

## **CHA2DS2-VASc score predicts intracoronary thrombus burden in patients with ST-elevation myocardial infarction.**

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### **Abstract**

**Objective:** To evaluate the role of CHA2DS2-VASc score in predicting the intracoronary thrombus burden in patients with ST-Elevation Myocardial Infarction (STEMI).

**Background:** High intracoronary thrombus burden is associated with reduced procedural success, larger infarct size, and mortality after Primary Percutaneous Coronary Intervention (PPCI). Prediction of thrombus burden before PPCI might be useful by enabling the detection of patients at risk for these complications.

**Methods:** We retrospectively evaluated 164 consecutive patients who presented with STEMI within 12 h after the onset of chest pain between January 2015 and June 2016. PPCI was performed within 1 h after admission. Thrombus burden was graded according to Thrombolysis in Myocardial Infarction (TIMI) thrombus score. The patients were stratified into low (grades 1, 2 and 3) and high thrombus burden groups (grades 4 and 5). CHA2DS2-VASc score was calculated for each patient.

**Results:** Thrombus burden was low in 94 (57%) patients and high in 70 (43%) patients. CHA2DS2-VASc score was higher in patients with high thrombus burden compared to patients with low thrombus burden ( $4.41 \pm 1.7$  vs.  $1.47 \pm 1.1$ ,  $p < 0.001$ ). Logistic regression analysis revealed that one-point increment in CHA2DS2VASc score was associated with three times higher risk of having high thrombus burden (odds ratio 3.28, 95% CI: 2.57-5.70). The area under the ROC curve for a cut-off value of CHA2DS2-VASc score  $> 2$  to predict high thrombus burden was 0.925, with a sensitivity of 91% and a specificity of 82%.

**Conclusion:** CHA2DS2-VASc score is a simple tool that predicts thrombus burden in STEMI patients undergoing PPCI.

**Keywords:** CHA2DS2-VASc score, ST-elevation myocardial infarction (STEMI), Thrombus burden.

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### **Introduction**

ST-Elevation Myocardial Infarction (STEMI) comprises approximately 25-40% of myocardial infarction presentations [1]. Essential mechanism of coronary occlusion is atherosclerotic plaque rupture or erosion and subsequent thrombus formation. Large intracoronary thrombus burden is known to be associated with reduced procedural success during the Primary Percutaneous Coronary Intervention (PPCI), larger infarct size, increased ischemic complications and mortality [2-5]. Prediction of thrombus burden may be useful before starting intervention because it enables detection of patients at risk for these complications.

CHA2DS2-VASc score is easily applied in daily practice to predict thromboembolic risk in atrial fibrillation patients. Furthermore, it predicts major adverse cardiac events after

PPCI, and it is associated with increased 1 y mortality rate in patients with Acute Coronary Syndrome (ACS) [6,7].

We aimed to evaluate the role of CHA2DS2-VASc score in predicting the amount of intracoronary thrombus burden in STEMI patients undergoing PPCI.

### **Methods**

We retrospectively evaluated 164 consecutive patients admitted to our hospital with STEMI between January 2015 and June 2016. STEMI was diagnosed based on a history of a typical chest pain lasting at least 30 min and ST-segment elevation of 1 mm or more in at least two contiguous leads or 2 mm or more in leads V1 through V3 on the electrocardiography. Patients admitted to the hospital within 12 h after the onset of chest pain were enrolled. All patients underwent PPCI within 1 h after hospital admission. All PPCI procedures were

performed using the standard femoral approach. Aspirin 300 mg, clopidogrel 600 mg, and heparin 100 u/kg were administered before the procedure. None of the patients were pre-treated with a thrombolytic agent or a glycoprotein IIb/IIIa inhibitor. Exclusion criteria were as follows: chest pain longer than 12 h, stent thrombosis, cardiogenic shock, previous revascularization, pacemaker implantation, oral anticoagulation use, atrial fibrillation during or before admission, severe renal or hepatic insufficiency and bleeding diathesis. This study protocol was approved by the local ethics committee. Data from subjects were analyzed retrospectively.

