Usefulness of the CHA_2DS_2-VASc Score to Predict Adverse Outcomes in Acute Coronary Syndrome Patients Without Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

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The prognostic value of the CHA_2DS_2-VASc score in acute coronary syndrome (ACS) patients without atrial fibrillation (AF) who underwent percutaneous coronary intervention remains uncertain. We examine the association of the CHA_2DS_2-VASc score and major adverse cardiovascular events (MACE) in this population and compared its risk prediction with 2 other commonly used risk scores (Global Registry of Acute Coronary Events [GRACE] and thrombolysis in myocardial infarction [TIMI]). A total of 3,745 consecutive ACS patients without AF who underwent percutaneous coronary intervention during 2013 to 2017 were classified into 4 groups according to the CHA_2DS_2-VASc score: low (0 to 1), moderate (2 to 3), high (4 to 5), and very high (>5). Incidences of MACE including cardiovascular death, nonfatal myocardial infarction, or stroke in-hospital and during a median follow-up of 33 months were compared among the 4 groups. Receiver-operating characteristic curves were generated to compare CHA_2DS_2-VASc with GRACE and TIMI for risk prediction. The incidences of in-hospital MACE (3.5%, 6.6%, 7.6%, and 9.1%, p <0.001) and mid-term follow-up MACE (4.5%, 7.1%, 13.1%, and 16.1%, p <0.001) were significantly higher as the CHA_2DS_2-VASc score increased. The CHA_2DS_2-VASc score was an independent predictor of subsequent MACE (hazard ratio = 1.31, 95% CI 1.24 to 1.39, p <0.001), and the very high-risk score group showed 3.8-fold increased risk of MACE than the low-risk score group. Receiver-operating characteristic curves showed that the CHA_2DS_2-VASc score was comparable to the GRACE score and to TIMI-STEMI, but, better than the TIMI-NSTEMI/unstable angina pectoris score in terms of predicting MACE. In conclusion, higher CHA_2DS_2-VASc score was independently associated with increased risk of MACE in the ACS patients without AF who underwent PCI. **(Am J Cardiol 2019;124:476−484)**

The CHA_2DS_2-VASc score including congestive heart failure (CHF), hypertension, age ≥75 years, type-2 diabetes, previous stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, and gender category, as a refinement form of $CHADS_2$ score, is a well-validated tool for stroke risk stratification and guiding antithrombotic therapy in patients with atrial fibrillation (AF).[1] Recently, several studies have demonstrated that higher $CHADS_2$/CHA_2DS_2-VASc scores were associated with increased cardiocerebrovascular mortality regardless of the presence of AF.[2−7] A few non-AF studies have explored this simple risk stratification method in patients with acute myocardial infarction (MI), but, not all patients received primary percutaneous coronary intervention (PCI).[8−10] It is unknown whether the CHA_2DS_2-VASc score can be useful in risk prediction for subsequent major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) without AF who underwent PCI.

Global Registry of Acute Coronary Events (GRACE)[11,12] and thrombolysis in MI (TIMI)[13] risk scores were developed to identify high-risk ACS patients who may benefit most from early aggressive therapies. Both risk scores have become commonly used risk prediction tools for MACE after ACS. However, they are complex and require acute clinical, laboratory, electrocardiography (ECG) parameters, and even angiographic evaluation. Can the CHA_2DS_2-VASc score simply using patient demographic and history information reliably assess risk of MACE after ACS? We, therefore, retrospectively assessed the prognostic value of the CHA_2DS_2-VASc score for both in-hospital and follow-up MACE in a cohort of ACS patients without known AF who underwent PCI, and compared the CHA_2DS_2-VASc score to the GRACE and TIMI scores for risk prediction of subsequent MACE.

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Methods

This retrospective observational cohort study included all patients (n = 5,348) who were consecutively admitted for a diagnosis of ACS and underwent PCI between January 2013 and December 2017. ACS includes ST-elevation MI (STEMI), non−ST-elevation MI (NSTEMI), and unstable angina pectoris (UAP). ACS was diagnosed based on symptoms, ECG changes, cardiac biomarkers, or history of coronary artery disease (CAD). Acute MI was defined as typical increase and decrease of cardiac biomarker values and at least one of the following[14]: (1) symptoms of ischemia; (2) development of pathologic Q wave in ≥2 contiguous electrocardiogram leads; (3) new significant ST-segment or T-wave change or new-onset left bundle branch block; (4) identification of intracoronary lesion by angiography.

Patient demographic information, medical history, cardiovascular risk factors, laboratory assessments, medical therapy for ACS, and revascularization procedures were collected and recorded in the Cardiovascular Center Beijing Friendship Hospital Database Bank. As shown in Figure 1, 1,406 were excluded for known AF if they had medical history for AF, or AF on admission or during the hospitalization, 197 were removed for missing data, finally, 3,745 patients were included in this analysis. After discharge, all patients were followed up until June 2018.

All procedures performed in studies involving human participants were in accordance with the Institutional Ethics Committee of the Beijing Friendship Hospital affiliated to Capital Medical University (2018-P2-125-01) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was considered minimal risk by the Institutional Ethics Committee; therefore, formal consent is not required.

