A Novel Risk Scoring System to Predict Cardiovascular Death in Patients With Acute Myocardial Infarction: CHA₂DS₂-VASc-CF Score

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Abstract

The present study aimed to determine the long-term prognostic validity of the CHA₂DS₂-VASc score in patients with acute myocardial infarction (AMI). In addition, we formulated a novel scoring system, the CHA₂DS₂-VASc-CF (which includes cigarette smoking and a family history of coronary artery disease as risk factors). This study included 4373 consecutive patients with AMI who presented to the emergency department of our hospital and underwent cardiac catheterization procedures between December 2009 and September 2016. Among these patients, 1427 were diagnosed with ST elevation myocardial infarction (STEMI) and 2946 were diagnosed with non-STEMI. The study included 4373 patients. The study population was divided into 2 groups according to the occurrence of cardiovascular death during the follow-up period. Multivariate logistic regression analysis showed that the CHA₂DS₂-VASc-CF score, CHA₂DS₂-VASc score, major adverse cardiac events, current cigarette smoking, older age, hypertension, and family history of coronary artery disease were significantly higher, and that the left ventricular ejection fraction and glomerular filtration rate were significantly lower in the cardiovascular death (+) group. Using a cutoff score of >3 for the CHA₂DS₂-VASc-CF score, long-term cardiovascular death was predicted with a sensitivity of 78.4% and specificity of 76.4%. The CHA₂DS₂-VASc-CF score is suitable for use in all patients with AMI, regardless of the type of treatment, presence of atrial fibrillation, and type of AMI. This risk score, which is easy to calculate, provides important prognostic data. In the future, we think that interventional cardiologists will be able to use this novel scoring system to identify patients with a high risk of long-term cardiovascular death.

Keywords

acute myocardial infarction, CHA₂DS₂-VASc, CHA₂DS₂-VASc-CF, risk score

Introduction

As the incidence of acute myocardial infarction (AMI) increased and the acute coronary events survival rate improved, the risk-stratification system used for long-term post-AMI prognosis increased in importance. All patients with AMI should undergo early and late risk stratification. Early risk stratification in patients with non-ST elevation myocardial infarction (NSTEMI) provides a guide to the in-hospital treatment decision-making process, especially early invasive treatment, whereas late risk stratification aids long-term patient management and the prediction of prognosis.¹ Patients with ST elevation myocardial infarction (STEMI) should undergo early and late risk stratification as well, but early reperfusion is the first-line choice of treatment, even in cases with low risk at initial evaluation. Late risk stratification in patients with STEMI should be used to identify patients with increased risk of cardiovascular mortality.²

Early and late risk stratification in patients with AMI is intended to identify high-risk patients, as such patients benefit most from aggressive treatment. There are various risk

prediction models for patients with NSTEMI and STEMI. The Thrombolysis in Myocardial Infarction (TIMI) risk score and Global Registry of Acute Coronary Events (Grace) Risk score are the most commonly used risk prediction scores.³⁻⁵ The CHA₂DS₂-VASc score is a simple scoring system used to predict thromboembolic risk in patients with atrial fibrillation and considers such risk factors for cardiovascular mortality as heart failure and age. The long-term validity of the CHADS₂ score—the predecessor of the CHA₂DS₂-VASc score—as a prognostic marker in patients with AMI, independent of atrial fibrillation, has been reported.⁶ Recent studies have shown that the

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CHA₂DS₂-VASc score can be considered a prognostic marker of in-hospital and long-term mortality in patients with STEMI.^{7,8} The present retrospective cohort study aimed to determine the long-term prognostic validity of the CHA₂DS₂-VASc score in patients with AMI. In addition, we formulated a novel scoring system, the CHA₂DS₂-VASc-CF (which includes cigarette smoking and a family history of coronary artery disease [CAD] as risk factors) and compared the risk prediction of this novel risk score with that of the CHA₂DS₂-VASc score.

Materials and Methods

This single-center study included 4373 consecutive patients with AMI who presented to the emergency department of our hospital and underwent cardiac catheterization procedures between December 2009 and September 2016. Follow-up data were obtained from digital records, patient files, or by telephone interview with patients, family members, or primary care physicians. Among these patients, 1427 were diagnosed as STEMI and 2946 were diagnosed as NSTEMI. ST elevation myocardial infarction was defined as ischemic symptoms for ≥ 10 minutes at rest within 72 hours of presentation and electrocardiographic changes associated with STEMI (new left bundle-branch block or persistent ST segment elevation > 1 mm in ≥ 2 contiguous electrocardiographic leads). Non-ST elevation myocardial infarction was defined as ischemic symptoms for ≥ 10 minutes at rest that occurred within 24 hours of presentation and elevated cardiac markers of necrosis (troponin I).⁹ Patients with a history of or newly diagnosed atrial fibrillation, those with unstable angina pectoris, and those in which an intracoronary lesion was not observed via angiography were excluded.

