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Predictive value of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores for failed reperfusion after thrombolytic therapy in patients with ST-segment elevation myocardial infarction

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Abstract

Background: *Thrombolytic therapy is recommended for patients with acute ST-segment elevation myocardial infarction (STEMI) who cannot undergo primary percutaneous coronary intervention within the first 120 min. The aim of this study was to demonstrate the value of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in predicting failed reperfusion in STEMI patients treated with thrombolytic therapy.*

Methods: *A total of 537 consecutive patients were enrolled in the study; 139 had failed thrombolysis while the remaining 398 fulfilled the criteria for successful thrombolysis. Thrombolysis failure was defined with the lack of symptom relief, < 50% ST resolution-related electrocardiography within 90 min from initiation of the thrombolytic therapy, presence of hemodynamic or electrical instability or in-hospital mortality. CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores, which incorporate hyperlipidemia, smoking, switches between female and male gender, were previously shown to be markers of the severity of coronary artery disease (CAD).*

Results: *History of hypertension, diabetes mellitus, hyperlipidemia, heart failure, smoking, and CAD were significantly common in failed reperfusion patients (for all; $p < 0.05$). For prediction of failed reperfusion, the cut-off value of CHA_2DS_2-VASc* score was *≥ 2 with a sensitivity of 80.90% and a specificity of 41.01% (area under curve [AUC]* 0.660*; 95% confidence interval [CI] 0.618–0.700; $p < 0.001$) and the cut-off value of CHA_2DS_2-VASc-HS* score was *≥ 3 with a sensitivity of 76.13% and a specificity of 67.63% (AUC 0.764; 95% CI 0.725–0.799; $p < 0.001$). The CHA_2DS_2-VASc-HS score was found to be statistically and significantly better than CHA_2DS_2-VASc score to predict failed reperfusion ($p < 0.001$).*

Conclusions: *The findings suggest that the CHA_2DS_2-VASc and especially CHA_2DS_2-VASc-HS scores could be considered as predictors of risk of failed reperfusion in STEMI patients.* (Cardiol J 2019; 26, 2: 169–175)

Key words: CHA_2DS_2-VASc score, thrombolytic therapy, failed thrombolysis

Introduction

Acute reperfusion, performed either with thrombolytic therapy or primary percutaneous coronary intervention (PCI), is the mainstay of treatment for patients experiencing an acute ST-segment elevation myocardial infarction (STEMI). Although contemporary guidelines for

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acute STEMI patients recommend primary PCI as the preferred reperfusion strategy, most patients do not present to a PCI-capable hospital [1]. Thus, thrombolysis remains the treatment of choice for STEMI patients when a PCI cannot be performed within the first 120 min or it is delayed due to patient transfer. A routine coronary angiography is recommended 2–24 h after thrombolytic therapy, and a rescue PCI should be performed when thrombolytic therapy fails [1]. Reperfusion fails in almost one third of patients receiving thrombolytic therapy, and these patients require a rescue PCI [2, 3]. Estimating the risk of reperfusion failure in individual patients before initiation of thrombolytic therapy may be helpful to determine the optimal treatment strategy especially for patients admitted to non-PCI capable hospitals. Previous studies reported that parameters such as red cell distribution width, mean platelet volume, platelet distribution width and C-reactive protein (CRP) on admission may be helpful in predicting failed reperfusion [4–7]. However, according to available literature, there is currently no scoring system which can be used to predict failed reperfusion in STEMI patients to whom thrombolytic therapy is given. The CHA_2DS_2-VASc score is traditionally used for thromboembolic risk stratification in atrial fibrillation (AF) patients [8]. The components of the CHA_2DS_2-VASc score, namely hypertension (HT), diabetes mellitus (DM), old age, and heart failure, were also shown to be risk factors for poor clinical outcomes in cardiovascular diseases. Recent studies demonstrated that CHA_2DS_2-VASC score can also predict poor clinical outcomes in stable coronary artery disease (CAD) and acute coronary syndrome, irrespective of the presence of AF [9, 10]. Cetin et al. [9] demonstrated that $CHADS_2$, CHA_2DS_2-VASc and the newly defined CHA_2DS_2-VASc-HS scores can predict the severity of CAD in diagnostic coronary angiography, and it was reported that CAD severity increased with higher scores. In that study, the authors replaced the female gender in CHA_2DS_2-VASc score with male gender, and they also incorporated hyperlipidemia and smoking as risk factors for the development of CAD. The present study aimed to demonstrate the value of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in predicting failed reperfusion in STEMI patients treated with thrombolytic therapy.

