DS_2-VASc score in calculating the relative risk of AMI in AF patients using receiver-operating characteristics (ROC) curve analysis. The area under the ROC curve (AUC, a measure of the *c*-index) is a rough guide for quantifying the discriminatory capacity. The statistical significance of the difference between 2 AUCs was tested with the method of DeLong et al[23]. The analyses were performed using computer software packages (SPSS-21.0, SPSS Inc, and R 3.4.2, R Development Core Team). Only *p*-values <0.05 were considered as statistically significant.

External Validation Cohort

To validate the new risk score, we included an external validation cohort from the Cardiology Center, Shandong Provincial Hospital affiliated to Shandong University, Jinan, China. The patients included in the external validation cohort met the same inclusion and exclusion criteria used for the internal derivation cohort.

Results

Baseline Characteristics

A total of 2419 AF patients were enrolled in the internal cohort, including 215 in AMI group and 2204 in non-AMI group. The baseline characteristics of the internal cohort are shown in Table I. The median age of patients was 70 years (IQR 60-78) and 40.7% of them were females. Compared with non-AMI patients, AMI patients were older, had higher rates of heart failure, hypertension, hyperlipidemia, DM, history of stroke/TIA, vascular disease, and current smoking. Accordingly, the proportion of patients who were receiving cardiovascular medications [antiplatelets, statins, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs)] at baseline increased in AMI group. The median value (IQR) of the CHA_2DS_2-VASc scores was significantly higher in AMI group than that in non-AMI group [4 (3-5) *vs.* 3 (1-4), p <0.001].

Univariate and Multivariate Analyses

Of the clinical and laboratory variables measured in our study, 9 were found to be independently predictive of event risk and were used to construct the risk algorithm: age ≥65 years, heart failure, hypertension, DM, hyperlipidemia, history of stroke/TIA, vascular disease, current smoking, and resting heart rate >90 beats/min. These variables, together with the odds ratios, and the 95% confidence intervals, are shown in Table II. The scoring system and the assigned scores are shown in Table III. If a patient had ≤2.5 points, the probability of AMI was low with 2.6% in the internal cohort and 5.9% in the external validation cohort. A score of 3.0 to 4.0 was moderate probability with 10.9% having AMI in the internal cohort and 18.4% in the external validation cohort; a score of ≥4.5 was a high probability for AMI with 34.1% in the internal cohort and 33.6% in the validation cohort. These results, 95% confidence intervals and AMI rates are in Table IV. The difference in the prevalence of AMI in the three categories was statistically significant (p <0.001). We designated a score of <3.5 as AMI unlikely and this gave an AMI rate of 3.7% in the internal cohort and 7.2% in the validation cohort. A score of ≥3.5 gave an AMI rate of 21% in the internal cohort and 25% in the validation cohort and is designated AMI likely (Table V).

Table I. Baseline characteristics of the internal derivation cohort.