The CHA_2DS_2-VASc score was calculated by assigning 2 points for a history of stroke or age ≥75 years and 1 point for each of other components including CHF, hypertension, type-2 diabetes, vascular disease, age 65 to 74 years, and female gender. HF was based on a previous diagnosis of HF or current treatment for HF. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or ongoing therapy for hypertension. Type-2 diabetes was defined as glycosylated hemoglobin (HbA1c) ≥6.5%, a nonfasting plasma glucose concentration ≥200 mg/dl, fasting plasma glucose concentration ≥126 mg/dl, 2-hour plasma glucose concentration ≥200 mg/dl from a 75-g oral glucose tolerance test, or treated with oral hypoglycemic medications or insulin. International Classification of Diseases-9 (ICD-9) or International Classification of Diseases-10 (ICD-10) codes were used to help to identify the chronic conditions such as hypertension and diabetes. As shown in Figure 1, the study cohort was classified into 4 groups according to the CHA_2DS_2-VASc score[1]: low risk (0 to 1 point); moderate risk (2 to 3 points); high risk (4 to 5 points); and very high risk (>5 points).

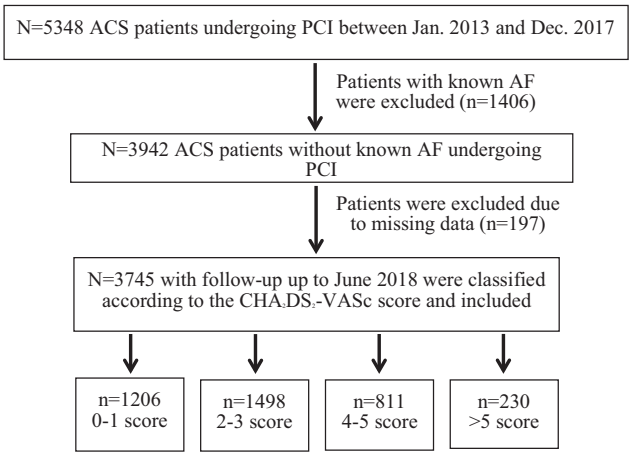

Figure 1. Patient selection flow. ACS = acute coronary syndrome; AF = atrial fibrillation; PCI = percutaneous coronary intervention.

The GRACE risk score,[11] using parameters of age, Killip class, heart rate, systolic BP, ST-segment deviation and cardiac arrest at admission, elevated biomarkers of myocardial necrosis, and baseline creatinine level, was calculated (low [1 to 108], intermediate [109 to 140], and high [>140]).

The TIMI risk score was also used for risk assessment. TIMI-STEMI[15] was calculated using age, Killip class, heart rate >100 bpm, systolic BP <100 mm Hg, weight, history of diabetes, hypertension, and angina (low [0 to 3], intermediate [4 to 6], and high [7 to 14]). TIMI-NSTEMI/UAP[13] was calculated based on age, ≥3 CAD risk factors, history of CAD with stenosis ≥50%, aspirin use, severe angina, ST-segment deviation, and cardiac maker (low [0 to 2], intermediate [3 to 4], and high [5 to 7]).

In addition, dyslipidemia was identified as a serum total cholesterol concentration ≥220 mg/dl (≥5.72 mmol/L), a low-density lipoprotein (LDL) cholesterol concentration ≥140 mg/dl (≥3.63 mmol/L), triglycerides ≥150 mg/dl (≥1.7 mmol/L), or receiving lipid-lowering therapy. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 calculated using the Modification of Diet in Renal Disease formula.[16]

A composite of MACE including cardiovascular death, nonfatal MI, or stroke was defined as the primary study end point. Cardiovascular death was defined as death attributed to MI, CHF, or documented sudden cardiac death. Stroke was referred to ischemic stroke, which was defined as the presence of a new neurological deficit lasting for at least 24 hours with definite evidence of infarction detected by magnetic resonance imaging or computed tomography. In-hospital MACE was identified using medical records in Cardiovascular Center Beijing Friendship Hospital Database Bank. Subsequent MACE after hospital discharge was collected during routine clinical follow-up visits post-ACS. Secondary study end points included cardiovascular death, nonfatal MI, and stroke separately and repeat PCI that was not due to in-stent thrombosis or as planned procedure.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 22 (IBM Inc, Armonk, New York) software. Continuous variables were described as the mean ± standard deviation or median and interquartile range as appropriate, and categorical variables were expressed as numbers or percentage. Patient characteristics among the 4 groups according to CHA_2DS_2-VASc score were compared by the Kruskal-Wallis test for continuous variables, and by chi-square test or Fisher's exact test for categorical variables. The primary and second end points were compared among the 4 CHA_2DS_2-VASc score groups by chi-square test. Cumulative event curves

with the Mantel-Haenszel log-rank test were used for comparing MACE over time among the 4 risk groups.

In addition, multivariate Cox proportional hazards analysis was used to estimate the hazard ratios (HR) and 95% confidence intervals (CI). Baseline risk factors and co-morbidities (age, gender, body mass index, smoking status, hypertension, diabetes, CKD, and previous vascular diseases), clinical presentation characteristics, and laboratory parameters (heart rate on admission, systolic BP on admission, anterior location of MI, peak troponin-I, *N*-terminal probrain natriuretic peptide [NT pro-BNP], HbA1c, LDL cholesterol), and treatment variables (coronary angiography, antiplatelet drugs, angiotensin-converting enzyme inhibitor/angiotensin receptor antagonists, beta blockers,