### Angiographic analysis

Coronary angiograms that were stored in hospital database were reviewed. All angiograms prior to the intervention were assessed for Infarct-Related Artery (IRA), which was determined by angiographic and electrocardiographic features, and for thrombus grade, which was based on visual estimation. The angiographic sequence of IRA that best demonstrated the thrombus was selected for analysis. Analysis of the angiograms was performed by 2 experienced cardiologists who were blinded to CHA2DS2-VASc scores of patients. In case of disagreement, another cardiologist's opinion was obtained. Thrombus burden was graded according to TIMI thrombus score as follows: Grade 0, no thrombus; Grade 1, possible thrombus; Grade 2, the thrombus' greatest dimension is <1/2 vessel diameter; Grade 3, greatest dimension >1/2 to <2 vessel diameters; Grade 4, greatest dimension >2 vessel diameters; Grade 5, total vessel occlusion due to thrombus [8]. The patients were stratified into low thrombus burden (grades 1, 2 and 3) and high thrombus burden groups (grades 4 and 5) according to thrombus score.

### CHA2DS2-VASc score

CHA2DS2-VASc score was calculated for each patient using the data available in the patient files recorded during hospitalization. According to CHA2DS2-VASc scoring system, patients were given 1 point for congestive heart failure (signs/symptoms of heart failure and ejection fraction <40%),

hypertension (taking anti-hypertensive medicine or systolic and diastolic blood pressure  $\geq$  140/90 mmHg), diabetes mellitus (defined as a fasting blood glucose level >126 mg/dl or blood glucose level  $\geq$  200 mg/dl or using anti-diabetic drugs), history of vascular disease (peripheral artery disease defined as stenosis of at least 50% in non-coronary artery circulation), age 65-74 y, female sex and 2 points for age 75 y or older and previous stroke or transient ischemic attack [9].

### Statistical analysis

The data are presented as mean  $\pm$  standard deviation or n (%). The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Continuous variables were analyzed with either Student's t-test or Mann-Whitney U-test. Categorical variables were analyzed with either the Chi-square test or Fisher's exact test. In logistic regression analysis, high thrombus burden was accepted as dependent variable. Optimal cut-off value was calculated by using Youden index. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of CHA2DS2-VASc score and its cut-off value for predicting high thrombus burden.

### Results

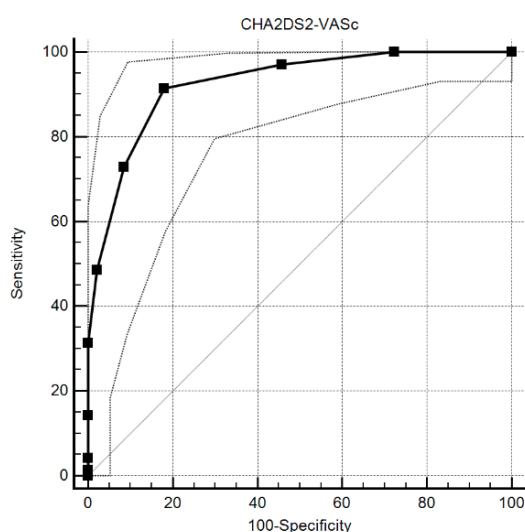
A total of 164 patients (117 male (71.3%), mean age: 61.2  $\pm$  11.6 y) were included in this study. Of the patients, 94 (57%) had low thrombus burden and 70 (43%) had high thrombus burden. The baseline clinical, laboratory and angiographical characteristics of patients in low and high thrombus burden groups were presented in Table 1. Patients with high thrombus burden were significantly older (65.8  $\pm$  11.6 y vs. 57.8  $\pm$  10.3 y,  $p < 0.001$ ) and had higher prevalence of diabetes mellitus and hypertension ( $p < 0.001$  and  $p < 0.001$ , respectively). Patients with high thrombus burden had more commonly multi-vessel disease than patients with low thrombus burden (75.7% vs. 54.3%,  $p = 0.005$ ). There wasn't a significant difference between two groups in terms of presence of anterior *versus* non-anterior myocardial infarction. The duration between the onset of chest pain and angiography was similar in two groups (262  $\pm$  190 min vs. 284  $\pm$  205 min,  $p = 0.51$ ).

**Table 1.** Clinical, laboratory and angiographical characteristics among high thrombus burden and low thrombus burden groups.