Methods

In the present study, data was obtained from 537 consecutive STEMI patients, who were admitted to our tertiary-care center from January 2008 to April 2015 and who received thrombolytic therapy based on a clinical decision of the attending cardiologist.The study was designed retrospectively, and complied with the principles of the Declaration of Helsinki and the local ethics committee approved the study protocol. The thrombolytic agent administered was a tissue plasminogen activator (t-PA; alteplase) or tenectoplase or reteplase. The choice of thrombolytic agent was based on the decision of the treating physician according to recommended doses [11]. Failed thrombolysis was defined according to the following criteria; lack of symptom relief (worsening ischemia or persistent chest pain), presence of hemodynamic or electrical instability, ST-segment resolution-related electrocardiography leads within 90 min from the initiation of the thrombolytic therapy, and in-hospital mortality. Totally 139 patients were defined as failed reperfusion according to these criteria. Clinical and demographic characteristics including age, gender, history of DM, HT, hyperlipidemia, current cigarette smoking, family history of premature CAD, and chronic heart failure were obtained from medical history, physical examination, electrocardiographic findings, laboratory data and digital and/or non-digital hospital records. low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride measurements, and renal function tests were performed by standardized laboratory methods. LDL-C concentrations were calculated using the Friedewald formula [12]. Hypertension was defined as repeated measurements of systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or chronic treatment with antihypertensive medications. Type 2 DM was defined as a previous diagnosis and/or a fasting blood glucose of > 126 mg/dL or the use of anti-diabetic medications. Hyperlipidemia was defined by a total cholesterol level above 200 mg/dL or use of lipid-lowering medications. Cigarette smoking was defined as smoking ≥ 1 cigarettes a day for at least 1 year, without an attempt to quit. Family history was defined as the presence of heart disease or sudden cardiac death in a male first-degree relative aged < 55 years or in a female first-degree relative aged < 65 years. Chronic heart failure was defined as reduced left ventricular ejection fraction ($< 40\%$).

The CHA_2DS_2-VASc nomenclature represents heart failure (C), hypertension (H), age ≥ 75 years (A_2), diabetes mellitus (D), stroke (S_2), vascular disease (V), age 65 to 74 years (A) and female gender (as a sex category [Sc]). The CHA_2DS_2-VASc score

Table 1. CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores.

Nomenclature		CHA_2DS_2-VASc-HS	CHA_2DS_2-VASc
C	Congestive heart failure	1	1
H	Hypertension	1	1
A_2	Age ≥75 years	2	2
D	Diabetes mellitus	1	1
S_2	History of stroke or TIA	2	2
V	Vascular disease	1	1
A	Age 65–74 years	1	1
Sc	Sex category (male gender)	1	1 (female gender)
H	Hyperlipidemia	1	–
S	Smoker	1	–
Total maximum		11	9

TIA — transient ischemic attack

was calculated by assigning 1 point for each of the presence of chronic heart failure, HT, DM, age 65–74 years, female gender and vascular disease and by assigning 2 points for history of stroke and age > 75 years. The CHA_2DS_2-VASc-HS score comprises hyperlipidemia (H) and smoking (S) in addition to the components of CHA_2DS_2-VASc score and male gender instead of female gender (Table 1). The maximum CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores were 9 and 11, respectively.

Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc 15 statistical software (Ostend, Belgium). Continuous data were presented as means and standard deviation. The Kolmogorov-Smirnov test was used to evaluate whether continuous variables were normally distributed. Differences in continuous variables between the two groups were determined by Student's t-test or Mann-Whitney U-test. Categorical variables were summarized as percentages and were compared by the χ^2 test or Fisher's exact test. The receiver operating characteristics (ROC) curve was also used to demonstrate the sensitivity and specificity of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores and their cut-off values for predicting failed reperfusion. The area under curve (AUC) comparison of these scoring systems was performed using the Delong method [13]. A p value < 0.05 was considered statistically significant.

Results

The patients were divided into two groups according to the failure (n = 139) or success (n = 398) of thrombolysis. The mean age of patients was 59.9 ± 11.0 years and 82.7% of them were male (Table 2). The mean CHA_2DS_2-VASc score was significantly higher in failed reperfusion group than successful reperfusion group (2.1 ± 1.4 vs. 1.3 ± 1.2, respectively; p < 0.001). Similarly, the mean CHA_2DS_2-VASc-HS score was significantly higher in failed reperfusion group than successful reperfusion group (4.1 ± 1.7 vs. 2.6 ± ± 1.1, respectively; p < 0.001). For the prediction of failed reperfusion, the cut-off value of CHA_2DS_2--VASc score was ≥ 2 with a sensitivity of 80.90% and a specificity of 41.01% (AUC 0.660; 95% confidence interval [CI] 0.618–0.700; p < 0.001) and the cut-off value of CHA_2DS_2-VASc-HS score was ≥ 3 with a sensitivity of 76.1% and a specificity of 67.6% (AUC 0.764; 95% CI 0.725–0.799; p < 0.001) in the ROC curve analyses (Fig. 1). The AUC comparisons of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scoring systems were performed based on failed reperfusion (Fig. 2). Pairwise comparisons of ROC curves were also performed and the results are demonstrated in Figure 2. Based on these results, the CHA_2DS_2-VASc-HS score was found to be better at a statistically significant level than CHA_2DS_2-VASc score to predict failed reperfusion in STEMI patients (p < 0.001). The baseline characteristics of both groups are summarized in Table 2. History of HT, DM, hyperlipidemia, heart failure, smoking, and CAD were significantly more