Table 1
Comparison of baseline characteristics according to CHA_2DS_2-VASc score

Variable	0-1 n = 1206	2-3 n = 1498	4-5 n = 811	>5 n = 230	p value
Age (years)	55.8 ± 8.0	63.1 ± 9.6	72.5 ± 8.4	76.1 ± 6.1	**<0.001**
Women	60 (5%)	434 (29%)	421 (52%)	156 (68%)	**<0.001**
Body mass index (kg/m^2)	25.8 ± 3.2	26.0 ± 3.5	25.7 ± 3.6	25.4 ± 3.5	**0.03**
Current smoker	784 (65%)	569 (38%)	162 (20%)	34 (15%)	**<0.001**
Heart rate (beats/min)	73 ± 13	73 ± 12	72 ± 12	71 ± 12	0.13
Systolic blood pressure (mm Hg)	125 ± 18	131 ± 20	136 ± 20	136 ± 22	**<0.001**
Diastolic blood pressure (mm Hg)	75 ± 12	75 ± 12	74 ± 11	72 ± 12	**<0.001**
Unstable angina pectoris	434 (36%)	779 (52%)	446 (55%)	129 (56%)	**<0.001**
ST elevation myocardial infarction	517 (41%)	404 (27%)	176 (22%)	46 (20%)	**<0.001**
Non-ST elevation myocardial infarction	290 (23%)	314 (21%)	194 (24%)	57 (25%)	0.22
Anterior myocardial infarction	264 (21%)	210 (14%)	89 (11%)	21 (9%)	**<0.001**
Hypertension	517 (41%)	1183 (79%)	713 (88%)	211 (92%)	**<0.001**
Diabetes mellitus	176 (14%)	719 (48%)	454 (56%)	161 (70%)	**<0.001**
Dyslipidemia	517 (41%)	629 (42%)	365 (45%)	97 (42%)	0.38
Chronic kidney disease	38 (3%)	75 (5%)	49 (6%)	16 (7%)	**<0.001**
Peak creatine kinase-myocardial band (IU/L)	10.4 (1.5-107.8)	3.3 (1.0-47.2)	3.0 (1.0-22.2)	3.0 (1.0-16.0)	**<0.001**
Peak troponin-I (ng/ml)	1.00 (0.02-10.3)	0.27 (0.01-5.18)	0.20 (0.01-2.98)	0.25 (0.01-2.56)	**<0.001**
Hemoglobin A1c (%)	6.0 ± 1.1	6.8 ± 1.6	6.9 ± 1.4	7.2 ± 1.6	**<0.001**
Total- cholesterol (mg/dl)/(mmol/L)	179 ± 42/ 4.6 ± 1.1	166 ± 43/ 4.3 ± 1.1	164 ± 41/ 4.3 ± 1.1	165 ± 40/ 4.3 ± 1.1	**<0.001**
Low density lipoprotein - cholesterol (mg/dl)/(mmol/L)	104 ± 30/ 2.7 ± 0.8	97 ± 29/ 2.5 ± 0.8	93 ± 31/ 2.4 ± 0.8	90 ± 28/ 2.4 ± 0.8	**<0.001**
High density lipoprotein - cholesterol (mg/dl)/(mmol/L)	37 ± 6/ 1.05 ± 0.24	42 ± 5/ 1.07 ± 0.27	43 ± 9/ 1.10 ± 0.28	43 ± 9/ 1.11 ± 0.27	**<0.001**
Triglycerides (mg/dl)/(mmol/L)	168 ± 35/ 1.9 ± 1.4	159 ± 27/ 1.8 ± 1.3	142 ± 18/ 1.6 ± 1.1	141 ± 10/ 1.6 ± 0.8	**<0.001**
High sensitivity c-reactive protein (mg/L)	3 (1-11)	3 (1-10)	2 (1-9)	3 (1-10)	0.06
Estimated glomerular filtration rate (ml/min/1.73 m^2)	89 ± 17	82 ± 19	70 ± 18	64 ± 18	**<0.001**
Hemoglobin (g/ml)	142.5 ± 14.6	135.5 ± 15.7	127.3 ± 15.5	122.9 ± 15.4	**<0.001**
Left ventricular ejection fraction at discharge (%)	62 ± 9	62 ± 10	62 ± 10	62 ± 10	0.69
N-terminal probrain natriuretic peptide (pg/ml)	398 (109-1165)	392 (116-1639)	555 (176-2841)	677 (224-3041)	**<0.001**
Prior chronic heart failure	1 (0.1%)	6 (0.4%)	10 (1.2%)	7 (3.0%)	**<0.001**
Prior myocardial infarction	38 (3%)	180 (12%)	130 (16%)	39 (17%)	**<0.001**
Prior unstable angina pectoris	48%	51%	51%	57%	0.10
Prior percutaneous coronary intervention	126 (10%)	314 (21%)	186 (23%)	50 (22%)	**<0.001**
Prior coronary artery bypass grafting	13 (1%)	30 (2%)	24 (3%)	11 (5%)	**0.001**
Prior cerebrovascular accident	0	15 (1%)	16 (2%)	21 (9%)	**<0.001**
Prior peripheral vascular disease	13 (1%)	90 (6%)	105 (13%)	62 (27%)	**<0.001**
No. of coronary artery narrowed					
1	126 (10%)	90 (6%)	24 (3%)	7 (3%)	**<0.001**
2	239 (19%)	180 (12%)	65 (8%)	23 (10%)	**<0.001**
3 or left main	895 (71%)	1228 (82%)	722 (89%)	200 (87%)	**<0.001**
GRACE score	127 ± 25	135 ± 30	153 ± 31	163 ± 30	**<0.001**
TIMI STEMI score	3 (2-4)	5 (3-6)	6 (5-8)	7 (6-8)	**<0.001**
TIMI NSTEMI/UAP score	5 (4-5)	5 (4-6)	5 (5-6)	6 (5-6)	**<0.001**
Medical therapy					
Aspirin	1235 (98%)	1468 (98%)	787 (97%)	218 (95%)	**0.01**
Clopidogrel	1171 (93%)	1423 (95%)	746 (92%)	211 (92%)	**0.04**
Beta-blocker	932 (74%)	1138 (76%)	584 (72%)	159 (69%)	0.08
Angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist	705 (56%)	989 (66%)	535 (66%)	154 (67%)	**<0.001**
Statin	1159 (92%)	1378 (92%)	738 (91%)	207 (90%)	0.57