The study population was divided into 2 groups according to the occurrence of cardiovascular death during the follow-up period. The CHA₂DS₂-VASc score and CHA₂DS₂-VASc-CF score were calculated separately on the patients' index events. Next, the patients were divided into 4 groups according to their CHA₂DS₂-VASc-CF score. All the parameters included in these scores were obtained from the hospital database. In addition, demographic, clinical, laboratory, and echocardiographic data were collected from the patients' electronic medical records, via telephone contact (with either the general practitioner or the patient), and via coupling of municipal mortality records or information system.

The components of CHA₂DS₂-VASc score and CHA₂DS₂-VASc-CF score include congestive heart failure (1 point), hypertension (1 point), age (> 75 years [2 points]), diabetes mellitus (1 point), history of stroke or transient ischemic attack (2 points), history of vascular disease (1 point), age (> 65 years [1 point]), female gender (1 point), cigarette smoking (1 point), and family history of premature CAD (1 point).¹⁰

Hypertension was defined as a history of antihypertensive medication use, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg. Diabetes mellitus was defined as a history of use of insulin or antidiabetic agents, or a fasting glucose level ≥ 126 mgdL⁻¹. Chronic heart failure

was defined as a $< 40\%$ decrease in the left ventricular ejection fraction or congestive heart failure. Vascular disease was defined as a history of MI, peripheral arterial disease, or complex aortic plaques. A family history of CAD was defined as ≥ 1 first-degree relatives with premature CAD (in men before the age of 55 years and in women before the age of 65 years). Mortality due to AMI, sudden cardiac death or arrhythmia, heart failure, and stroke were considered cardiovascular death. Major adverse cardiac events (MACEs) were defined as cardiovascular death, reinfarction, and repeat target vessel revascularization. The study protocol was approved by the Ankara Numune Education and Research Hospital Ethics Committee.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22 (IBM Corp, Armonk, New York). The distribution pattern of the variables was analyzed using the Kolmogorov-Smirnov test. Continuous data are presented as mean (standard deviation [SD]), or median and interquartile range (IQR), according to the distribution pattern of the variables. Student *t* test was used to compare parametric continuous variables, and the Mann-Whitney *U* test was used to compare nonparametric continuous variables. Categorical variables were compared using the χ^2 test, the results of which are presented as percentages.

Univariate logistic regression analysis was used to calculate the effects of multiple variables on cardiovascular death. Variables with an unadjusted *P* value $< .05$ based on logistic regression analysis were considered potential risk markers and were included in the multivariate logistic regression analysis model. Potential risk markers were eliminated using forward stepwise multivariate logistic regression analysis. *P* values $< .05$ were considered statistically significant at the 95% confidence interval (CI). The receiver–operating characteristics (ROC) curve was used to show the sensitivity and specificity of CHA₂DS₂-VASc and CHA₂DS₂-VASc-CF scores and the optimal cutoff value of each for predicting long-term cardiovascular death.

Finally, the study population was divided into quartiles for descriptive purposes according to the CHA₂DS₂-VASc-CF score. We used Cox regression modeling to examine the association between CHA₂DS₂-VASc-CF score quartiles and cardiovascular death. Kaplan-Meier estimate curves were used to determine the correlations between CHA₂DS₂-VASc-CF score quartiles, MACEs, and cardiovascular death.

Results

The study included 4373 patients. Baseline demographic and clinical data according to the occurrence of cardiovascular death are shown in Table 1. The follow-up period and body mass index did not differ significantly between the patients with and without cardiovascular death. Mean age of patients in the cardiovascular death (–) group was significantly higher than in the cardiovascular death (+) group. The prevalence of diabetes mellitus, hypertension, hyperlipidemia, a family

Table 1. Baseline Demographic and Clinical Data According to the Occurrence of Cardiovascular Death.

