Prognostic value of CHA₂DS₂-VASc score in predicting high SYNTAX score and in-hospital mortality for non-ST elevation myocardial infarction in patients without atrial fibrillation

Mehmet Kadri Akboğa ☀, Samet Yılmaz ☀, Rıdvan Yalçın ☀

Department of Cardiology, Faculty of Medicine, Gazi University; Ankara-Turkey

1Department of Cardiology, Faculty of Medicine, Pamukkale University; Denizli-Turkey

ABSTRACT

Objective: To evaluate the prognostic value of preprocedural CHA₂DS₂-VASc [congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, previous stroke or transient ischemic attack (TIA) (doubled), vascular disease, age 65-74 years, female gender] score in predicting high SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score and in-hospital mortality for non-atrial fibrillation (AF) patients presenting with non-ST elevation myocardial infarction (NSTEMI). The CHA₂DS₂-VASc score used to determine thromboembolic risks in AF was recently reported to predict major adverse clinical outcomes in patients with the acute coronary syndrome, irrespective of AF.

Methods: A total of 906 patients with a diagnosis of NSTEMI who underwent coronary angiography were retrospectively enrolled and divided into three groups according to their SYNTAX scores (low, intermediate, and high). The CHA₂DS₂-VASc score of each patient was calculated.

Results: SYNTAX score had a significant positive correlation with the CHA₂DS₂-VASc score (r=0.320; p<0.001) in the Spearman correlation analysis. The CHA₂DS₂-VASc score [Odds ratio, 1.445; 95% confidence interval (CI), 1.268-1.648, p<0.001], left ventricular ejection fraction, creatinine, C-reactive protein, and high-density and low-density lipoprotein cholesterol levels were demonstrated to be independent predictors of high SYNTAX score. The CHA₂DS₂-VASc score [Hazard ratio (HR), 1.867; 95% CI: 1.462-2.384; p<0.001], the SYNTAX score (HR, 1.049; p=0.003), and age (HR, 1.057; p=0.002) were independently associated with higher risk of in-hospital mortality in a multiple Cox-regression model. Kaplan-Meier survival curves stratified by the CHA₂DS₂-VASc score (<4 vs. ≥4) also showed that higher CHA₂DS₂-VASc scores were associated with higher in-hospital mortality.

Conclusions: In non-AF patients with NSTEMI, CHA₂DS₂-VASc and SYNTAX scores are useful for prognosis assessment and can be used to identify patients at higher risk for in-hospital mortality.

Keywords: CHA₂DS₂-VASc score, coronary atherosclerotic burden, in-hospital mortality, prognosis, NSTEMI

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Patients taking antihypertensive medications were categorized as hypertensives. Dyslipidemia was defined according to the European Society of Cardiology guidelines (10). Patients taking statins at the time of presentation and having lower low-density lipoprotein cholesterol (LDL-C) levels than guideline thresholds were also accepted as having dyslipidemia. Diabetics were determined as those patients who had already been diagnosed with diabetes and were taking antidiabetic medications and other patients who did not know their diabetes status but had high blood glucose according to the American Diabetes Association’s criteria (11).

The components of the \( \text{CHA}_2\text{DS}_2\text{-VASc} \) score were described as follows: chronic heart failure is LVEF <40%; the presence of hypertension; the presence of diabetes; older age, stroke, and/or TIA history; and vascular disease is the presence of previous MI or CAD, peripheral arterial disease, or the presence of atherosclerotic plaques in the aorta. Patients get 1 point for the presence of each criterion except for age above 75 years and history of stroke/TIA. These two criteria were scored 2 points each. Echocardiography was performed in a routine left decubitus position using the Vivid 7 machine (GE, Norway). LVEF was calculated by the modified Simpson method.

CAG was performed on the femoral or radial arteries depending on the choice of the operator. Routine Judkins catheters were used to cannulate left and right coronary ostia. Left anterior descending and left circumflex coronary arteries were evaluated in the left caudal, left cranial, right caudal, and right cranial views. Additional views could be taken on the request of the operator. The right coronary artery was evaluated by the left anterior oblique and left cranial views. The coronary angiograms were examined by two specialists blinded to the clinical and laboratory findings of the cases. Coronary obstructions that blocked at least 50% of the artery were determined to calculate the SYNTAX score. The SYNTAX score was calculated using a calculator (version 2.10) from www.syntaxscore.com. The SYNTAX score was calculated by one investigator with an intraobserver variability of 94%.

The patients were categorized into three groups according to their SYNTAX score [n=434 patients in the low SYNTAX score (≤22) group, n=276 patients in the intermediate SYNTAX score (23-32) group, and n=276 patients in the high SYNTAX score (≥33) group].

