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Evaluation of CHA2DS2-VASc Score as a Predictor of Platelet Reactivity in Acute Myocardial Infarction Patients Treated by Percutaneous Coronary Intervention

[1]Ghada Selim, [1]Ahmed Tamara, [2]Lobna Refaat, [3]Mohamed Awadein, [4]Ahmed Elbarbary

[1]Cardiology Department, Faculty of Medicine, Ain Shams University,Egypt,

[2]Clinical Pathology Department, [3]Internal Medicine Department and

[4]Cardilogy Department, Faculty of Medicine, Misr University for Science and Technology (MUST), Egypt

***Corresponding author: Ghada Selim**, **Mobile:** (+20)01277691115

ABSTRACT

Background: The CHA2DS2-VASC score was evaluated as a risk stratification tool used in predicting outcomes in clinical settings other than preventing stroke in patients with atrial fibrillation (AF). But, its use in coronary artery disease patients who recently had percutaneous coronary intervention (PCI) was not thoroughly studied.

Aim of work: determining the availability of using CHA2DS2-VASc score as an effective and simple platelet reactivity predictor in acute myocardial infarction (AMI) patients managed with percutaneous coronary intervention.

Subjects and methods: Our prospective study included 180 consecutive acute myocardial infarction patients who were submitted to percutaneous coronary intervention and were hospitalized within twelve hours of symptoms onset. They were categorized, according to their CHA2DS2-VASc risk scores, into two groups: low-risk (0–1 score) and high-risk (2–9 score). Following PCI, using light transmittance aggregometry, platelet reactivity was determined utilizing adenosine diphosphate (ADP)-induced platelet aggregation.

Results: We found a significant difference between high and low CHA2DS2-VASc score groups regarding sex, BMI, hyperlipidemia, ST-elevation, statins use, and the number of diseased vessels. As regards mean platelet ADP-induced aggregation reactivity, a significant correlation between reduced mean platelet ADP-induced aggregation reactivity and low CHA2DS2-VASc score was detected in comparison to the high score (42.53 ± 16.21 and 50.67 ± 18.1, respectively, and P = 0.002).

Conclusion: The CHA2DS2VASc score may be a significant independent platelet reactivity predictor in acute myocardial infarction patients managed with PCI, and thus it can be utilized in assessing the acute stent thrombosis risk in acute myocardial infarction (AMI) patients after PCI.

Keywords: Acute myocardial infarction, CHA2DS2-VASc score, Platelet functions testing.

INTRODUCTION

CHA2DS2-VASc Score is the most frequently used method in atrial fibrillation for predicting thromboembolic risk. CHA2DS2 is an acronym for (Congestive heart failure, hypertension, advanced age (> 65 = 1 point, > 75 = 2 points), diabetes, and stroke/transient ischemic attack history (2 points). VASc refers to vascular disease (peripheral arterial disease, aortic atheroma, and prior myocardial infarction), and this scoring system also includes a gender component (female sex). Each risk factor is worth one point, with the exception of age > 75 and stroke/TIA, which are worth two points[1].

ACI is the leading mortality cause in millions of lives annually in the developed countries. Non-ST segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) are the two types of acute myocardial infarction. Reperfusion of the heart is the key in the treatment of myocardial infarction. The earlier the treatment, the better is the prognosis [2]. In acute coronary syndrome (ACS) patients, most of the CHA2DS2-VASc score items independently predicted poor cardiovascular outcomes [3].

The CHA2DS2-VASc score was shown to be significantly related to vascular endothelial dysfunction (VED), as assessed by brachial flow-mediated dilation (bFMD) and brachial-ankle pulse wave velocity (baPWV). Cardiovascular disorders, for example, myocardial infarction and ischemic stroke were found to be pathophysiologically accompanied by VED as measured by bFMD or elevated baPWV. In general, platelet aggregation and adhesion are induced by VED, as well as fibrin synthesis, both of which are necessary for systemic hypercoagulability[4]. A significant association between VED and risk factors for cardiovascular disorders, such as diabetes or heart failure (all of which are CHA2DS2-VASc score elements) was detected. VED was shown to be a critical point of vulnerability for coronary plaque and other cardiovascular problems such as vascular remodeling [5].