Data are presented as mean ± SD, median (interquartile range), or percentage of patients. Bold values indicate p <0.05.

and statins) were included in the univariate analysis. This multivariate analysis with adjusting for any possible confounding variables identified in the univariate analysis was performed to identify the independent risk predictors. Considering components of the CHA_2DS_2-VASc score are likely intercorrelated, hence those variables were excluded in the multivariate analysis.

Receiver-operating characteristic curves were generated for predictive accuracy of MACE using the CHA_2DS_2-VASc, GRACE, and TIMI scores. The areas under the curve (AUC) for the 3 scores were compared using DeLong et al's method.[17]

Results

Of 3,745 patients in this analysis, 30% of the study population had STEMI, 22% had NSTEMI, and 48% had UA. As illustrated in Figure 1, 1,206 (32%) were classified as low CHA_2DS_2-VASc risk, 1,498 (40%) as moderate risk, 811 (22%) as high risk, and 230 (6%) as very high risk.

Baseline characteristics were compared among the 4 CHA_2DS_2-VASc risk groups as shown in Table 1. As expected, patients with high CHA_2DS_2-VASc score were older and more females, higher prevalence of hypertension, type-2 diabetes, CKD, and previous cardiovascular disease including previous MI, CHF, coronary revascularization, cerebrovascular and peripheral arterial disease. Also, use of angiotensin-converting enzyme inhibitor/angiotensin receptor antagonists increased with higher CHA_2DS_2-VASc score. Interestingly, patients with lower CHA_2DS_2-VASc score were more likely to present with STEMI and have an anterior infarct, and, of course, more likely to receive antiplatelet therapy. There were more smokers, higher diastolic BP, higher levels of cardiac enzymes, total cholesterol, LDL cholesterol, and triglycerides in the lower CHA_2DS_2-VASc score groups. In contrast, higher systolic BP, more triple-vessel or left main disease, higher levels of NT pro-BNP and HbA1c, and lower levels of estimated glomerular filtration rate and hemoglobin were found in the higher CHA_2DS_2-VASc score groups.

Overall, incidence of in-hospital MACE was 6.0% (n = 224) during a median in-hospital stay of 7 days. Cardiovascular death occurred in 20 cases, nonfatal MI in 183 patients, ischemic stroke in 21 patients, and 15 unplanned repeat PCI. As shown in Figure 2, incidence of in-hospital MACE was significantly step-wise higher with increased CHA_2DS_2-VASc score groups (3.5%, 6.6%, 7.6%, and 9.1%, p <0.001). The secondary end point comparisons showed that cardiovascular mortality rates (0.2%, 0.4%, 1.0%, and 1.3%, p = 0.04) among the 4 CHA_2DS_2-VASc score groups, nonfatal MI (2.8%, 5.5%, 6.0%, and 7.4%, p <0.001), ischemic stroke (0.5%, 0.5%, 0.7%, and 2.2%, p = 0.03), and unplanned repeat PCI (0.1%, 0.4%, 0.6%, and 1.3%, p = 0.03; Figure 2).

Among 3,745 patients in this analysis, 93% completed the clinical follow-up with a median duration of 33 months. A total of cumulative incidence of MACE was 8.1% (n = 304) during the follow-up. As detailed in Figure 3, a higher CHA_2DS_2-VASc score was associated with increased follow-up MACE (4.5%, 7.1%, 13.1%, and 16.1%, p <0.001 by log-rank test).

The Kaplan-Meier event curves (Figure 3) showed that higher CHA_2DS_2-VASc scores were significantly associated with increased incidences of mid-term cardiovascular mortality, stroke, and repeat PCI; however, the incidence of nonfatal MI did not reach statistically significant.

Univariate analysis identified a list of demographic, clinical, CAD characteristics, biomarkers, and treatment-related factors that were significantly associated with risk of subsequent MACE in ACS patients without AF who underwent PCI as shown in Table 2. In the multivariate analysis, CHA_2DS_2-VASc score was significantly and independently associated with risk of MACE (HR = 1.32, 95% CI 1.25−1.40, p <0.001). In addition, levels of peak

