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CHA_2DS_2-VASc Score is a Predictor of No-Reflow in Patients With ST-Segment Elevation Myocardial Infarction Who Underwent Primary Percutaneous Intervention

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Abstract

Thrombosis and distal embolization play crucial role in the etiology of no-reflow. CHA_2DS_2-VASc score is used to estimate the risk of thromboembolism in patients with atrial fibrillation. We tested the hypothesis that CHA_2DS_2-VASc can predict no-reflow among patients who underwent primary percutaneous coronary intervention (PCI). A total number of 2375 consecutive patients with ST-segment elevation myocardial infarction were assessed for the study. Patients were divided into 2 groups as no-reflow (n = 111) and control (n = 1670) groups according to post-PCI no-reflow status. CHA_2DS_2-VASc scores were calculated for all patients. CHA_2DS_2-VASc scores were significantly higher in the no-reflow group compared to the control group. After a multivariate regression analysis, CHA_2DS_2-VASc score remained as an independent predictor (odds ratio: 1.58, 95% confidence interval: 1.33-1,88, $P < .001$) of no-reflow. Receiver–operating characteristics analysis revealed the cutoff value of CHA_2DS_2-VASc score ≥ 2 as a predictor of no-reflow with a sensitivity of 66% and a specificity of 59%. Moreover, in-hospital mortality was also associated with significantly higher CHA_2DS_2-VASc scores. In conclusion, CHA_2DS_2-VASc score is associated with higher risk of no-reflow and in-hospital mortality rates in patients who underwent primary PCI.

Keywords

CHA_2DS_2-VASc score, STEMI, primary PCI, no-reflow, in-hospital mortality

Introduction

No-reflow is defined as inadequate myocardial perfusion, despite mechanical reopening of the responsible lesion with percutaneous coronary intervention (PCI).[1] It occurs in approximately 5% to 10% of the patients after primary PCI.[2] Microvascular obstruction due to thrombosis, distal embolization, and microvascular spasm are the suggested mechanisms for no-reflow.[1] No-reflow is associated with adverse outcomes including heart failure, stroke, and cardiac mortality regardless of the infarct size.[3-5] Although many risk factors were suggested, there is no widely accepted risk stratification method for the prediction of no-reflow.

CHA_2DS_2-VASc score is a sum of several risk factors for thromboembolism, which is the major complication of atrial fibrillation.[6] Use of CHA_2DS_2-VASc risk score is recommended by the current guidelines for the estimation of thromboembolic events in patients with atrial fibrillation.[6,7] Moreover, it was shown to be a predictor of adverse outcomes after acute coronary syndromes.[8]

In this study, we tested the hypothesis that CHA_2DS_2-VASc score can predict no-reflow among patients with ST-segment elevation myocardial infarction (STEMI) who were treated with primary PCI.

Methods

Study Population

This retrospective study was conducted among 2375 consecutive patients with a diagnosis of acute STEMI who were

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admitted to our tertiary cardiovascular center and underwent primary PCI between January 2012 and January 2014. Patients with a pain duration of more than 12 hours were not included in the study. Patients with venous graft as infarct-related artery (n = 24), no intervention owing to normal coronary anatomy, noncritical stenosis, inappropriate coronary anatomy for stenting or a decision of emergency surgery (n = 269), and only percutaneous transluminal coronary angioplasty (n = 295) were excluded. Six patients without informed consent forms for coronary angiography were also excluded. Routine blood tests including hemogram, lipid panel, electrolytes, liver, and renal functions were obtained from all patients besides 12-lead electrocardiography. Laboratory findings, clinical, and demographic features were acquired from hospital records retrospectively. Information about mortality was also obtained from hospital records. This study was approved by the local ethics committee.

Coronary Angiography and Primary PCI

All patients underwent coronary angiography using a standard technique. First, they were administered 300 mg of acetylsalicylic acid. Clopidogrel of 600 mg (75 mg × 8 tablets) was given to patients who were administered clopidogrel within 2 hours of the procedure. Otherwise 300 mg (75 mg × 4 tablets) clopidogrel was given. Patients who were not treated with enoxaparin before the coronary angiography were given intravenous heparin at 1 mg/kg immediately after the decision of coronary intervention. For those with an initial enoxaparin dose of 1 mg/kg, a booster enoxaparin of 0.3 mg/kg was given intravenously within 8 hours of the first dose.

Stenting of infarct-related artery was successfully completed in all patients immediately after the coronary angiography. Thrombus aspiration was applied in patients with high thrombus burden according to operator's choice. Tirofiban infusion (0.15 mg/kg/min) was given to selected patients with no contraindications or tendency for bleeding.