Characteristics	Total sample (n = 2419)	AMI (n = 215)	Non-AMI (n = 2204)	*p*-value
Type of AF				
Paroxysmal	1247 (51.6)	107 (49.8)	1140 (51.7)	0.584
Persistent/Permanent	1172 (48.4)	108 (50.2)	1064 (48.3)	0.584
Age, years	70 (60-78)	74 (68-81)	70 (59-78)	<0.001
CHA_2DS_2-VASc score components				
Heart failure	707 (29.2)	115 (53.5)	592 (26.9)	<0.001
Hypertension	1131 (46.8)	147 (68.4)	984 (44.6)	<0.001
≥75 years	903 (37.3)	104 (48.4)	799 (36.3)	<0.001
Diabetes mellitus	470 (19.4)	82 (38.1)	388 (17.6)	<0.001
History of stroke/TIA	332 (13.7)	62 (28.8)	270 (12.3)	<0.001
Previous MI	199 (8.2)	57 (28.6)	142 (6.4)	<0.001
Vascular disease	360 (14.8)	67 (31.2)	293 (13.3)	<0.001
Peripheral vascular disease	201 (8.3)	33 (15.3)	168 (7.6)	<0.001
Female sex	985 (40.7)	80 (37.2)	905 (41.1)	0.272
65-74 years	659 (27.2)	73 (34.0)	586 (26.6)	0.021
Comorbidities				
Hyperlipidemia	552 (22.8)	80 (37.2)	472 (21.4)	<0.001
Obesity	944 (39)	68 (31.6)	876 (39.7)	0.020
Chronic kidney disease	250 (10.3)	39 (18.1)	211 (9.6)	<0.001
Current smoking	717 (29.6)	88 (40.9)	629 (28.5)	<0.001
Heart rate (>90 beats/min)	1172 (48.4)	156 (72.6)	1016 (46.1)	<0.001
Heart rate, beats/min	90 (84-99)	98 (90-122)	88 (83-98)	<0.001
Previous medications				
Antiplatelets	733 (30.3)	102 (47.4)	631 (28.6)	<0.001
Aspirin	678 (28.0)	97 (45.1)	581 (26.4)	<0.001
Clopidogrel	109 (4.5)	20 (9.3)	89 (4.0)	<0.001
Anticoagulants	484 (20.0)	21 (9.8)	463 (21.0)	<0.001
Dabigatran	103 (4.3)	0.00	103 (4.7)	<0.001
Warfarin	381 (15.8)	21 (9.8)	360 (16.3)	0.012
β-Blockers	1105 (45.7)	102 (47.4)	1003 (45.5)	0.587
ACEI/ARBs	922 (38.1)	134 (62.3)	788 (35.8)	<0.001
Antiarrhythmics	300 (12.4)	26 (12.1)	274 (12.4)	0.886
Digoxin	626 (25.9)	61 (28.4)	565 (25.6)	0.382
Statins	509 (21)	91 (42.3)	418 (19)	<0.001
CHA_2DS_2-VASc score	3 (1-4)	4 (3-5)	3 (1-4)	<0.001

Data are expressed as median (interquartile range) or count (percentage). Abbreviations: ACEI/ARBs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AMI, acute myocardial infarction; AF, atrial fibrillation; TIA, transient ischemic attack.

ROC Analysis

As shown in Figure 1, the AUC-based *c*-index obtained by means of the logistic regression function was 0.81 (95% CI 0.78-0.84), while the c-index obtained with our scoring scheme did not differ significantly at 0.80 (95% CI 0.77-0.83), indicating that the ability of our scoring scheme to predict the relative risk of AMI was equivalent to that of the logistic regression algorithm. The *c*-index derived from the use of the CHA_2DS_2-VASc score (0.71, 95% CI 0.68-0.75) was significantly less than that achieved with our scoring scheme (0.71 *vs.* 0.80) (p <0.001, DeLong test).

Table II. Baseline characteristics of the external validation cohort.

Characteristics	Total sample (n = 1810)	AMI (n = 200)	Non-AMI (n = 2204)	*p*-value
Type of AF				
Paroxysmal	828 (45.7)	108 (54)	720 (44.7)	0.013
Persistent/Permanent	982 (54.3)	92 (46)	890 (55.3)	0.013
Age, years	66 (57-75)	71 (63-77)	66 (56-74)	<0.001
CHA_2DS_2-VASc score components				
Heart failure	318 (17.6)	56 (28)	262 (16.3)	<0.001
Hypertension	740 (40.9)	101 (50.5)	639 (39.7)	<0.001
≥75 years	468 (25.9)	71 (35.5)	397 (24.7)	<0.001
Diabetes mellitus	434 (24)	79 (39.5)	355 (22)	<0.001
History of stroke/TIA	281 (15.5)	48 (24)	233 (14.5)	<0.001
Previous MI	194 (10.7)	51 (25.5)	143 (8.9)	<0.001
Vascular disease	157 (8.7)	32 (16)	125 (7.8)	<0.001
Peripheral vascular disease	149 (8.2)	30 (15)	119 (7.4)	<0.001
Female sex	749 (41.4)	78 (39)	661 (41.1)	0.577
65-74 years	546 (30.2)	75 (37.5)	471 (29.3)	0.021
Comorbidities				
Hyperlipidemia	471 (26)	70 (35)	401 (24.9)	0.002
Obesity	432 (23.9)	44 (22)	388 (24.1)	0.511
Chronic kidney disease	195 (10.8)	39 (19.5)	156 (9.7)	<0.001
Current smoking	497 (27.5)	79 (39.5)	418 (26)	<0.001
Heart rate (>90 beats/min)	889 (49.2)	132 (66)	757 (47)	<0.001
Heart rate, beats/min	94 (85-110)	108 (88-127)	92 (84-108)	<0.001
Previous medications				
Antiplatelets	572 (31.6)	91 (45.5)	481 (29.9)	<0.001
Anticoagulants	484 (24.3)	41 (20.5)	399 (24.8)	0.191
β-Blockers	849 (46.9)	82 (41)	767 (47.6)	0.076
ACEI/ARBs	747 (41.3)	131 (65.5)	616 (38.3)	<0.001
Antiarrhythmics	257 (14.2)	20 (10)	237 (14.7)	0.071
Digoxin	474 (26.2)	45 (22.5)	429 (26.6)	0.208
Statins	506 (28)	83 (41.5)	423 (26.3)	<0.001
CHA_2DS_2-VASc score	2 (1-3)	3 (2-4)	2 (1-3)	<0.001