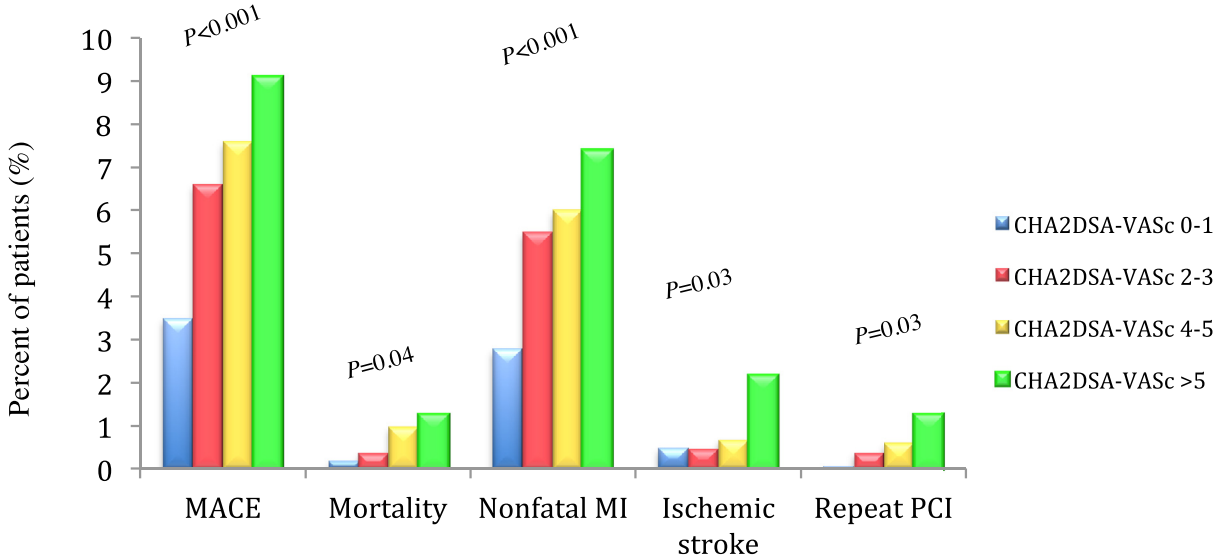

Figure 2. The in-hospital major adverse cardiac events (MACE) based on the CHA_2DS_2-VASc score. The incidences of MACE, in-hospital mortality, nonfatal MI, ischemic stroke, and repeat PCI were increasing as the CHA_2DS_2-VASc score increased. MI = myocardial infarction; PCI = percutaneous coronary intervention.

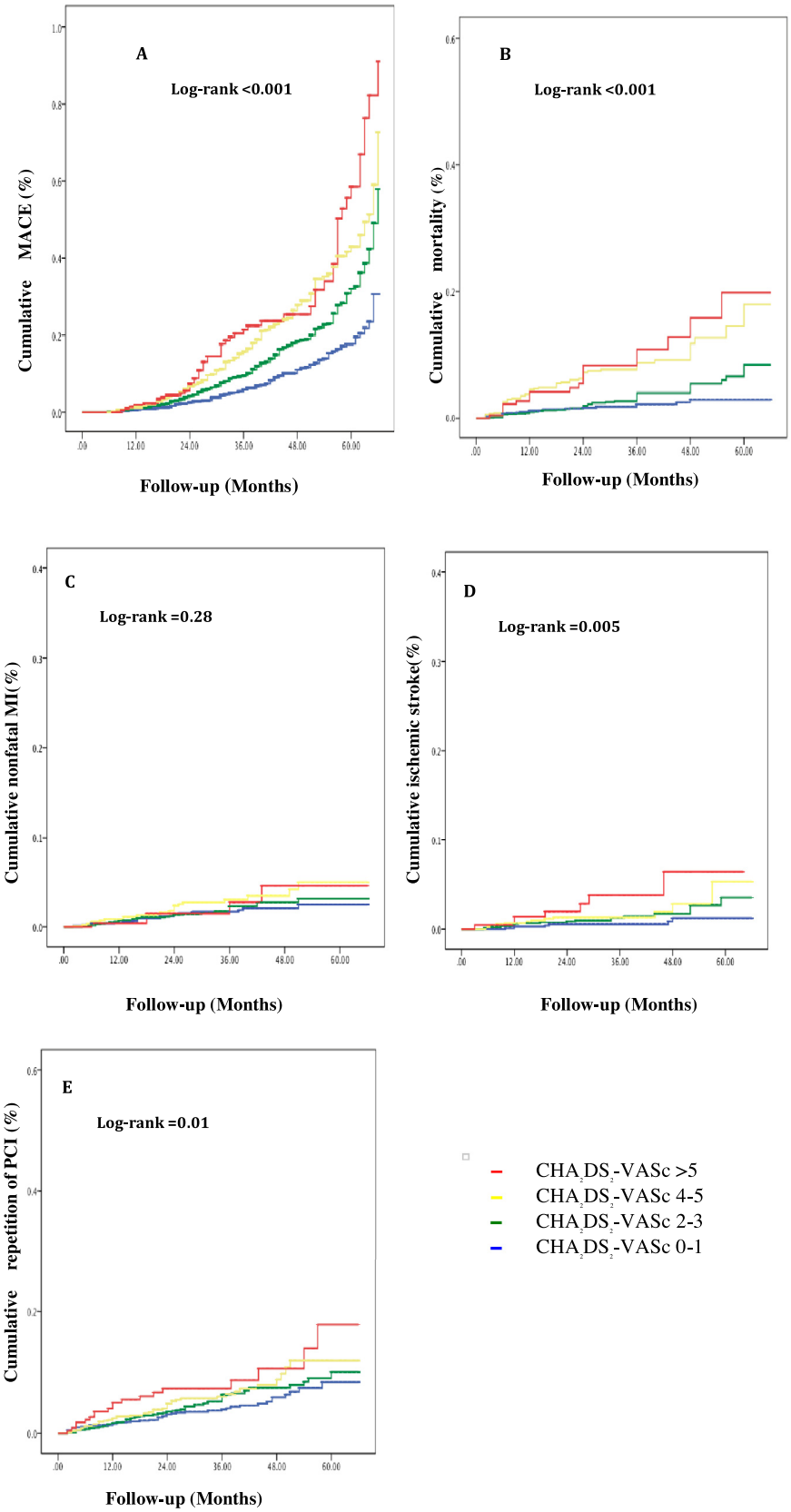

Figure 3. Kaplan-Meier analyses during follow-up according to CHA_2DS_2-VASc score. Cumulative incidence of MACE *(A)*, cardiovascular mortality *(B)*, nonfatal MI *(C)*, ischemic stroke *(D)*, and repeat PCI *(E)*. MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2
Cox proportional hazards regression analyses for major adverse cardiovascular events