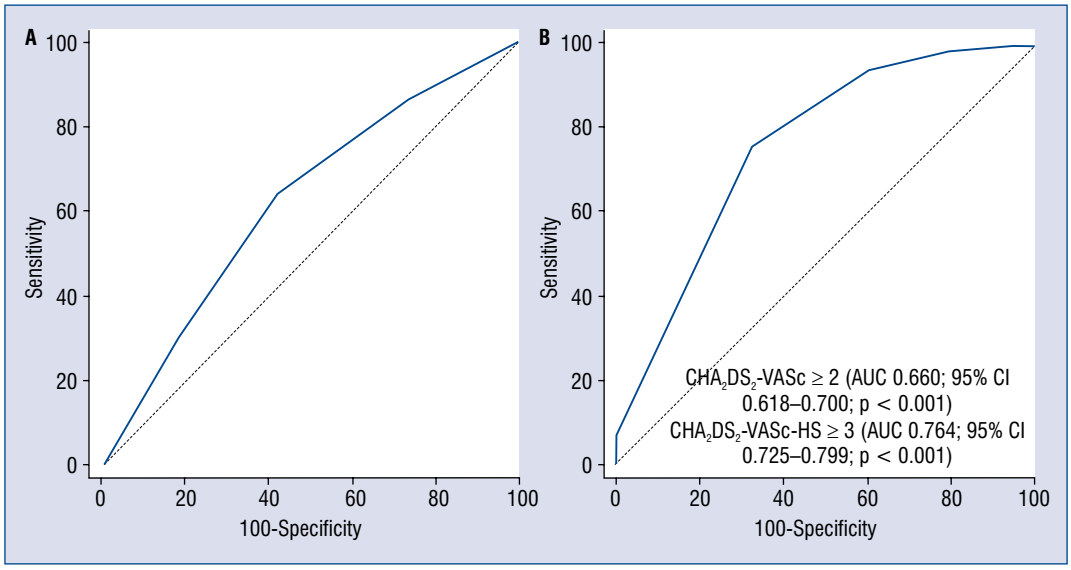

Figure 1. Receiver-operating characteristics analysis curves showing cutoff values for CHA_2DS_2VASc (**A**) and CHA_2DS_2-VASc-HS (**B**) scores for failed thrombolysis in patients with ST-segment elevation myocardial infarction (STEMI).

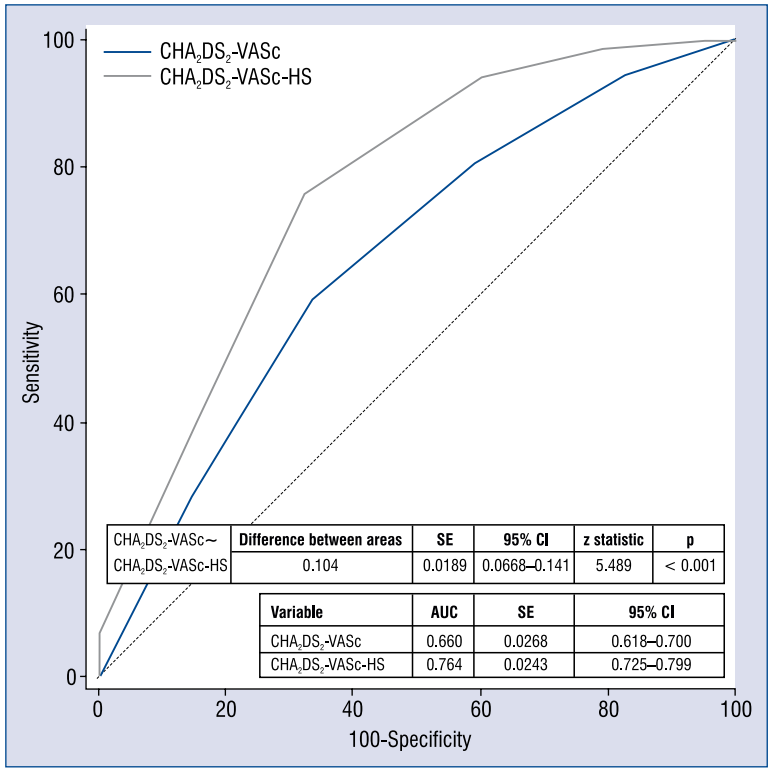

Figure 2. Comparison of receiver-operating characteristics analysis curves according failed reperfusion.

common in failed reperfusion group compared to the successful reperfusion group (for all; $p < 0.05$). There was no difference between two groups in terms of gender distribution, but the mean age of the patients in the failed reperfusion group was significantly higher than that of the successful reperfusion group (59.6 ± 12.3, 57.3 ± ± 10.5, respectively; $p = 0.032$). There were no statistically significant differences between two groups in levels of laboratory parameters such

Table 2. Baseline demographics and clinical characteristics.