Variables	No CV Death, n = 3986 (91.2%)	CV Death, n = 387 (8.8%)	P Value
Age, mean (SD)	54 (10)	63 (11)	<.001
Female, n (%)	754 (18.9%)	165 (42.6%)	<.001
Diabetes mellitus, n (%)	842 (21.1%)	180 (46.6%)	<.001
Hypertension, n (%)	1522 (38.2%)	226 (58.5%)	<.001
Current smoker, n (%)	2538 (63.7%)	264 (68.2%)	<.001
Family history of CAD, n (%)	858 (21.5%)	96 (24.8%)	<.001
Hyperlipidemia, n (%)	1396 (35.0%)	152 (39.3%)	.004
Follow-up period (months), median (IQR)	22 (14-40)	21 (11-39)	.155
Glomerular filtration rate, mL/min/1.73 m ² , mean (SD)	93.7 (29.4)	72.17 (27.63)	<.001
Left ventricular ejection fraction, %, mean (SD)	48.37 (7.28)	41.59 (10.64)	<.001
Hemoglobin-A ₁ C, %, mean (SD)	6.53 (0.95)	6.66 (0.75)	.002
Body mass index (kg/m ²), mean (SD)	26.7 (3.8)	26.8 (3.7)	.667
ST-elevation myocardial infarction, n (%)	1282 (32.1%)	145 (37.4%)	.002
Major cardiovascular events (MACE), n (%)	714 (17.9%)	202 (52.2%)	<.001
CHA ₂ DS ₂ -VAS(c), mean (SD)	1.92 (1.22)	3.34 (1.71)	<.001
CHA ₂ DS ₂ -VAS(c)-CF, mean (SD)	2.37 (1.45)	5.09 (1.94)	<.001

Abbreviations: CAD, coronary artery disease; IQR, interquartile range; MACE, Major cardiovascular event; SD, standard deviation.

Table 2. Univariate and Multivariate Logistic Regression Analyses to Predict Cardiovascular Death.

Variables	Univariate Regression Analyses		Multivariate Regression Analyses	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Age, mean (SD)	1.108 (1.096-1.120)	<.001	1.008 (1.001-1.016)	.049
Female, n (%)	1.154 (1.124-1.191)	<.001	1.004 (0.985-1.023)	.245
Diabetes mellitus, n (%)	4.067 (3.285-5.035)	<.001	1.955 (1.580-2.440)	.001
Hypertension, n (%)	3.392 (2.719-4.232)	<.001	1.672 (1.495-1.913)	.003
Current smoker, n (%)	1.347 (1.280-1.430)	<.001	1.290 (1.055-1.490)	.006
Family history of CAD, n (%)	2.032 (1.793-2.372)	<.001	1.560 (1.392-1.802)	.019
Hyperlipidemia, n (%)	1.633 (1.499-1.803)	.004	1.213 (0.840-1.686)	.565
Glomerular filtration rate, mean (SD)	0.962 (0.957-0.966)	<.001	0.982 (0.977-0.988)	.038
Left ventricular ejection fraction, mean (SD)	0.917 (0.906-0.927)	<.001	0.934 (0.922-0.974)	.004
Hemoglobin-A ₁ C, mean (SD)	1.173 (1.069-1.287)	.001	1.040 (0.950-1.090)	.352
ST-elevation myocardial infarction, n (%)	2.073 (1.577-2.724)	<.001	1.365 (0.855-1.875)	.105
Major cardiovascular events (MACE), n (%)	5.002 (4.033-6.204)	<.001	2.530 (1.745-3.669)	<.001
CHA ₂ DS ₂ -VAS(c), mean (SD)	2.332 (2.161-2.516)	<.001	2.177 (1.971-2.406)	.001
CHA ₂ DS ₂ -VAS(c)-CF, mean (SD)	7.131 (5.946-8.553)	<.001	8.590 (6.693-10.597)	<.001

Abbreviations: CAD, coronary artery disease; MACE, major cardiovascular events; SD, standard deviation.

history of CAD, the number of female patients, and current cigarette smoking, and type of MI, hemoglobin A₁C level, MACEs, and CHA₂DS₂-VASc and CHA₂DS₂-VASc-CF scores were higher in the cardiovascular death (+) group. On the other hand, the left ventricular ejection fraction and the glomerular filtration rate were lower in the cardiovascular death (+) group.