Variable	Univariate regression			Multivariate regression		
	HR	95% CI	p value	HR	95% CI	p value
CHA_2DS_2-VASc score	1.37	1.31-1.44	**<0.001**	1.32	1.25-1.40	**<0.001**
Age	1.03	1.02-1.04	**<0.001**			
Women	1.10	0.91-1.33	0.32			
Body mass index	0.96	0.93-0.98	**0.001**	0.98	0.96-1.01	0.21
Current smoker	1.41	1.17-1.69	**<0.001**	0.83	0.68-1.02	0.08
Heart rate	1.00	0.99-1.01	0.74			
Systolic blood pressure	1.01	1.00-1.01	**0.01**			
Anterior myocardial infarction	1.25	0.97-1.61	0.09			
Hypertension	0.78	0.64-0.94	**0.01**			
Diabetes mellitus	0.75	0.63-0.89	**0.001**			
Chronic kidney disease	0.58	0.42-0.81	**0.001**	0.97	0.64-1.45	0.87
Peak troponin-I	0.99	0.98-0.99	**<0.001**	0.99	0.98-0.99	**<0.001**
Hemoglobin A1c	1.09	1.03-1.16	**0.004**			
Low density lipoprotein - cholesterol	0.64	0.56-0.73	**<0.001**	0.80	0.73-0.88	**<0.001**
Estimated glomerular filtration rate	0.99	0.98-0.99	**<0.001**	1.00	0.99-1.01	0.84
N-terminal probrain natriuretic peptide	1.00	1.00-1.00	**<0.001**	1.00	1.00-1.00	**0.01**
Number of vessel coronary disease	1.47	1.21-1.79	**<0.001**	1.22	1.00-1.50	**0.04**
Prior chronic heart failure	0.59	0.22-1.57	0.29			
Prior myocardial infarction	0.36	0.29-0.44	**<0.001**			
Prior cerebrovascular accident	0.63	0.50-0.78	**<0.001**			
Prior peripheral vascular disease	0.41	0.30-0.54	**<0.001**			
Aspirin	2.76	1.97-3.85	**<0.001**	1.47	0.94-2.30	**0.04**
Angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist	1.26	1.05-1.51	**0.01**	1.18	0.98-1.44	0.09
Statin	1.65	1.26-2.16	**<0.001**	1.03	0.73-1.44	0.89
Beta-blocker	1.30	1.08-1.58	**0.006**	1.32	0.94-1.42	0.18

Predictors ($p < 0.05$) of clinical outcome identified through univariate analysis were tested in a multivariate analysis. Bold values indicate $p < 0.05$.

troponin-I, LDL-C, NT pro-BNP, number of diseased coronary vessels, and use of aspirin were independently associated with risk of MACE (Table 2).

Furthermore, adjusted HR of MACE increased significantly in the higher CHA_2DS_2-VASc score groups than the low-risk group. Compared with the low-risk group, HR raised to 1.82 (95% CI 1.43 to 2.33) in the moderate risk, HR = 2.81 (95% CI 2.18 to 3.63) in the high-risk, and HR = 3.82 (95% CI 2.74 to 5.32) in the very high-risk group, all $p < 0.001$.

As shown in Figure 4, receiver-operating characteristic curves showed comparable AUC between CHA_2DS_2-VASc (AUC = 0.71, 95% CI 0.68 to 0.74) and GRACE (AUC = 0.69, 95% CI 0.66 to 0.72) with p = 0.49 by C-statistics for in-hospital MACE, and between CHA_2DS_2-VASc (AUC = 0.67, 95% CI 0.65 to 0.70) and GRACE (AUC = 0.65, 95% CI 0.63 to 0.68) with p = 0.25 for follow-up MACE. In patients with STEMI, CHA_2DS_2-VASc was comparable to TIMI-STEMI for in-hospital MACE (AUC = 0.74, 95% CI 0.67 to 0.81, vs AUC = 0.73, 95% CI 0.66 to 0.81, p = 0.93) and for follow-up MACE (AUC = 0.71, 95% CI 0.67 to 0.76, vs AUC = 0.66, 95% CI 0.61 to 0.71, p = 0.13; Figure 4). However, CHA_2DS_2-VASc showed significantly larger AUC than TIMI-NSTEMI/UAP (AUC = 0.69, 95% CI 0.65 to 0.72, vs AUC = 0.59, 95% CI 0.55 to 0.64, $p < 0.001$) for in-hospital MACE, and also for follow-up MACE (AUC = 0.66, 95% CI 0.63 to 0.69 vs AUC = 0.57, 95% CI 0.53 to 0.60, $p < 0.001$) as shown in Figure 4.