Data are expressed as median (interquartile range) or count (percentage). Abbreviations: ACEI/ARBs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; AMI, acute myocardial infarction; AF, atrial fibrillation; TIA, transient ischemic attack.

External Validation Cohort

The baseline characteristics of 1810 non-valvular AF patients included in the external validation cohort are reported in Table VI. Of the 1810 AF patients enrolled, 200 were diagnosed with AMI. The median age of patients was 66 years (IQR 57-75) and 41.1% of them were females. The median value (IQR) of the CHA_2DS_2-VASc scores was 2 (1-3). In comparison to the derivation cohort, a lower prevalence of heart failure (17.6%), vascular disease (8.7%), and obesity (23.9%) were detected. When a ROC curve was performed, our scoring scheme also had a good ability to discriminate the AF patients experiencing AMI with a *c*-index of 0.73 (95% CI 0.69-0.77) significantly more than that of the CHA_2DS_2-VASc score (0.65, 95% CI 0.62-0.69) (p <0.001, DeLong test) (Figure 1).

Table III. Factors significantly associated with AMI in stepwise logistic regression analysis and univariate analysis.

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**CI**	***p*-value**	**OR**	**CI**	***p*-value**
Age						
< 65 years	Reference	Reference		Reference	Reference	
65-74 years	2.68	1.80-4.07	<0.001	2.36	1.54-3.67	<0.001
≥ 75 years	2.81	1.93-4.17	<0.001	2.12	1.40-3.26	<0.001
Heart failure	3.13	2.36-4.16	<0.001	2.36	1.74-3.21	<0.001
Hypertension	2.68	2.00-3.63	<0.001	2.18	1.58-3.04	<0.001
DM	2.89	2.14-3.87	<0.001	2.14	1.54-2.95	<0.001
Stroke/TIA	2.39	1.72-3.29	<0.001	1.56	1.08-2.23	0.016
Vascular disease	2.95	2.15-4.03	<0.001	2.51	1.77-3.54	<0.001
Hyperlipidemia	2.17	1.61-2.91	<0.001	2.04	1.47-2.80	<0.001
Current smoking	1.69	1.17-2.42	0.005	1.85	1.34-2.55	<0.001
Heart rate						
> 90 beats/min	3.09	2.28-4.25	<0.001	2.04	1.47-2.80	<0.001

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack.

Table IV. Variables to determine patient score and points assigned (in []).

Risk Factors	Points
Congestive heart failure	[1]
Hypertension	[1]
Age (≥65 years)	[1]
Diabetes mellitus	[1]
Stroke/transient ischemic attack	[0.5]
Vascular disease	[1]
Current smoking	[0.5]
Heart Rate (>90 beats/min)	[1]
Hyperlipidemia	[0.5]

Table V. AMI rates in the derivation and the validation groups using low, moderate and high pretest probability categories.