The preceding sequential linkages may suggest a relation between the adverse CV disorders and the CHA2DS2-VASc score. Among patients treated with P2Y12 inhibitors, platelet function testing (PFT) was extensively used in ACS to predict myocardial infarction, stent thrombosis, and bleeding events after PCI. Low platelet reactivity (LPR) and high platelet reactivity (HPR) patients had an increased risk of bleeding and ischemic events, respectively. Whereas, those with optimal platelet reactivity (OPR) had a decreased ischemic and

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bleeding events risk. Guidance by PFT may have a favorable impact on patient' outcomes. In individuals using clopidogrel, numerous studies revealed a varied response of platelet reactivity, as non-responders were around 16% of them [6, 7]. Among ACS patients, there is a shortage of evidence on clinical factors for platelet reactivity prediction.

The CHA2DS2VASc score was found to be useful in the prediction of poor cardiovascular outcomes risk in ACS patients. Higher CHA2DS2VASc scores have been found to be independently related to increased mortality during hospitalization and in the long-term [8, 9].

For the purpose of estimating thromboembolism risk in nonvalvular atrial fibrillation patients, the CHADs and CHA2DS2VASc risk scores were created and validated primarily. On the other hand, prior research examined this score as regards its therapeutic use and significance in a variety of clinical situations and revealed that the CHA2DS2VASc risk score might be an independent predictor of no-reflow in STEMI patients [10]. Among ACS patients, recent research found that mortality prediction in CHADS2 and CHA2DS2-VASc scores was not significantly different. However, CHA2DS2-VASc score components not involved in the CHADS2 are in link with worse outcomes in ACS patients [11].

In terms of clinical outcomes predictive value, the CHA2DS2-VASc score outperformed the CHADS2. Nonetheless, these scores usage for adverse outcomes prediction in ACS patients after PCI were not well investigated [12].

High residual platelet reactivity (HRPR) during clopidogrel therapy, as demonstrated by numerous studies, is a major cardiovascular disorders predictor in patients undergoing PCI, even in the case that platelet reactivity-guided antiplatelet therapy has not been shown to be helpful in these events' prevention [13].

PFT is unfortunately not commonly accessible for routine clinical usage, and physicians may have difficulties in interpreting the data. As a result, simplified clinical risk scores, including HPR main risk variables, may be a feasible option for platelet reactivity prediction.

Aim of work: This study aimed to assess the utility of the CHA2DS2-VASc score as a simple and effective measure in the platelet reactivity prediction in AMI patients managed by percutaneous coronary intervention.

SUBJECTS AND METHODS

A prospective comparative study at Souad Kafafi University Hospital (MUST University) was done. The study comprised 180 consecutive patients diagnosed with AMI who were hospitalized within twelve hours of the symptoms start and underwent PCI.

Ethical approval:

The study was approved by the MUST university ethical Committee Board, the study began from June 2020 to March 2021 and informed written consent was obtained from all patients included in our study.

Patients aged 18 years and above were included in our study.

Exclusion criteria: oral anticoagulants therapy, glycoprotein (GP) IIB\IIIA antagonist therapy within 48 hours of withdrawing a blood sample, blood transfusion within the past month, and pregnant females.

All patients administrated aspirin loading dosage (300 mg), then a 100–150 mg daily dose, and clopidogrel loading dose (600 mg) then a 75 mg daily dose.

The CHA2DS2-VASc score was determined and two groups of patients were created based on their CHA2DS2-VASc risk scores: (1) low-risk (0–1 score) and (2) high-risk (2–9) [14].

PCI and medications

Studied patients had coronary angiography and infarct-related artery stenting was effectively done promptly following coronary angiography, either with or without balloon angioplasty. Among patients with a significant thrombus load, thrombus aspiration was not always necessary and was done according to the decision of the interventional cardiologist. The cardiologists also made the decision about using the glycoprotein IIb-IIIa inhibitor tirofiban at a 12.5 mg/50 ml dosage.