The TIMI flow grades and myocardial blush grades were evaluated by 2 operators. The frame rate of cine images were 30 frames/s. Analysis of cineangiograms was performed by using an Axiom (Siemens Medical Solution, Erlangen, Germany) workstation.

Definitions

ST-segment elevation myocardial infarction was diagnosed according to criteria of ischemic symptoms with new ST-segment elevation in at least 2 contiguous leads of $\geq$0.2 mV in men or $\geq$0.15 mV in women in leads V2 to V3 and/or of $\geq$1 mm (0.1 mV) in other contiguous leads, new left bundle branch block, and elevated troponin levels.[9]

No-reflow was defined angiographically as TIMI flow $\leq$2 or a myocardial blush grade 0 to 1, despite mechanical reopening of the infarct-related lesion.[10] Diagnosis was made in the absence of dissection or thrombotic obstruction of the coronary artery. Definition of TIMI flow grade was as follows: no antegrade flow beyond the lesion was defined as grade 0, incomplete filling of the distal coronary bed beyond the lesion was defined as grade 1, slow antegrade flow, despite complete opacification of the entire coronary bed was defined as grade 2, and opacification of the entire coronary bed with normal speed was defined as grade 3.[11] Myocardial blush grade was defined as follows: no myocardial contrast density as grade 0, minimal myocardial contrast density as grade 1, moderate myocardial contrast density that is less than the territory perfused by any noninfarct-related coronary artery as grade 2, and normal myocardial contrast density compared to any noninfarct-related coronary artery territory as grade 3.[12]

The CHA_2DS_2-VASc score was calculated by summing the points assigned to each of the risk factors, which include congestive heart failure (1 point), hypertension (1 point), age $\geq$75 (2 points), diabetes mellitus (1 point), previous stroke, transient ischemic attack or thromboembolism (2 points), vascular disease (history of MI, peripheral arterial disease, or complex aortic plaques) (1 point), age between 65 and 74 years (1 point), and female gender (1 point). Definition of congestive heart failure was based on a previous diagnosis of heart failure. Hypertension was defined as usage of antihypertensive medication or a previous diagnosis of hypertension.[13] Diabetes mellitus was defined as a previous diagnosis of diabetes mellitus or usage of insulin or oral hypoglycemic agents at the time of admission.[14] Stroke and transient ischemic attack were assessed with patient history, and only the events owing to thromboembolism were included as a component of CHA_2DS_2-VASc score. Stenosis of $\geq$50% in noncoronary arteries was defined as peripheral arterial disease.

Definition of chronic renal failure was based on a creatinine clearance of less than 60 mL/minute, which was calculated by Cockroft formula.[15] Cardiogenic shock was defined as a systolic blood pressure of less than 90 mm Hg with clinical evidence of impaired organ perfusion. KILLIP class I was defined as no evidence of heart failure, whereas any finding of heart failure was defined as class >1.

Statistics

Normally distributed scale variables were expressed as mean $\pm$ standard deviation. Nonnormally distributed variables were expressed as median and interquartile range. Categorical variables were expressed in numbers and percentages. Analyses of categorical variables were performed by chi-square test. Parametric scale variables were analyzed by independent sample *t* test, and nonparametric scale variables were analyzed by Mann-Whitney *U* test. Univariate and multivariate logistic regression analyses were performed to determine the independent predictors of no-reflow in patients with STEMI. Variables that could be a predictor of no-reflow and with a significant *P* value in Table 1 were entered into univariate analysis. Variables with a *P* value <.05 in univariate regression were included into multiple logistic regression analysis. We also performed a separate multivariate analysis to assess the predictive power of the individual components of CHA_2DS_2-VASc score. The results of regression analysis were presented as odds ratio

Table 1. Demographic, Clinical, and Angiographic Features of the Patients.