The parameters with *P* values <.05 based on univariate logistic regression analysis were used for multivariate logistic regression analysis (age, female gender, diabetes mellitus, hypertension, current cigarette smoking, hyperlipidemia, family history of CAD, type of MI, hemoglobin A₁C, left ventricular ejection fraction, glomerular filtration rate, MACEs, CHA₂DS₂-VASc score, and CHA₂DS₂-VASc-CF score). This multivariate logistic regression analysis showed that the

CHA₂DS₂-VASc-CF score, CHA₂DS₂-VASc score, MACEs, current cigarette smoking, older age, hypertension, and family history of CAD were significantly higher and that the left ventricular ejection fraction and glomerular filtration rate were significantly lower in the cardiovascular death (+) group (Table 2). The ROC curve was used to analyze the discriminatory capability of the CHA₂DS₂-VASc score and CHA₂DS₂-VASc-CF score to predict long-term cardiovascular death; the area under the curve was 0.739 (95% CI: 0.715-0.763; *P* < .001) and 0.840 (95% CI: 0.815-0.862; *P* < .001), respectively. Using a cutoff score of >2 for the CHA₂DS₂-VASc score and >3 for the CHA₂DS₂-VASc-CF score, long-term cardiovascular death was predicted with a sensitivity of 61.5% and specificity of 74.2%, and a sensitivity of 78.4% and specificity of 76.4%, respectively (Figure 1). Descriptive and the results of

Figure 1. The receiver–operating characteristics (ROC) curve was used to analyze the discriminatory capability of the CHA₂DS₂-VASc score and CHA₂DS₂-VASc-CF score to predict long-term cardiovascular death.

Cox regression analysis for predicting long-term cardiovascular death according to CHA₂DS₂-VASc-CF score are shown in Table 3. For descriptive purposes, the patients were divided into 4 groups according to their CHA₂DS₂-VASc-CF score (Table 3) as follows: group 1: ≤ 1 ; group 2: 2-3; group 3: 4-5; and group 4: ≥ 6 . Long-term cardiovascular mortality was found to be significantly different among the CHA₂DS₂-VASc-CF score groups. As shown in Table 3, group 4 has the highest percentage of long-term cardiovascular mortality ($P < .001$).

The Kaplan-Meier MACEs and survival estimate curves for each of the CHA₂DS₂-VASc-CF score groups are shown in Figures 2 and 3, respectively. As shown in these figures, the occurrence of both MACEs (Figure 2) and long-term cardiovascular mortality (Figure 3) significantly increased in higher CHA₂DS₂-VASc-CF groups.

Discussion

The present study's most important finding is that the CHA₂DS₂-VASc-CF score at presentation can predict long-term cardiovascular death better than the CHA₂DS₂-VASc score. A CHA₂DS₂-VASc-CF score >3 can predict long-term cardiovascular death, with a sensitivity of 78.4% and specificity of 76.4%. In addition, long-term MACEs can also be predicted using this novel score. Furthermore, the CHA₂DS₂-VASc-CF score can be used as a risk-stratification system in patients with AMI, irrespective of the type of MI, presence of atrial fibrillation, and type of treatment.

Most patients with CAD have at least 1 coronary risk factor; the presence of more than one of these risk factors increases the risk of CAD.^{11,12} It is of great importance to assess the risk of CAD to provide appropriate medical treatment and account for morbidity and mortality. Therefore, several risk prediction

algorithms, including major CAD risk factors, have been developed. Clinicians need simple, reliable, reproducible, and quantitative tools to identify patients' risks and recommend prevention strategies. Although the GRACE and TIMI risk scores are well-known for risk stratification in patients with AMI and are recommended by multiple organizations, these risk scores require a computerized system.³⁻⁵ In contrast to the complexity of the GRACE and TIMI risk scores, the CHADS₂ score is a fast, wide-ranging, and practical for risk stratification.¹³ As the predictive power of the CHA₂DS₂-VASc score is greater than that of the CHADS₂ score, it is reasonable to use CHA₂DS₂-VASc score to easily and accurately predict long-term cardiovascular death in patients with AMI. Likewise, Bozbay et al⁷ and Kim et al⁸ reported that the CHA₂DS₂-VASc score is a powerful predictor of cardiovascular death in patients with AMI,^{7, 8,14} and Cetin et al¹⁵ suggested that the CHA₂DS₂-VASc score is independently correlated with the severity of CAD. In another study, Kurtul et al demonstrated that CHA₂DS₂-VASc score can predict contrast-induced nephropathy after percutaneous coronary intervention for acute coronary syndrome.¹⁶