Parameters	Successful thrombolysis (n = 398)	Failed thrombolysis (n = 139)	P
Age [year]	57.3 ± 10.5	59.6 ± 12.3	0.032
Male	327 (82.2%)	117 (84.2%)	0.935
Diabetes mellitus	92 (23.1%)	49 (35.3%)	0.005
Hypertension	162 (40.6%)	99 (71.2%)	< 0.001
Hyperlipidemia	77 (23.9%)	50 (35.9%)	< 0.001
Heart failure	25 (6.3%)	19 (13.7%)	0.006
Stroke	–	–	–
Smoking	234 (62.3%)	114 (82.0%)	< 0.001
Coronary artery disease	68 (17.1%)	41 (29.5%)	0.002
Coronary artery bypass grafting	21 (5.3%)	8 (5.8%)	0.830
Family history	99 (24.9%)	31 (22.3%)	0.533
Obesity	79 (24.5%)	32 (23.0%)	0.727
CHA_2DS_2-VASc	1.3 ± 1.2	2.1 ± 1.4	< 0.001
CHA_2DS_2-VASc-HS	2.6 ± 1.1	4.1 ± 1.7	< 0.001
Anterior myocardial infarction	125 (31.4%)	42 (30.2%)	0.794
Time from symptom onset to treatment [h]	2.1 ± 0.7	2.1 ± 0.8	0.596
Heart rate [bpm]	75.4 ± 16.8	74.4 ± 17.8	0.554
Systolic blood pressure [mmHg]	128 ± 30	137± 34	0.002
Diastolic blood pressure [mmHg]	76 ± 17	82 ± 19	0.001
Hemoglobin [g/dL]	14.4 ±2.8	14.6 ±2.6	0.792
Creatinine [mg/dL]	0.8 ± 0.1	0.8 ± 0.1	0.856
Total cholesterol [mg/dL]	184 ± 40	201± 51	< 0.001
Low density lipoprotein cholesterol [mg/dL]	108 ± 35	118 ± 45	0.009
High density lipoprotein cholesterol [mg/dL]	41 ± 11	43 ± 17	0.112
Triglycerides [mg/dL]	151 ± 91	146 ± 82	0.131

Data are shown as mean ± standard deviation or number (percentage).

as hemoglobin, creatinine, HDL-C and triglycerides. In contrast, total cholesterol and LDL-C levels were statistically and significantly higher in the failed reperfusion group than in the successful reperfusion group. Similarly, both systolic and diastolic blood pressure levels were statistically and significantly higher in failed reperfusion group than in the successful reperfusion group (Table 2).

Discussion

This study demonstrated that the CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores may be used as simple yet powerful tools to aid in prediction of failed reperfusion after thrombolytic therapy in STEMI patients. In addition, CHA_2DS_2-VASc-HS score was found to be of higher value in predicting failed reperfusion compared to the CHA_2DS_2-VASc score.

STEMI is a significantly worldwide cause of mortality and morbidity. While PCI is the golden standard for the treatment of STEMI patients, thrombolytic therapy is recommended in case a PCI cannot be performed by an experienced team within 90 min after first medical contact [11]. Delayed PCI was shown to be associated with poor clinical outcomes. While there is no clearly defined time for how long PCI can be delayed, it was shown that PCI can still be more beneficial than thrombolytic therapy in case of delays of up to 120 min [14, 15]. The most commonly used strategies to evaluate reperfusion after thrombolytic therapy include regression of ST segment resolution, complete recovery from pain or monitoring reperfusion arrhythmia. Still, all these parameters can be evaluated only after thrombolytic therapy.

Several studies previously investigated the potential predictors of failed reperfusion. Zairis et al. [4] showed that plasma level of CRP on admission

is a predictor of reperfusion failure after thrombolytic therapy in patients with STEMI. Baysal et al. [5] reported that there was a strong and independent association between increased red cell distribution width and failed thrombolysis in the setting of acute STEMI. Pereg et al. [6] reported in their study that a higher mean platelet volume correlated with failed thrombolysis in patients presenting with STEMI. In addition, Cetin et al. [7] demonstrated that an increased platelet distribution width was associated with failed reperfusion in STEMI patients. However, based on available research, there is currently no simple and practical scoring system that can be used to predict failed reperfusion. The CHA_2DS_2-VASc scores were initially developed for thromboembolism risk stratification in patients with AF [16]. Recent researches have extended the use of the CHA_2DS_2-VASc score to non-AF populations [9, 17–19].