Discussion

It is well established that patients with ACS are at increased risk for subsequent MACE.[18–20] Effective risk prediction remains clinically important. In addition to the GRACE and TIMI risk scores for improved MACE risk prediction, we proposed a hypothesis that the CHA_2DS_2-VASc score, a simple risk assessment tool, can also predict MACE in this population. Our study examined the associations of CHA_2DS_2-VASc score with in-hospital and follow-up MACE in a cohort of ACS patients without known AF who underwent PCI. We found that (1) in-hospital MACE rate was significantly higher as the CHA_2DS_2-VASc score increased from low to moderate, to high, and to very high (3.5%, 6.6%, 7.6%, and 9.1%, $p < 0.001$ for trend); (2) follow-up MACE occurred significantly more with increased CHA_2DS_2-VASc score (4.5%, 7.1%, 13.1%, and 16.1%, $p < 0.001$ for trend); and (3) CHA_2DS_2-VASc score was an independent predictor of subsequent MACE (HR = 1.31, 95% CI 1.24 to 1.39, $p < 0.001$). Furthermore, the very high-risk group showed 3.8-fold increased risk of MACE than the low-risk group (HR = 3.82, 95% CI 2.74 to 5.32, $p < 0.001$).

Previous studies of assessing the CHA_2DS_2-VASc score as a useful tool for risk prediction of subsequent MACE in patients with ACS have demonstrated that the CHA_2DS_2-VASc score ≥2 was associated with higher rate of MACE in 3,184 ACS patients, but, not all treated with PCI.[5] Another study in 2,647 AMI patients showed that every