Platelet reactivity measurement

Following PCI, using light transmittance aggregometry, platelet reactivity was determined utilizing adenosine diphosphate (ADP)-induced platelet aggregation. Product information: Revohem ADP reagent; REF: AP200422. Manufacturer; HYPHEN BioMed: 155 rue de Ergany, France. Four days post-admission, platelet reactivity was determined by antecubital vein blood withdrawal and collection in 3.2% sodium-citrated tubes [interquartile range (IQR) 4-5]. Then, it was classified as low (< 19 U), optimum (19-46 U), or high (> 46 U). Following that, through a receiver operating characteristic curve analysis, platelet reactivity prediction capabilities of CHA2DS2-VASc scores were assessed.

Patients' data at the time of admission and treatment in the hospital, clinical presentation, comorbidities, renal function tests, hemoglobin, ECG, troponin, creatinine kinase, and angiographic features were all noted.

Statistical Analysis

Analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY) and R software version 3.5.3 (R Foundation for Statistical Computing, Beijing, China). Continuous variables with parametric distributions are reported as the mean ± standard deviation (SD), and those with nonparametric distributions are reported as median and interquartile ranges. Categorical variables are reported as numbers and percentages. We analyzed differences in 2 continuous variables using the student's *t*-test or the Mann–Whitney *U* test.

Differences in categorical variables were tested using the chi-square test or Fisher's exact test, as appropriate.

We constructed survival curves as stratified by baseline CHA_2DS_2-VASc scores using the Kaplan–Meier procedure with Mantel–Haenszel log-rank testing for significance. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional-hazard regression analyses.

The validity of the proportionality assumption was verified for all covariates by a visual examination of the log (minus log) curves and a test based on Schoenfeld residuals. A 2-sided *P*-value ≤ 0.05 was considered significant.

RESULTS

Based on the CHA2DS2-VASc score, patients were categorized into:

- Low-risk group (0–1 score)
- High-risk group (2–9 score)

Table (1): Demographic and clinical data in the studied population

Variable	**High CHA2DS2-VASc score** (n=104)	**Low CHA2DS2-VASc score** (n=76)	***P***
Age (years)	59.76 ± 8.62	58.59 ± 9.47	.389
Sex, n (%)			
Male	75 (72.1%)	44 (57.9%)	**.047***
Female	29 (27.9%)	32 (42.1%)	
BMI (kg/m^2)	28.51 ± 3.74	26.37 ± 3.65	**.001***
ADP**	50.67 ± 18.1	42.53 ± 16.21	**.002***
Comorbidities, n (%)			
Smoking	44 (42.3%)	28 (36.8%)	.459
Hyperlipidemia	60 (57.7%)	31 (40.8%)	**.025***
DM	48 (46.2%)	30 (39.5%)	.372
HTN	59 (56.7%)	32 (42.1%)	.053
CKD	10 (9.6%)	2 (2.6%)	.064
Previous history, n (%)			
Angina or MI	29 (27.9%)	12 (15.8%)	.056
PCI	16 (15.4%)	9 (11.8%)	.497
CABG	8 (7.7%)	6 (7.9%)	.960
Family history of CAD, n (%)	39 (37.5%)	28 (36.8%)	.928
ST-elevation, n (%)			
ST-elevation MI	72 (69.2%)	41 (53.9%)	**.036***
Non-ST-elevation MI	32 (30.8%)	35 (46.1%)	
Medication, n (%)			
ACEIs or ARBs	47 (45.2%)	24 (31.6%)	.065
β-blockers	25 (24%)	13 (17.1%)	.261
Statins	56 (53.8%)	28 (36.8%)	**.024**
Acetyl salicylic acid	40 (38.5%)	20 (26.37%)	.088
No. Of diseased vessels, n (%)			
1	23 (22.1%)	30 (39.5%)	
2	43 (41.3%)	27 (35.5%)	**.035***
3	38 (36.5%)	19 (25%)	