### Statistical analysis

Statistical analysis was performed using SPSS 22.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA). The distribution pattern of the parameters. Whether they were normal or not, was determined by the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were presented as mean ± standard deviation, variables with nonnormal distribution were presented as median (interquartile range), and categorical variables were presented with number and percentage values. The analysis of variance (ANOVA) test or the Kruskal-Wallis test was used to compare continuous variables according to the SYNTAX score groups. A Chi-square test was used to compare categorical variables. The Spearman correlation coefficient was computed to examine the relationship between the \( \text{CHA}_2\text{DS}_2\text{-VASc} \) score and death after CAG. The prognostic value of CHA2DS2-VASc score was also independently associated with a higher risk of in-hospital mortality.

The predictive and prognostic value of CHA2DS2-VASc score for the SYNTAX score and in-hospital mortality in NSTEMI nevertheless remains unclear. Thus, this study aims to investigate the predictive and prognostic value of preprocedural CHA2DS2-VASc score for the SYNTAX score and in-hospital mortality in patients presenting with NSTEMI.

### Methods

#### Study population

A total of 1203 patients with a diagnosis of NSTEMI who underwent CAG between January 1, 2017 and January 1, 2020 were retrospectively screened for this study. The diagnosis of NSTEMI was made according to current clinical guidelines, which include positive cardiac markers including troponin-I level (upper limit of troponin-I was 0.06 ng/mL in our laboratory) without ST-segment elevation on routine electrocardiogram (1). The exclusion criteria were the presence of malignancy (n=1), chronic inflammatory diseases (n=1), hepatic diseases (n=1), hemolytic diseases (n=1), dialysis (n=14), rheumatologic diseases (n=1), thyroid hormone abnormalities (n=2) or any active infectious diseases (n=25), and AF (n=251). After implementing these exclusion criteria, 906 patients were enrolled for the final analysis. The study protocol was approved by our hospital’s Ethics Committee.

Basic demographic information regarding age and sex, and CAD risk factors (hypertension, diabetes, dyslipidemia, history of smoking, and family history) were obtained from the hospital database. Blood results taken before CAG were screened from hospital records, and fasting blood glucose and cholesterol parameters were determined. Left ventricular ejection fraction (LVEF) was also gathered from echocardiography records; echocardiography was done before or after CAG but not after hospital discharge. Patients taking antihypertensive medications were
VASc score and the SYNTAX score. A one-way ANOVA or the Freidman test was used to assess the differences among groups. Bonferroni analysis was used as a post hoc test. Possible collinearity was checked using the tolerance and variance inflation factor (VIF). Variables with a tolerance of less than 0.10 and a VIF of 10 and above were withdrawn from the multiple regression and survival models. Multiple logistic regression analysis was used to determine the independent variables related to the high SYNTAX score (≥33). Possible confounding factors for which the unadjusted p-value was <0.10 in univariate regression analysis [the CHA\textsuperscript{2}-DS\textsuperscript{2}-VASc score, age, LVEF, hemoglobin, platelet, white blood cell, admission serum creatinine, C-reactive protein (CRP), high-density lipoprotein cholesterol (HDL-C), and LDL-C] were identified as potential risk markers and included in the multiple logistic regression model. The effects of different variables on in-hospital mortality were assessed by Cox regression analysis. The survival curves during hospitalization for the CHA\textsuperscript{2}-DS\textsuperscript{2}-VASc groups were analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. A p-value of <0.05 was considered statistically significant.

Results

A total of 906 patients were enrolled in this retrospective study. From the low SYNTAX score group to high SYNTAX score group, many components including the CHA\textsuperscript{2}-DS\textsuperscript{2}-VASc score, the presence of chronic total occlusion, and multivessel disease showed a significant increase; whereas LVEF showed a significant decrease (p<0.05). Moreover, there was a higher rate of in-hospital mortality in the higher SYNTAX score group (2.5%, 6.5%, 15.8%, respectively, for the three groups; p<0.001) (Table 1).

### Table 1. Baseline clinical and angiographic characteristics of the study groups according to SYNTAX score tertiles (n=906)