There are some recently published studies investigating CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in patients with acute coronary syndrome [17–20]. Bozbay et al. [20] showed that CHA_2DS_2--VASc score was a predictor of in-hospital and long-term adverse clinical outcomes in STEMI patients. Unal et al. [17] demonstrated that CHA_2DS_2-VASc score was an independent predictor of stent thrombosis. Moreover, in their study including patients who underwent coronary angiography for STEMI, Ipek et al. [19] found that CHA_2DS_2-VASc score was associated with a higher risk of no-reflow and in-hospital mortality rates in patients who underwent primary PCI due to STEMI. A study by Orvin et al. [21] reported that the CHA_2DS_2-VASc score predicted all-cause mortality and death or nonfatal myocardial infarction in a significant and linear manner. Cetin et al. [9] investigated patients who underwent diagnostic angiography and found that $CHADS_2$, CHA_2DS_2-VASc and CHA_2DS_2-VASc--HS scores were significantly correlated with the number of diseased coronary vessels and the Gensini score. In that study, they developed a new scoring system named CHA_2DS_2-VASc-HS, which incorporated hyperlipidemia and smoking, and replaced male with female gender in the CHA_2DS_2--VASc score [9]. Similarly, Tasolar et al. [18] found a positive correlation between CHA_2DS_2-VASc-HS score and the severity and complexity of CAD in patients with non-ST elevation acute coronary syndrome [18].

The present results underlined the significance of the CHA_2DS_2-VASc and especially CHA_2DS_2-VASc-HS scores as predictors of failed reperfusion after thrombolytic therapy in STEMI patients. But, this was the first study performed on STEMI patients who were given thrombolytic therapy.

In the present study, the significantly elevated CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in patients in the failed reperfusion group can be explained by the association between these scores and the extent and severity of CAD. Moreover, in addition to predicting the severity and seriousness of CAD, higher scores also reflect increased thrombogenicity and thrombus load [22]. The findings of this study are important as they support the fact that increasing mean risk scores indicate a higher probability of failed reperfusion. The significance of both scores in predicting failed reperfusion is because their components, including HT, DM, old age and heart failure are also separately associated with CAD severity and poor outcomes in STEMI patients [9, 18, 19]. Moreover, incorporation of hyperlipidemia and smoking as risk factors for CAD into the newly developed CHA_2DS_2-VASc score further increased the predictive value for failed thrombosis. In the CHA_2DS_2-VASc-HS score, female gender in the CHA_2DS_2-VASc score is switched with male gender, which is a risk factor for CAD. However, due to the low proportion of female patients in this study, the potential impact of gender on failed reperfusion could not be demonstrated. Additional assessments should be performed in larger and distinct populations.

The CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores represent simple, very useful and easy--to-remember bedside score for predicting failed reperfusion after thrombolysis in STEMI patients. It is believed herein, that these scores, especially CHA_2DS_2-VASc-HS, could be used in daily practice to estimate failed reperfusion risk for patients admitted to non-capable PCI hospitals. In addition, these simple scores can help physicians to determine transfer strategy for PCI-capable hospital such as ambulance or aircraft. If patients have a high risk of failed reperfusion, they may be referred by aircraft, rather than ambulance for faster transfer.

Limitation of the study

One of the major limitations of this study is that it was a single-center study. The absence of patients with a history of ischemic or hemorrhagic stroke also represents another major limitation. Nevertheless, stroke was not excluded from the scoring systems in order to guide future studies and avoid contravening the generic scoring systems.

Conclusions

Findings of the present study are important as they demonstrated that the simple and practical CHA_2DS_2-VASc and CHA_2DS_2VASc-HS scores can be useful in predicting failed reperfusion before thrombolytic therapy. In addition, these scores can help physicians who work in non-capable PCI hospitals to estimate risk of failed reperfusion.

Conflict of interest: None declared

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