*significant,**ADP= adenosine diphosphate -induced platelet aggregation

In the present study, high and low CHA2DS2-VASc score groups were significantly different regarding sex, BMI, hyperlipidemia, ST-elevation, statins use, and the number of diseased vessels. As regards smoking, hyperlipidemia, hypertension, and CKD, they were higher in the high CHADVASC group but without significant difference. A significant correlation between low CHA2DS2-VASc score and low mean platelet ADP-induced aggregation reactivity was found in comparison to high CHA2DS2-VASc score (42.53 ± 16.21 and 50.67 ± 18.1, respectively, and P value=0.002) (table 1).

Table (2): Multivariate regression analysis for identifying the independent predictors of platelet ADP-induced aggregation reactivity among AMI patients

	OR	***Sig.***	***95% CI***
Age	.573	.569	.146 - 1.167
Male gender	12.15	.273	.139 - 16.79
BMI	1.145	**.025***	.906 - 1.448
Smoking	.465	.547	.039 - 5.592
DM	1.295	**.009***	.836 - 1.387
HTN	1.267	.106	.951 - 1.688
Dyslipidemia	1.792	**.039***	1.636 - 1.987
Non-ST-elevation MI	1.865	**.021***	.941 - 1.988
Previous PCI/CABG	3.725	.456	.117 - 8.321
2 diseased vessels or more	1.214	**.015***	1.054 – 1.397
CHADS2-VASc	1.267	**.002***	.951 - 1.688

*significant

BMI, DM, dyslipidemia, non-ST-elevation MI, and higher CHADS2-VASc were significantly independent predictors of platelet reactivity (table 2).

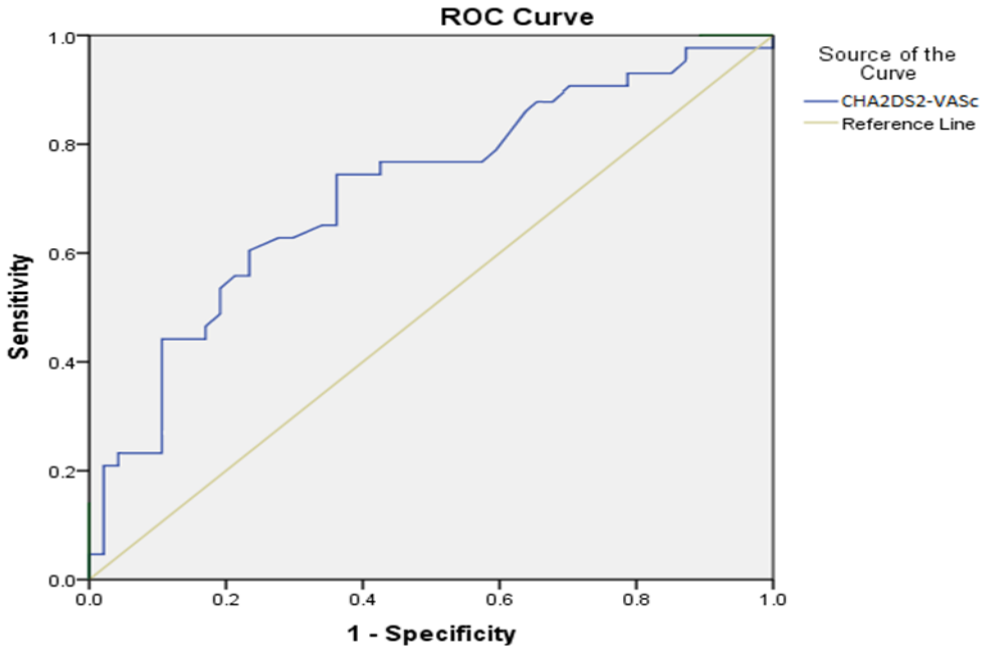

Figure (1): ROC curve analysis to determine CHA2DS2-VASc score as a possible platelet reactivity predictor.