| Parameters                        | SYNTAX score | P-value |
|-----------------------------------|--------------|---------|
|                                   | Low group (≤22; n=434) | Intermediate group (23-32; n=276) | High group (≥33; n=196) |
| Age, years (mean ± SD)            | 59.4±12.2\textsuperscript{a, b} | 62.1±10.2\textsuperscript{a} | 64.6±9.6\textsuperscript{b} | <0.001 |
| Male sex, n (%)                   | 295 (68.0) | 194 (70.3) | 141 (71.9) | 0.574 |
| Hypertension, n (%)               | 178 (41.0) | 142 (51.4) | 114 (58.2) | <0.001 |
| Diabetes mellitus, n (%)          | 101 (23.3) | 76 (27.5) | 70 (35.7) | 0.005 |
| Active smoker, n (%)              | 162 (37.3) | 101 (36.6) | 83 (42.3) | 0.393 |
| Family history of CAD, n (%)      | 75 (17.3) | 56 (20.3) | 45 (23.0) | 0.226 |
| Prior medication, n (%)           |              |              |              |         |
| RAS blocker                       | 130 (30.0) | 100 (36.2) | 64 (32.7) | 0.219 |
| Diuretic                          | 39 (9.0) | 37 (13.4) | 23 (11.7) | 0.169 |
| CCB                               | 67 (15.4) | 40 (14.5) | 29 (14.8) | 0.938 |
| β-blocker                         | 57 (13.1) | 48 (17.4) | 33 (16.8) | 0.238 |
| Statin                            | 48 (11.1) | 35 (12.7) | 23 (11.7) | 0.807 |
| Antiagregant                      | 52 (12.0) | 40 (14.5) | 33 (16.8) | 0.242 |
| Oral antidiabetic                 | 83 (19.1) | 62 (22.5) | 48 (24.5) | 0.267 |
| LVEF (%)                          | 52.1±7.2\textsuperscript{a, b} | 47.3±8.5\textsuperscript{a} | 43.9±7.7\textsuperscript{b} | <0.001 |
| Presence of CTO, n (%)            | 82 (18.9) | 147 (53.3) | 121 (61.7) | <0.001 |
| Multivessel disease, n (%)        | 233 (53.7) | 189 (68.5) | 155 (79.1) | <0.001 |
| Location of coronary lesions      |              |              |              |         |
| LMCA, n (%)                       | 33 (7.6) | 38 (13.8) | 34 (17.3) | 0.001 |
| LAD, n (%)                        | 236 (54.4) | 150 (54.3) | 152 (77.6) | <0.001 |
| LCx, n (%)                        | 31 (29.0) | 48 (40.3) | 76 (39.0) | 0.146 |
| RCA, n (%)                        | 44 (41.4) | 53 (44.9) | 123 (63.1) | <0.001 |
| CHA\textsuperscript{2}-DS\textsuperscript{2}-VASc score | 2.6±1.3\textsuperscript{a, b} | 3.2±1.3\textsuperscript{a} | 3.8±1.5\textsuperscript{b} | <0.001 |
| In-hospital mortality, n (%)      | 11 (2.5)\textsuperscript{a} | 18 (6.5)\textsuperscript{a} | 31 (15.8)\textsuperscript{b} | <0.001 |

Data were given as mean ± SD or %.
\textsuperscript{a}Significantly different from SYNTAX high group in Bonferroni analysis as a post hoc test.
\textsuperscript{b}Significantly different from SYNTAX intermediate group in Bonferroni analysis as a post hoc test.
CAD - coronary artery disease; CCB - calcium channel blocker; CHA\textsuperscript{2}-DS\textsuperscript{2}-VASc - congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke, vascular disease, age 65-74 years, female gender; CTO - chronic total occlusion; LAD - left anterior descending artery; LCx - left circumflex artery; LMCA - left main coronary artery; LVEF - left ventricular ejection fraction; RAS - renin-angiotensin system; RCA - right coronary artery
The laboratory parameters of the study groups are presented in Table 2. Platelet counts, white blood cell counts, admission serum creatinine, and CRP (not high sensitivity) levels were significantly increasing; whereas hemoglobin and HDL-C levels were significantly decreasing in parallel to the severity of the SYNTAX score. All patients received P2Y12 treatment during the in-hospital stay (55.2% ticagrelor, 35.4% clopidogrel, and 9.2% prasugrel). The mean hospital stay of the patients was 3.2±2.1 days. In the Spearman rank correlation analysis, the SYNTAX score had a significant positive correlation with the CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score (r=0.320, p<0.001). In the univariable logistic regression analysis, age, LVEF, the CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score, hemoglobin, platelet, white blood cell, admission creatinine, CRP, HDL-C, and LDL-C were possible independent predictors of high SYNTAX score. In the multiple logistic regression analysis, the CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score [Odds ratio, 1.445; 95% confidence interval (CI), 1.268-1.648; p<0.001], LVEF, admission creatinine, CRP, HDL-C, and LDL-C remained independent predictors of high SYNTAX score (Table 3). Furthermore, in the multiple Cox-regression analysis, the CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score [Hazard ratio (HR), 1.867; 95% CI, 1.462-2.384; p<0.001], SYNTAX score (HR, 1.049; p=0.003), and age (HR, 1.057; p=0.002) were independently associated with higher risk of in-hospital mortality (Table 4). Finally, Kaplan-Meier survival curves stratified by the CHA\textsuperscript{2}DS\textsuperscript{2}-VASc score (<4 vs. ≥4) showed that higher CHA\textsuperscript{2}DS\textsuperscript{2}-VASc scores were associated with higher in-hospital mortality as shown in Figure 1.