	Derivation group	Validation group
Score by model	**AMI rate**	**AMI rate**
Low risk (≤2.5)	2.6% [36/1365] (1.8%-3.5%)	5.9 % [71/1206] (4.6%-7.2%)
Moderate risk (3-4)	10.9% [85/778] (8.9%-13.3%)	18.4% [89/485] (14.4%-22.3%)
High risk (≥4.5)	34.1% [94/276] (27.8%-38.9%)	33.6% [40/119] (25.6%-42.1%)

( )=95% confidence interval.

Table VI. AMI rates in the derivation and the validation groups using AMI likely and unlikely categories.

	Derivation group	Validation group
Score by model	**AMI rate**	**AMI rate**
<3.5	3.7% [62/1692] (3.1%-5.2%)	7.2 % [103/1422] (6.3%-9.2%)
≥3.5	21% [153/727] (18.2%-24.6%)	25% [97/388] (21.6%-29.4%)

( )=95% confidence interval.

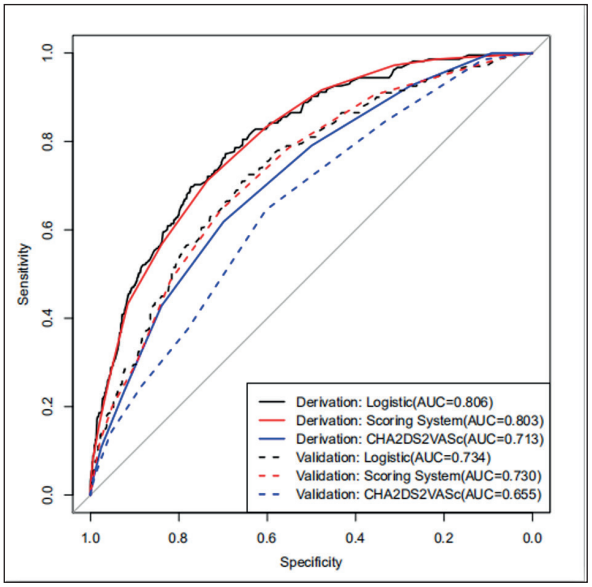

Figure 1. ROC curves of the score model and CHA_2DS_2-VASc score in predicting AMI in AF patients. ROC, receiver-operating characteristics; AMI, acute myocardial infarction; AF, atrial fibrillation; AUC, area under the receiver operating characteristic curve.

Discussion

In this report, we have shown that a new simple clinical prediction rule can categorize the probability of AMI in AF patients. We created two scoring systems. One system divides patients into low (≤2.5 points), moderate (3.0 to 4.0 points), and high (≥4.5 points) probability and could be easily applied. However, the second scoring system may be easier to use since it classifies patients as AMI unlikely (<3.5 points) or AMI likely (≥3.5 points). Reproducibility of the model is suggested by the similar accuracy in the external validation cohort. The new rule with good discriminative abilities performs better than the CHA_2DS_2-VASc score in predicting AMI among AF patients.

During the past few years, there has been an increasing interest in the bidirectional relation between AF and AMI. AMI is an established risk factor for AF, and AF is a well-known complication after AMI, with a reported incidence of 2% to 22%[24]. In this clinical setting, the rapid and irregular ventricular rates during the arrhythmia may cause further impairment of the coronary circulation and left ventricular function in addition to the adverse consequences of neurohormonal activation and jeopardize the prognosis of AMI[25]. Considering the reverse causation, atherosclerosis of coronary arteries with ensuing development of AMI is a typical feature of AF clinical history. In the Atherosclerosis Risk in Communities (ARIC) study[11] including participants who were CAD-free, AF was associated with a 63% increased risk of AMI. Another study[10] demonstrated that prevalent AF was associated with a 2-fold higher incidence of AMI. The coexistence of atherosclerotic risk factors, systemic inflammation, platelet activation, and tachyarrhythmias may account for the increased risk of AMI in AF patients. The occurrence of AMI in AF patients may lead to dismal prognosis and require more complex antithrombotic treatments, yielding serious problems of management[26].