CHA2DS2-VASc showed an AUC of 0.705 with 72% sensitivity, 68% specificity, and a P-value of 0.009 (figure 1).

DISCUSSION

CHADS and CHA2DS2-VASc scores were first designed to help patients with atrial fibrillation by estimating their systemic embolism or stroke risk. Recently, in a large number of patient cohorts, it was proven that they might also estimate short- and long-term cardiovascular outcomes [3]. However, their prognostic value in ACS patients after PCI was not thoroughly explored [15, 16].

Indeed, independence of the cardioembolic pathway, the majority of these two scoring systems variables are significant risk factors for atherosclerotic cardiovascular disorders. Thus, it is claimed that, beyond AF standard scope, these scores may have significant applications in the prediction of more pathophysiologically related CV disorders [17].

Regardless of the AF presence or absence, the CHA2DS2-VASc scoring system has been shown to be effective in nonfatal ischemia events and mortality prediction in a variety of patients [18]. Determining the utility of CHA2DS2-VASc scores as platelet reactivity predictors in acute myocardial infarction patients managed with the PCI was this study purpose.

High and low CHA2DS2-VASc score groups were significantly different regarding sex, BMI, CHA2DS2-VASc score, hyperlipidemia, ST-elevation, statins use, and the number of diseased vessels.

A significant correlation was found between low CHA2DS2-VASc score and lower mean platelet ADP-induced aggregation in comparison to the high score in the current study.

In the current study, ROC curve analysis was done to evaluate CHA2DS2-VASc as a possible predictor of platelet reactivity. CHADS2-VASc showed an AUC of 0.705 with a sensitivity of 72% and specificity of 68% (P = 0.009).

In comparison to the study of **Xiaoteng *et al.*** [3] that enrolled 915 ACS patients undergoing PCI aged 60 ± 10 years, about one-quarter (23.4%) were female, and the mean BMI was 25.8 ±3.3. They observed that patients with low CHADS2 scores had low mean ADP-induced platelet aggregation and had OPR, compared to those with high CHADS2 scores, who demonstrated HPR [45.5 U (16) vs. 54.8 U (15), respectively, p = 0.01]. Age and diabetes (regression coefficient = 0.21 and 7.86, respectively and p = 0.0396 and 0.0006, respectively). In addition, CHADS2 and CHA2DS2-VASc scores (regression coefficient = 3.69 and 1.86, respectively and p = 0.0001 and 0.0014, respectively) were found to be independent predictors of increased platelet reactivity using multivariable regression analysis. In agreement with our findings, **Xiaoteng *et al.*** [3] demonstrated that CHA2DS2-VASc score had an AUC of 0.59 (0.03) (95% CI 0.53 to 0.65, z statistic = 2.61, p = 0.0091) for predicting platelet reactivity. The two predictors were not significantly different (difference between AUC of 0.02 (0.02) 95%CI 0.02 to 0.06, z statistic = 0.95, p = 0.3422). CHADS2 score had a sensitivity of 49% and specificity 68%, and for CHA2DS2-VASc score, they were 66% and 50%, respectively.