Variables	All patients n=164	Low thrombus n=94	High thrombus n=70	p
Age (y)	61.2 $\pm$ 11.6	57.8 $\pm$ 10.3	65.8 $\pm$ 11.6	<0.001
Men (%)	71.3	73.6	68.6	0.498
Diabetes mellitus (%)	47	27.7	72.9	<0.001
Hypertension (%)	52.8	42.6	80	<0.001
Smokers (%)	65.2	66	64.3	0.824
Hyperlipidaemia (%)	42.1	38.3	47.1	0.256
Mean ejection fraction (%)	43.5 $\pm$ 8.7	47.5 $\pm$ 7.3	38.0 $\pm$ 7.5	<0.001
CHA2DS2-VASc score (median $\pm$ IQR)	2 $\pm$ 3	1 $\pm$ 2	4 $\pm$ 3	<0.001

Anterior MI (%)	41.5	37.1	47.1	0.351
Multi-vessel disease (%)	63.4	54.3	75.7	0.005
Chest pain to angiography time (min)	271 ± 196	262 ± 190	284 ± 205	0.51
Mean haemoglobin(g/dl)	13.0 ± 1.3	13.1 ± 1.6	12.9 ± 1.6	0.39
Mean white blood cell count (/ml <sup>3</sup> )	10768 ± 3040	10782 ± 3108	10750 ± 2967	0.945
Mean platelet count (/ml <sup>3</sup> )	253124 ± 71433	257000 ± 70000	247000 ± 73000	0.305
Mean total cholesterol level (mg/dl)	192.3 ± 41.3	193.0 ± 41	190.0 ± 40	0.585
Mean low density lipoprotein level (mg/dl)	117.9 ± 36.5	116.1 ± 37	119.5 ± 35	0.693
Mean high density lipoprotein level (mg/dl)	38.8 ± 9.8	38.5 ± 9	39.0 ± 10	0.231
Mean triglyceride level (mg/dl)	172.0 ± 108.9	189.6 ± 142	148.1 ± 110	0.48

Median CHA2DS2-VASc score of the study population was 2 ± 3 (Median ± IQR). CHA2DS2-VASc score was higher in patients with high thrombus burden compared to patients with low thrombus burden (4 ± 3 vs. 1 ± 2, p<0.001). Logistic regression analysis revealed that one-point increment in CHA2DS2-VASc score was associated with three times higher risk of having high thrombus burden in IRA (odds ratio 3.28, 95% CI: 2.57-5.70). ROC analysis revealed the cut-off value of CHA2DS2-VASc score>2 as a predictor of high thrombus burden with a sensitivity of 91% and a specificity of 82% (AUC:0.925, 95% CI 0.874-0.961; p<0.001) (Figure 1).



**Figure 1.** Receiver operating characteristics analysis curve shows the cut-off CHA2DS2-VASc value for high thrombus burden in patients with STEMI. (CHA2DS 2-VASc>2 with a sensitivity of 91.43% and a specificity of 81.91% (Area under Curve (AUC): 0.925, 95% confidence interval 0.874-0.961; p<0.001).

Among the determinants of VASc scoring system; Heart Failure (HR: 5.6, p=0.003), Hypertension (HR: 8.9, p=0.002), Diabetes Mellitus (HR: 7.9, p=0.001) and Multi-vessel disease (HR: 7.7, p=0.002) are found to be related to High thrombus burden in multivariate binary logistic regression analysis, with a classification accuracy of 90%.

When additional variables are added to the model (Smoking, Hyperlipidemia, MI type, IRA, Number of Vessels, HG, WBC, Platelet, MPV, LDL, HDL, TG, Anti-agregan use) they are not found to be significant determinants of high thrombus burden.

In another multivariate binary logistic model where VASc score group were added to these additional variables it is found that Higher VASc score (HR:48, p<0.001) is related to High thrombus burden, with a classification accuracy of 86%.

### Discussion

In this study, we found that CHA2DS2-VASc was increased in STEMI patients with high thrombus burden and one-point increment in CHA2DS2-VASc score was associated with three times higher risk of having high thrombus burden in IRA.

The main mechanism of acute coronary occlusion in the setting of STEMI is intracoronary thrombus formation at the site of plaque rupture or erosion. Previous studies demonstrated that large thrombus burden is present in 38-53% of myocardial infarction patients [10-12]. In our study, 43% of the patients had high thrombus burden. Importantly, high intracoronary thrombus burden is known to be associated with increased procedural complications such as unsuccessful angiographic reperfusion. Reduced epicardial and myocardial perfusions, slow flow and no-reflow were higher in patients with large thrombus burden than patients with small thrombus burden [13,14]. Patients with large thrombus were treated with longer and larger diameter stents [15]. Distal embolization during PPCI occurs more often in patients with high thrombus burden [16]. Angiographically evident thrombus was associated with reduced frequency of ≥ 70% ST-segment resolution in STEMI patients [8]. Also, a correlation was found between infarct size and thrombus burden. A study with cardiac magnetic resonance imaging has shown that the presence of large thrombus burden in the setting of PPCI is related to larger myocardial necrosis regardless of angiographically detectable distal embolization [4].