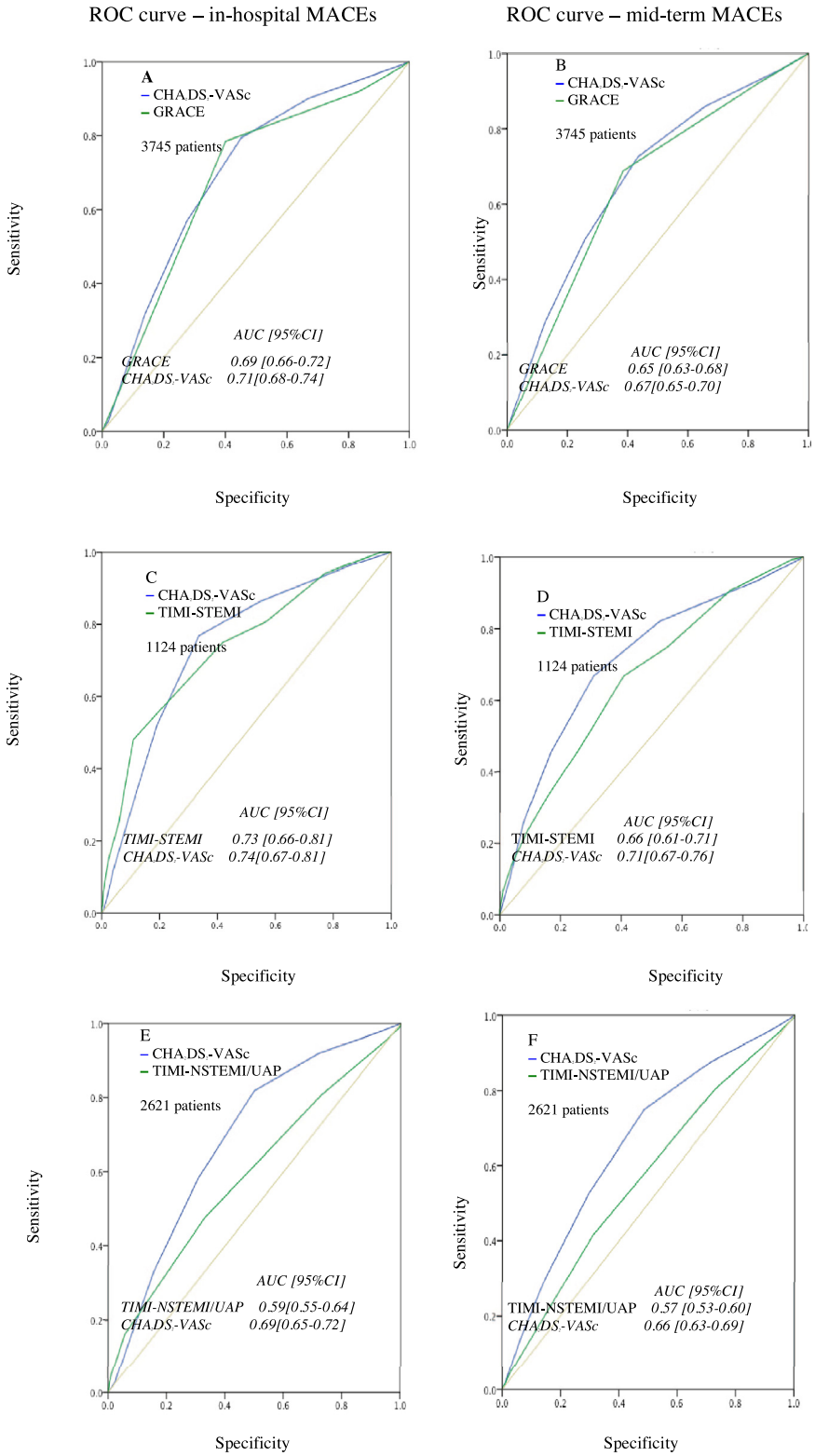

Figure 4. Receiver-operating characteristic (ROC) curves for predicting in-hospital (median in-hospital duration 7 days) and mid-term follow-up (median follow-up duration 33 months) MACE, respectively. CHA_2DS_2-VASc in *blue lines*, GRACE and TIMI-STEMI or TIMI-NSTEMI/UAP in *green lines*. *(A)* Areas under the curve (AUC) for GRACE and CHA_2DS_2-VASc scores were similar in predicting in-hospital MACE ($p = 0.49$). *(B)* AUC for GRACE and CHA_2DS_2-VASc scores were comparable in predicting mid-term MACE ($p = 0.25$). *(C)* AUC for TIMI-STEMI and CHA_2DS_2-VASc scores were similar in predicting in-hospital MACEs in the STEMI patients ($p = 0.93$). *(D)* AUC for TIMI-STEMI and CHA_2DS_2-VASc scores were comparable in predicting mid-term MACE in the STEMI patients ($p = 0.13$). *(E)* Comparison of AUC for TIMI-NSTEMI/UAP and CHA_2DS_2-VASc scores predicting in-hospital MACE in the NSTEMI/UAP patients (0.59 vs 0.69, $p < 0.001$). *(F)* Comparison of AUC for TIMI-NSTEMI/UAP and CHA_2DS_2-VASc scores predicting mid-term MACE in the NSTEMI/UAP patients (0.57 vs 0.66, $p < 0.001$). MACE = major adverse cardiac events. (Color version of figure is available online.)

point increase of the CHA_2DS_2-VASc score was independently associated with 23% increase in cardiovascular death during follow-up.[7] Barra et al[21] found that the CHA_2DS_2-VASc score predicted stroke and total mortality during a 6-month follow-up. Our findings not only provided additional evidence that increased CHA_2DS_2-VASc score was independently associated with subsequent MACE, but also demonstrated a clear dose relation of higher incidence of MACE with increased CHA_2DS_2-VASc score in more contemporary ACS patients without AF who underwent PCI.

It is not surprising that increased CHA_2DS_2-VASc score independently associated with risk of subsequent MACE. A number of observational studies[22–24] have shown the impact of each individual component of CHA_2DS_2-VASc on CVD outcomes. However, how well the CHA_2DS_2-VASc score using only demographic and clinical risk variables can predict future MACE comparing other risk stratification tools that include cardiac enzyme, ECG changes, and angiographic information had not been evaluated until our study. We showed that the CHA_2DS_2-VASc score was comparable to the GRACE score, which recommended by guideline[11] and TIMI-STEMI, both require ECG and cardiac enzyme information for prediction of both in-hospital and follow-up MACE. The CHA_2DS_2-VASc score performed significantly better than TIMI-NSTEMI/UAP, which requires angiographic information for prediction of both in-hospital and follow-up MACE. These findings shall give clinicians confidence to use the CHA_2DS_2-VASc score for risk prediction and provide an opportunity for an early risk stratification before ECG, enzyme, and angiographic information become available.

In addition to the CHA_2DS_2-VASc score, the multivariate analysis also identified higher levels of NT pro-BNP and a number of coronary artery disease were significantly associated with increased risk of MACE. Unexpectedly, higher levels of peak troponin-I and LDL-C at time of ACS were associated with lower risk of MACE. There was a possibility that cardiologists may have used higher troponin-I or LDL-C as indications for more aggressive secondary prevention after ACS and PCI. This explanation is supported by the recent published ODYSSEY Outcomes trial,[25] which showed that intensive LDL-C lowering with alirocumab, a PCSK9 inhibitor, was more beneficial in post-ACS patients with LDL-C ≥100 mg/dl. In contrast, use of aspirin, that is more likely in a higher risk population, was associated with increased risk of MACE. Of course, these findings will need further confirmation from prospective studies that not only collect MACE but also provide data on treatment and laboratory details during follow-up for more comprehensive evaluation on relation of intensity of secondary prevention and outcomes after ACS and PCI.

Our study has several limitations. First, we enrolled ACS patients without known AF, but we cannot rule out the possibility of asymptomatic paroxysmal AF. We did not perform ambulatory electrocardiography during the follow-up to capture AF. Nevertheless, Kim et al[26] reported that the CHA_2DS_2-VASc score had an impact on all-cause mortality in AMI patients irrespective of presence of AF. Second, the median follow-up was 33 months in our study. A number of patients who admitted in 2016 or 2017 had a significant shorter follow-up period. Longer follow-up studies are needed to confirm our findings. Finally, this is a single-center retrospective study that might not reflect heterogeneity of the ACS population and the cardiology practice.

In conclusion, increased CHA_2DS_2-VASc score was independently associated with MACE in hospital and during follow-up in ACS patients without known AF who underwent PCI. This simple risk assessment tool was comparable with the established risk scores for predicting future events.

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Disclosures

The authors have no conflicts of interest to disclose.

Authors' Contribution

Hongwei Li: contributed to the conception, design, analysis, and interpretation of data. Hui Peng and Zhijun Sun: contributed to the design, acquisition, analysis, and interpretation of data. Yue Zhang and Xiaosong Ding: contributed to the acquisition and analysis of data. Hui Chen: contributed to the analysis and interpretation of data. Xueqiao Zhao: contributed to the interpretation of data. Hui Peng and Zhijun Sun drafted the manuscript. Xueqiao Zhao and Hongwei Li contributed significantly to its revision. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary materials

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