Variables	Control, n = 1670	No-reflow, n = 111	P Value
Age, years, median, IQR	57 [17]	62 [19]	<.001
Female gender, n (%)	307 (18.4)	31 (27.9)	.01
Diabetes mellitus, n (%)	540 (32.3)	48 (43.2)	.02
Hypertension, n (%)	579 (34.7)	53 (47.7)	.01
Smoking, n (%)	538 (32.2)	34 (30.6)	.91
Hyperlipidemia, n (%)	596 (35.7)	47 (42.3)	.16
History of stroke/TIA, n (%)	31 (1.9)	9 (8.1)	<.001
Vascular disease, n (%)	229 (13.7)	28 (25.2)	.001
Previous MI	201 (12.0)	17 (15.3)	.31
Peripheral arterial disease	35 (2.1)	14 (12.6)	<.001
Previous by-pass surgery	34 (2.0)	7 (6.3)	.004
History of heart failure, n (%)	140 (8.4)	28 (25.2)	<.001
CHA_2DS_2-VASc score, median (IQR)	1 [2]	2 [3]	<.001
Anemia, n (%)	229 (13.7)	28 (25.2)	.002
Chronic renal failure, n (%)	150 (9)	25 (22.5)	<.001
MI type, n(%)			
Anterior	743 (44.5)	67 (60.4)	.001
Nonanterior	927 (55.5)	44 (39.6)	
KILLIP, n (%)			
I	1604 (96)	95 (85.6)	<.001
>I	66 (4)	16 (14.4)	
Stent length, mm, median (IQR)	20 [10]	24 [12]	<.001
Stent diameter, mm, median (IQR)	3 [0.75]	2.75 [0.50]	<.001
Tirofiban infusion, n (%)	829 (49.6)	76 (68.5)	<.001
Thrombus aspiration, n (%)	95 (5.7)	10 (9)	.15
Drug eluting stent, n(%)	640 (38.3)	41 (36.9)	.77
IABP	39 (2.3)	20 (18)	<.001
VT/VF, n(%)	109 (6.5)	32 (28.8)	<.001
Pacemaker, n (%)	46 (2.8)	9 (8.1)	.002
Acute stent thrombosis, n(%)	66 (4)	3 (2.7)	.49
CPR, n(%)	111 (6.6)	20 (18)	<.001
Duration of hospitalization, days, median (IQR)	5 [3]	8 [8]	<.001
In-hospital mortality, n (%)	51 (3.1)	21 (18.9)	<.001

Abbreviations: CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; IQR, interquartile range; MI, myocardial Infarction; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2. Univariate and Multivariate Regression Analysis of Predictors of No-Reflow in Study Population.

Variables	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
CHA_2DS_2-VASc score, 1-SD increase	1.75 (1.49-2.07)	<.001	1.58 (1.33-1.88)	<.001
Anemia	2.12 (1.35-3.33)	.001	–	–
CRF	0.34 (0.21-0.55)	<.001	–	–
Stent length, 1-SD increase	1.44 (1.22-1.71)	<.001	1.41 (1.18-1.69)	<.001
Stent diameter, 1-SD increase	0.58 (0.46-0.73)	<.001	0.64 (0.50-0.82)	<.001
KILLIP	0.24 (0.14-0.44)	<.001	2.53 (1.35-4.75)	.004
MI type	1.90 (1.28-2.81)	.001	1.69 (1.13-2.54)	.011

Abbreviations: CI, confidence interval; CRF, chronic renal failure; MI, myocardial infarction; OR, odds ratio.

with 95% confidence interval. Cutoff value of CHA_2DS_2-VASc score with a highest sensitivity and specificity was calculated by nonparametric receiver–operating characteristics (ROC) curve analysis. Significance levels were demonstrated by P values. P Values <.05 were accepted as statistically significant. The statistical analyses were performed with SPSS 16.0 for Windows (SPSS Inc, Chicago, Illinois).

Results

In total, 1781 patients in no-reflow and control groups (111 vs 1670, respectively) were analyzed. Demographic, clinical, and angiographic features of the patients are presented in Table 1. No-reflow diagnosis was made after the stent implantation for all patients. There were no significant difference in initial TIMI flow rates between the groups ($P = .08$). Patients in the no-reflow group were older than those in the control group (62 [19] vs 57 [17] $P < .001$). Median CHA_2DS_2-VASc score was significantly higher in no-reflow group compared to control group (2 [3] vs 1 [2] $P < .001$). Moreover, all components of CHA_2DS_2-VASc score, including history of heart failure (25.2% vs 8.4%, $P < .001$), hypertension (47.7% vs 34.7%, $P = .01$), age between 65 and 74 (9.5% vs 5.2%, $P = .001$), diabetes mellitus (43.2% vs 32.3%, $P = .02$), previous stroke/transient ischemic attack (8.1% vs 1.9%, $P < .001$), vascular disease (25.2% vs 13.7%, $P = .001$), age $\geq$ 75 (14.3% vs 5.8%, $P = .002$), and female gender (27.9% vs 18.4%, $P = .01$) were significantly higher in the no-reflow group.