Baseline thrombus and residual thrombus after aspiration thrombectomy predicts adverse events and myocardial damage. NSTEMI-ACS patients with baseline thrombus had

significantly higher rates of death, myocardial infarction, and stent thrombosis at 30 d and at 1 y than patients without baseline thrombus [5]. Large thrombus burden was an independent predictor of mortality and IRA stent thrombosis in STEMI patients treated with drug-eluting stents [17]. STEMI patients with greater residual thrombus after aspiration thrombectomy had worse reperfusion and greater myocardial damage [3].

CHA2DS2-VASc score is a well-known score, and it has been widely used to assess the risk of thrombus formation and embolism in patients with non-valvular atrial fibrillation. It is simple to use, time saving, and easily applied at bedside. It includes some of the traditional risk factors for coronary artery disease. Besides the application for the assessment of thromboembolic risk in patients with atrial fibrillation, it was also studied in patient groups with coronary artery disease. It was demonstrated that higher CHA2DS2-VASc score was independently associated with increased 1-y all-cause mortality in a study consisting of 13422 ACS patients [7]. Several other studies have evaluated whether CHA2DS2-VASc score can be used to predict the risk of adverse events among ACS patients. Similar findings were reported [18-20]. CHA2DS2-VASc score had prognostic value in ACS patients both with and without atrial fibrillation [20-22]. A retrospective analysis of 15681 patients with acute myocardial infarction revealed that CHA2DS2-VASc score was associated with long-term cardiac events such as myocardial infarction and all-cause death and it was found to be a more important predictor in STEMI patients than NSTEMI patients [23]. In a study of 12785 consecutive patients who underwent PCI, CHA2DS2-VASc score predicted all-cause mortality and death and nonfatal myocardial infarction in a significant and linear fashion [6]. CHA2DS2-VASc score correlated significantly with the number of diseased vessels and the severity of coronary artery disease [24]. Also, it is an independent predictor of no-reflow in STEMI patients [25]. But, data about the value of CHA2DS2-VASc score for prediction of baseline thrombus burden in STEMI patients is lacking. We found that CHA2DS2-VASc score was increased in patients with high thrombus burden compared to patients with low thrombus burden and CHA2DS2-VASc>2 had a good sensitivity and specificity to predict thrombus burden. There are some factors that are known to affect the thrombus formation, but not included in the calculation of this score. However, in multivariate analysis it is found that either the score itself, or the variables that are forming this score is the only significant predictor. This shows that in clinical practice instead of using multiple variables to come up to a conclusion, it may be better to rely on this score.

The optimal approach for the management of lesions with large thrombus burden is still evolving. Thrombus aspiration during PPCI remains controversial [26-28]. The advantage of predicting the amount of thrombus lies in several aspects: 1) Pre-procedural: identification of patients at high risk for angiographic complications; 2) Procedural: guiding management of high thrombus lesions with specific therapies;

3) Post procedural: prognosis and determining stent thrombosis risk.

### Study Limitations

Our study has several limitations. The main limitation is the retrospective design. Another major limitation of our study is small sample size. Although angiographically visible thrombus is a predictor of intraprocedural complications in ACS, angiographic assessment of thrombus amount is less sensitive and less specific than intravascular ultrasound or optical coherence tomography. Also, some of the patients may have had undiagnosed peripheral artery disease at the time of the enrolment and this may affect CHA2DS2-VASc score. For these reasons, further prospective studies with larger sample sizes are necessary. But, our study is a hypothesis-generating study and provides rapid and easy clues to predict coronary thrombus burden before the beginning of the invasive procedure.

### Conclusions

Our findings suggest that CHA2DS2-VASc score can predict thrombus burden in STEMI patients undergoing PPCI. CHA2DS2-VASc score has an easy to remember formula and can be applied quickly in emergent patients. Further studies are needed to evaluate the potential of CHA2DS2-VASc score as an additive and simple tool for identification of cases at risk for complications during PPCI due to high thrombus burden.

### Disclosure Statement

The authors have no conflict of interest to declare.

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