Several multivariable risk prediction algorithms have been developed to assess the individual risk of developing atherosclerotic cardiovascular disease, such as the Framingham general cardiovascular disease equations[27], the Systematic Coronary Risk Evaluation (SCORE) model[28], and the recent Pooled Cohort Equations (PCE) for atherosclerotic cardiovascular disease (ASCVD)[29]. However, these equations have all been developed in patients without AF and with an average younger age. Besides, participants in these studies used to derive the scores were enrolled several decades ago, with exposure to risk factors and prevention strategies differed from contemporary patients. Moreover, the scores need to be estimated with scoring sheets, calculators, or computers, which are not easily used in daily clinical practice. Given the adoption of CHA_2DS_2-VASc score for stroke risk assessment by practice sites across the world and the recent usage of this algorithm in coronary artery disease prognosis assessment, we began our work discussing the value of retaining this algorithm. We found that most of the components of CHA_2DS_2-VASc score, including heart failure, advanced age, hypertension, DM, history of stroke/TIA, vascular disease, were established as independent risk factors for AMI in AF patients after adjustment for other important confounders and medications. Furthermore, cigarette smoking and hyperlipidemia are also well-known independent risk factors for AMI. In the present study, not surprisingly, these two risk factors were observed to be independent and significant predictors of AMI. However, these two well-known risk factors had not been included in the CHA_2DS_2-VASc score. Several Asian cohort studies[30,31] in nonvalvular AF patients without any antithrombotic therapy showed that female sex was not a risk factor for thromboembolism. The recent revised Japanese

AF guideline has excluded female sex as a risk factor for stroke[32]. The present research demonstrated that the odds ratio of female to male sex for AMI was not significant.

Some studies[8,11] underscore the association between increased HR and the occurrence of AMI in AF patients. In a cohort of unselected hospital patients, one-fourth of all MIs were type 2 MIs, about half of which had no significant coronary artery disease, with tachyarrhythmias being one of the most frequent mechanisms[33]. In a porcine model, rapid atrial pacing could induce an increased oxidative stress, endothelial dysfunction, and ventricular ischemia despite the fact that the coronary vessels did not present atherosclerosis[34]. The present work demonstrated that resting HR of >90 beats/min was an independent risk factor for AMI compared to a HR of ≤90 beats/min, more than twice the risk, regardless of the use of β-blockade and other differences in baseline characteristics. Our study is in accordance with previous reports that high resting HR was an independent predictor of incident MI, incident AF, incident ischemic stroke, and cardiovascular death[34]. Besides, Sharashova et al[35] found that a high HR (≥95 beats/min) on admission in patients with AF and AMI was associated with an almost fivefold mortality risk. Moreover, the rate control approach is considered as front-line therapy in the management of AF[14]. We have postulated HR as a modifiable risk factor for AMI in AF patients. Therefore, we suggest strict heart rate control for those at high risk of AMI.

According to the magnitude of each factor both in multivariable analysis and the above analysis, we modified the CHA_2DS_2-VASc score adding hyperlipidemia, smoking, and high resting HR, while discarding female gender as major risk factor. Then, we formulated a new model, with a better prediction of AMI both in the internal cohorts and in the external validation cohort of AF patients. Of note, 22% of the participants in our study were older the age of 79. The occurrence of AF increases with age from 0.14% in those younger than 50, 4% in patients between 60 and 70 years old, to 14% in population over 80 years old[11]. So, our results reflect the general AF population more closely and provide a comprehensive, fast, and simple method for physicians in risk evaluation that requires no calculators or computers.

Before adopting our clinical prediction rule into practice, several points of caution need to be underlined. First, despite including two patient cohorts, they were retrospectively analyzed. The diagnosis of AMI was at the time of admission. The validation of the performance of the new model needs further prospective observational cohort studies. Secondly, our work included only Chinese patients; hence, our results may not be applicable to other racial or ethnic groups. Therefore, further prospective multicenter and larger-scale studies are warranted to validate the model's reliability. Despite these potential limitations, the model seems to be reproducible and most of the necessary information is easily elicited.

Conclusions

Early identification of AF patients at high risk of AMI should be performed as part of the holistic management of AF. The new model may be useful for improving AMI risk stratification for AF patients and the predictive accuracy is significantly superior to the CHA_2DS_2-VASc score.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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