No-reflow and control groups did not differ in duration of symptoms (3 [3] vs 3 [2] hours, respectively, $P = .08$) and door to balloon time (18.5 [5] vs 20 [5] minutes, respectively, $P = .39$). Significant differences in ventricular arrhythmias (28.8% vs 6.5%, $P < .001$), cardiopulmonary resuscitation (18% vs 6.6%, $P < .001$), duration of hospitalization (8 [8] vs 5 [3] $P < .001$), use of glycoprotein 2b/3a infusion (68.5% vs 49.6%, $P < .001$), pacemaker (8.1% vs 2.8%, $P = .002$), and intra-aortic balloon pump (18% vs 2.3%, $P < .001$) were interpreted as a consequence of no-reflow. Furthermore, in-hospital mortality rates were significantly higher in the no-reflow group (18.9% vs 3.1%, $P < .001$). With regard to angiographic features, higher stent length (24 [12] vs 20 [10] $P < .001$) and lower stent diameter (2.75 [0.50] vs. 3 [0.75], $P < .001$) were associated with no-reflow.

CHA_2DS_2-VASc scores were $\geq$2 in 73 (65.7%) patients in the no-reflow group compared to 679 (40.7%) patients in the control group. In the regression analysis for the potential risk factors of no-reflow, variables with a significant P value in descriptive analysis were regressed separately on no-reflow. Results of univariate and multivariate analysis are shown in Table 2. Risk factors involved in CHA_2DS_2-VASc score were excluded from this analysis to avoid multicollinearity. Ventricular arrhythmias, glycoprotein 2b/3a infusion, and intra-aortic balloon pump rates were also excluded from analyses

Table 3. Univariate and Multivariate Analysis of Predictive Power of Individual Risk Factors in CHA_2DS_2-VASc Score for No-Reflow.

Variables	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Congestive heart failure	3.69 (2.32-5.85)	<.001	3.70 (2.31-5.92)	<.001
Hypertension	1.72 (1.17-2.53)	.006	–	–
Age ≥75	2.69 (1.14-5.12)	.003	3.30 (1.66-6.56)	.001
Diabetes mellitus	1.59 (1.08-2.35)	.019	–	–
Stroke, TIA, or TE	4.67 (2.16-10.06)	<.001	3.53 (1.49-7.53)	.003
Vascular disease	2.12 (1.35-3.33)	.001	–	–
Age 65-74	1.92 (1.28-2.86)	.002	1.97 (1.28-3.03)	.002
Female gender	1.72 (1.12-2.65)	.014	–	–

Abbreviations: CI, confidence interval; TE, thromboembolic event; TIA, transient ischemic attack; OR, odds ratio.

due to being a consequence of no-reflow. Variables with a significant *P* value in univariate analysis were included into multivariate regression analysis. The multivariate analysis was repeated until all variables in the logistic regression were obtained to be significant. According to the results of the multivariate regression analysis, CHA_2DS_2-VASc score was an independent predictor (odds ratio [OR]: 1.58, 95% confidence interval [CI]: 1.33-1.88, $P < .001$) of no-reflow besides stent length (OR: 1.41, CI: 1.18-1.69, $P < .001$), lower stent diameter (OR: 0.64, 95% CI: 0.50-0.82, $P < .001$), anterior MI (OR: 1.69, 95% CI: 1.13-2.54, $P = .01$), and KILLIP classification (OR: 2.53, 95% CI: 1.35-4.75, $P = .004$). We also performed univariate and multivariate analyses to assess the predictive power of the individual components of the CHA_2DS_2-VASc score (Table 3). All components were significant in univariate analysis. However, congestive heart failure, stroke/transient ischemic attack/embolic events, age 65 to 74, and age ≥75 were independently associated with no-reflow according to multivariate analysis. Nonparametric ROC analysis revealed the cutoff value of CHA_2DS_2-VASc score ≥2 as a predictor of no-reflow with a sensitivity of 66% and a specificity of 59%, area under curve: 0.63 with 95% CI (0.57-0.70). We also analyzed the relationship between CHA_2DS_2-VASc score and mortality rates. Patients who died during the hospitalization had significantly higher CHA_2DS_2-VASc scores compared to those who survived (2 [3] vs 1 [2] respectively, $P < .001$).

Discussion

Our findings revealed that CHA_2DS_2-VASc score is a predictor of no-reflow after primary PCI in patients with STEMI. We also found CHA2DS2-VASc score ≥2 can be used as a cutoff value with a sensitivity of 66% and a specificity of 59%. Our results showed significantly higher in-hospital mortality rates among patients with no-reflow.