Although several cohorts of patients with or without AF confirm the prognostic value of the CHA2DS2-VASc score, evidence for its use in ACS patients undergoing PCI is limited. In recent research, **Asher *et al.*** [19] assessed 291 consecutive ACS patients who had PCI as regards the CHADS2, CHA2DS2-VASc, and platelet reactivity. Notably, 197 individuals (68%) developed STEMI, whereas the other 94 had NSTEMI. The median CHADS2 was 1 [IQR 1–2], and CHA2DS2-VASc was 2 [IQR 1–3]. A low CHA2DS2-VASc and CHADS2 scores were found in 41.6% and 57.7% of the patients, respectively. The mean age was 60 ±12 years old. General characteristics included prior PCI (14%), prior MI (17%), hypertension (69%), prior angina pectoris (9%), congestive heart failure (12%), CABG (5%), family history of CAD (24%), diabetes mellitus (32%), hyperlipidemia (52%), and prior TIA/stroke was reported in 17 patients [6]. **Ashoori *et al.*** [20] conducted a study in Tehran Heart Center registry where they assessed 1331 eligible STEMI patients for CHA2DS2-VASc score and no-reflow evidence by examining final angiographic findings from the original PCI operation. The mean age of the studied sample was 59.41 ± 11.78 years, and the EF was an average of 41.52 ± 7.4%. Males comprised the overwhelming majority of subjects (0.80). In the high CHA2DS2-VASc group, hypertension and diabetes mellitus showed a more significant prevalence. The frequency of DM (71.2% vs. 27.1%) and HTN was 87.5% vs. 33.0%. Among low-risk and high-risk groups, peripheral vascular diseases were found in 4.21% and 5.4%, respectively (p: 0.67). Furthermore, **Ashoori *et al.*** [20] stated that significant risk factors include female sex, high blood pressure, acute and chronic renal diseases, complicated atherosclerotic plaques with a high thrombus load, elevated levels of inflammatory biomarkers, and involvement of the LAD. Their results support the current findings that the CHA2DS2-VASc score and its elements have a strong association with cardiovascular events in ACS patients. Most of the CHA2DS2-VASc score elements showed a link with an increase in platelet reactivity, which may explain why higher risk individuals had a greater cardiovascular events incidence. Heart failure elevated platelet-derived molecules such as platelet/endothelial cell adhesion molecule-1 and platelet-derived osteonectin and whole-blood aggregation, independent of its primary etiology [22]**.** Additionally, it was demonstrated that in diabetes, both acute and chronic hyperglycemia activates platelets via increased activity of protein kinase C as a part of the transduction route that increases the reactivity of platelets. Additionally, it was demonstrated that hyperglycemia-induced hyperosmolarity states increase platelet P selectin and GP IIb/IIIa expression, resulting in increased platelet reactivity [23]**.**

Rozenbaum *et al.* [9] found that a high CHA2DS2-VASc score showed a relation with increased risk of in-hospital, 30-day, and one-year all-cause mortality, and also a higher incidence of 30-day combined endpoints of death, MI, and unscheduled revascularization. **Chua *et al.*** [11] revealed similar findings in another study, in which they found that a strong association was found between ≥ 2 CHA2DS2-VASc score, in comparison to a < 2 score, and increased risk of stroke, MI, and mortality after one year from discharge. **Puurunen *et al.*** [24] reported that a high CHA2DS2-VASc score significantly predicted transient ischemic attack, stroke, MI, stent thrombosis, repeat revascularization, mortality, or other arterial thromboembolism in 929 AF patients referred for PCI. Similarly, **Scudiero *et al.*** [25] found that during long-term follow-up, the CHA2DS2-VASc score independently predicted unfavorable outcomes such as stroke, MI, cardiac mortality, and any need for urgent coronary revascularization. In individuals with atrial fibrillation, the CHA2DS2-VASc score is frequently utilized to predict future thromboembolic events risk. Additionally, such devices have demonstrated a straightforward

capability for assessing significant unfavorable cardiovascular outcomes in acute coronary syndrome [26].

LIMITATIONS

Owing to the small-sample size and the fact that this was a single-center study, all patients received just clopidogrel. Despite these limitations, the strong relation between platelet reactivity and CHA2DS2-VASc score in ACS patients may provide clinicians with an extra efficient tool for making therapeutic decisions about high-risk ACS patients. However, despite their importance, the moderate AUC values indicate the need for more research to provide a more statistical validation of the current findings.

CONCLUSION

In acute myocardial infarction patients managed using PCI, the CHA2DS2VASc score appears to be an independent platelets reactivity predictor. As a result, this score may be used in the determination of acute stent thrombosis risk in AMI patients who undergo PCI. Additional research is required to verify our results and to assess their clinical usefulness.

RECOMMENDATION

Patients having a high CHA2DS2VASc risk score must be monitored more closely, as incidence of acute stent thrombosis risk is increased in this patient' group. Confirmation of our findings will need more prospective, multicenter, and bigger investigations.

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