The CHA₂DS₂-VASc score was developed to improve risk stratification in patients with atrial fibrillation patients and a low CHADS₂ score (0-1); patient aged 65 to 74 years, female gender, and vascular disease are additional components of the CHADS₂ score. All the components of the CHA₂DS₂-VASc score are important risk and prognostic factors for cardiovascular disease. It was reported that in-hospital mortality significantly and independently increases as patient age increases.¹⁷ Gustafsson et al¹⁸ observed that hypertension, diabetes mellitus, and a low left ventricular ejection fraction are long-term prognostic predictors following AMI. Malmberg et al¹⁹ also reported that diabetes mellitus was an independent predictor of all-cause mortality and cardiovascular death in patients with unstable angina or NSTEMI. Reynolds et al²⁰ reported that according to multivariate analysis, women have a higher (not significantly) risk of cardiovascular death post-AMI than men. Additionally, Ducrocq et al²¹ noted that a history of stroke is associated with an independent increase in the risk of AMI and death. A large-scale, long-term follow-up study reported that a history of peripheral arterial disease is a critical evidence of more widespread atherothrombotic disease and a substantial risk of subsequent cardiovascular events and death²²; therefore, all components of the CHA₂DS₂-VASc score are closely associated with clinical outcome in patients with AMI. Cigarette smoking and a family history of CAD are also well-known independent risk factors for cardiovascular events.²³ In the present study, not surprisingly, these 2 risk factors were also observed to be independent and significant predictors of long-term cardiovascular death; however, these well-known risk factors had not been used together with the CHA₂DS₂-VASc.

As such, in the present study, these 2 risk factors were added to the CHA₂DS₂-VASc score model (CHA₂DS₂-VASc-CF), and this novel scoring model was better at predicting long-term cardiovascular death than the standard CHA₂DS₂-VASc score. In addition, this novel risk scoring model also predicted

Table 3. Descriptive and the Results of Cox Regression Analysis to Predict Long-term Cardiovascular Death According to CHA₂DS₂-VAS(c)-CF Score.

Score	Number of Patients, %	Groups, %	Number of Death, n (%)	Hazard Ratio (95% CI)	P Value
0	142 (3.2)	0-1 (33.7)	32 (2.2)		
1	1334 (30.5)				
2	822 (18.8)	2-3 (35.9)	60 (3.8)	1.616 (1.105-2.363)	.013
3	750 (17.1)				
4	592 (13.5)	4-5 (21.5)	84 (8.9)	3.570 (2.748-4.637)	<.001
5	352 (8.0)				
6	256 (5.8)	≥6 (8.7)	211 (55.4)	22.601 (18.847-27.102)	<.001
7	84 (1.9)				
8	32 (0.7)				
9	7 (0.2)				
10	1 (0.02)				
11	1 (0.02)				
Total	4373 (100.0)		387 (8.8)		

Abbreviation: CI, confidence interval.

Figure 2. The Kaplan-Meier major adverse cardiac event (MACE) estimate curves for each of the CHA₂DS₂-VASc-CF score groups. **Figure 3.** The Kaplan-Meier survival estimate curves for each of the CHA₂DS₂-VASc-CF score groups.

the occurrence of MACEs. Using a cutoff score >3, this novel scoring system predicted long-term cardiovascular death with a sensitivity of 78.4% and specificity of 76.4%. The outcomes of high-risk patients can be predicted using this scoring system, without the need for information regarding vital signs at admission, which is convenient for the rapid screening of high-risk patients in clinics. The CHA₂DS₂-VASc-CF risk score, which is easy to calculate and does not require any software to calculate the total risk assessment, provides important prognostic data. The present findings show that the CHA₂DS₂-VASc-CF score is an independent and powerful predictor of long-term cardiovascular death and MACEs in patients with AMI, and that it can be used for risk stratification. In the future, we believe that interventional cardiologists will be able to use this novel scoring system to identify patients with a high risk of

long-term cardiovascular death and MACEs because the CHA₂DS₂-VASc-CF score is suitable for use in all patients with AMI, regardless of the type of treatment, presence of atrial fibrillation, and type of AMI.

Limitations

The present study has some limitations, including its nonrandomized single-center design and lack of calculation of other clinical and angiographic risk scores, such as TIMI, GRACE, and Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX). Finally, despite including a large patient cohort, they were retrospectively analyzed. We think additional prospective studies are needed to evaluate the prognostic role of the CHA₂DS₂-VASc-CF score with greater accuracy.

Declaration of Conflicting Interests

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