No-reflow is associated with larger myocardial necrosis and adverse cardiovascular outcomes regardless of infarct size.[3-5] Although there are some treatment options for no-reflow, none have satisfactory success rates. Moreover, efficacy of treatment varies depending on the patient's clinical status.[2] Low rates of successful treatment call for an alternative strategy for dealing with no-reflow. The DEFER-STEMI trial was designed to find an answer to this problem. In this randomized controlled trial, late stenting was tested in patients with high risk of no-reflow. Study results indicated that patients who experienced late stenting had lower no-reflow rates and myocardial salvage index at 6-month than those who had undergone immediate stenting.[16] This approach decreased no-reflow rates at the expense of recurrent STEMI. Thus, selection of the patients is essential. According to this new approach, late stenting in high risk patients requires a quick and easy risk evaluation method before the decision of stenting.

Previous studies indicated various predictors of no-reflow. As confirmed by our findings, cardiogenic shock, lesion length >20 mm, and lower stent diameter were demonstrated to be the predictors of no-reflow.[16,17] Similarly, heart failure and cardiogenic shock at admission were shown to be independent risk factors for no-reflow in another study.[4] In contrast to our cohort, female gender was also found to be associated with higher no-reflow rates.[18] Moreover, hypertension and ischemic cardiomyopathies were revealed as independent risk factors for no-reflow.[2] Although there are no studies assessing the correlation between peripheral arterial disease and no-reflow specifically, patients with peripheral arterial disease have been shown to have higher mortality and morbidity rates when presented in conjunction with acute coronary syndrome.[8,19]

CHA2DS2-VASc score, which is recommended by current guidelines to be used as a proven predictor of thromboembolic events among patients with atrial fibrillation, is a cluster of risk factors of thromboembolism and stroke.[6,7] Stroke and transient ischemic attack can occur as a result of nonatherosclerotic vascular pathologies as well as thromboembolism and atherosclerosis.[20] Abnormal vascular function was suggested as a mediator of stroke.[21] Microvascular dysfunction also plays role in no-reflow. Although thrombus burden and embolism make up the crucial part of the no-reflow etiology, microvascular dysfunction and obstruction occur in nearly half of patients after primary PCI.[2,22,23] A considerable amount of patients experience the no-reflow phenomenon due to microvascular obstruction.[2,4] As a component of CHA_2DS_2-VASc score, diabetes mellitus has been shown to be associated with impaired microvascular perfusion after PCI because of the tendency toward endothelial vasoconstriction and thrombosis.[24-26] Hypertension, diabetes mellitus, cardiomyopathy, and female gender were also demonstrated to be risk factors of coronary microvascular dysfunction.[27,28] In addition to its usage in atrial fibrillation, CHA_2DS_2-VASc score was also described as a convenient and useful predictor of vascular events such as subsequent MI, stroke, or death among patients with acute coronary syndrome and significant coronary stenosis before coronary angiography.[8,29]

Consequently, most of the risk factors for thromboembolism, endothelial, and microvascular dysfunction overlap with those involved in no-reflow etiology. CHA_2DS_2-VASc score

involves the risk factors related with atherosclerosis, vascular spasm, microvascular dysfunction as the common risk factors in no-reflow, and stroke.[30] Regarding the fact that CHA_2DS_2-VASc score has high predictive power of thromboembolic events and includes the common risk factors of no-reflow and thromboembolism concurrently, it can be used as an exclusive risk estimation tool in no-reflow.

Since STEMI is a time-sensitive emergency that requires prompt revascularization, the risk assessment tool must be well known and easy to use. We think a score system can be very useful in this regard. Previous studies do not provide a score system meeting these criteria. The SYNTAX scoring system, which is calculated based on angiographic findings and used to decide about revascularization method, was also indicated to be correlated with no-reflow among patients with STEMI.[31] Nevertheless, it is more time consuming and complicated to calculate compared to CHA_2DS_2-VASc score.

Study Limitations

A limitation of this study is the retrospective design. We think that there may be a bias in patients with acute MI related to the assessment of ejection fraction and heart failure component due to their being in acute clinical setting. Likewise, we could not assess complex aortic plaques. Therefore, calculation of CHA_2DS_2-VASc score may be the second limitation in patients with acute MI.

In conclusion, our findings suggest CHA_2DS_2-VASc score to be an independent predictor of no-reflow in patients who underwent primary PCI. CHA_2DS_2-VASc score can be very useful in this regard as an easily applicable instrument in prediction of high risk patients. Higher CHA_2DS_2-VASc scores were also associated with higher in-hospital mortality rates. Further prospective studies with larger cohorts may be needed to confirm the predictive value of CHA_2DS_2-VASc score in no-reflow.

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