**Discussion**

This study showed that in the highest SYNTAX score tertile, patients tended to be older and had lower LVEF compared to the intermediate and lower SYNTAX score tertiles. Also, in the highest tertile, the incidence of hypertension and diabetes mellitus was higher. In the multiple Cox-regression analysis, age, higher
SYNTAX score, and CHA2DS2-VASc score were related to inhospital mortality in patients with NSTEMI. Moreover, a higher CHA2DS2-VASc score and lower LVEF were independent predictors of a higher SYNTAX score.

Despite current advances in revascularization strategies and early invasive treatment, patients with NSTEMI may have still higher mortality. Therefore, recent studies have focused on the prognostic estimation of the above-mentioned population using different clinical predictors (12-14). Although the SYNTAX score was used to evaluate coronary atherosclerotic burden and complexity of CAD, it has been recently used to predict mortality, and both short- and long-term outcomes in different patient populations with CAD (15-18). Current risk scores in the NSTEMI population mainly include clinical, laboratory, and electrocardiographic markers (19). However, the SYNTAX score is principally related to coronary anatomy and the complexity of atherosclerosis and is detached from the patients’ clinical characteristics (17, 20). But it also provides the prognosis and guides the treatment strategy. Due to diffuse atherosclerosis and unfavorable coronary anatomy properties (i.e., more bifurcation, diffuse lesions, ostial locations), patients with higher SYNTAX scores are supposed to undergo more target vessel revascularization, and experience higher rates of MI and cardiac death (21, 22).

Similar to previously reported studies, we found that a higher SYNTAX score was a mortality predictor in the NSTEMI population in the hospital settings (18, 21). Along with age and CHA2DS2-VASc score, the SYNTAX score provided a prediction of death in hospitalized patients with NSTEMI. Therefore, the SYNTAX score may discriminate against patients with unfavorable coronary artery anatomy and, if combined with other risk factors, may yield better prognostic estimation.

The CHA2DS2-VASc score, which also includes alike risk factors for the manifestation or existence of CAD, is a clinical thromboembolic risk score for predicting the high-risk population for stroke in patients with nonvalvular AF (6, 7). However, in a recent study, it was suggested that the higher CHA2DS2-VASc score of equal to or above 4 was independently related with contrast-induced nephropathy after percutaneous coronary intervention in patients with acute MI (23). Besides, Yilmaz et al. (24) recently proposed that the CHA2DS2-VASc score was an independent causative parameter of in-stent restenosis in patients who had CAG for stable CAD. Hong et al. (25) also demonstrated that a higher CHA2DS2-VASc score was a strong predictor of all-cause mortality in patients who underwent implantable cardiac defibrillator device implantation.

The highest SYNTAX group was significantly older than the other groups in our study population. Older age is already a well-known risk factor for atherosclerosis and also a component of CHA2DS2-VASc score. Therefore, older age is directly

| Variables                        | Univariate Hazard ratio, 95% CI | P-value | Multiple Hazard ratio, 95% CI | P-value |
|----------------------------------|---------------------------------|---------|------------------------------|---------|
| Age                              | 1.057 (1.020-1.095)             | 0.002   |                              |         |
| LVEF                             | 0.978 (0.945-1.013)             | 0.215   |                              |         |
| CHA2DS2-VASc score               | 1.867 (1.462-2.384)             | <0.001  |                              |         |
| SYNTAX score                     | 1.049 (1.016-1.083)             | 0.003   |                              |         |
| Hemoglobin                       | 1.088 (0.867-1.366)             | 0.465   |                              |         |
| Platelet                         | 1.000 (0.997-1.004)             | 0.809   |                              |         |
| White blood cell                 | 0.998 (0.834-1.194)             | 0.983   |                              |         |
| Admission creatinine             | 2.340 (0.754-7.261)             | 0.141   |                              |         |
| C-reactive protein               | 0.989 (0.959-1.019)             | 0.453   |                              |         |
| HDL-C                            | 1.022 (0.999-1.046)             | 0.057   |                              |         |
| LDL-C                            | 0.996 (0.990-1.003)             | 0.257   |                              |         |

Table 4. Multiple Cox-regression analysis of risk factors for inhospital mortality in non-ST-segment elevation myocardial infarction

CHA2DS2-VASc: congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke, vascular disease, age 65-74 years, female gender; CI - confidence interval; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; OR - Odds ratio

CHA2DS2-VASc - congestive heart failure, hypertension, age >75 years, diabetes mellitus, previous stroke, vascular disease, age 65-74 years, female gender; CI - confidence interval; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol; LVEF - left ventricular ejection fraction

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related to mortality and morbidity in patients with cardiovascular disease.

We found a positive correlation between the SYNTAX score and the CHA$_2$DS$_2$-VASc score. This shows that the CHA$_2$DS$_2$-VASc score is higher in patients with more complex and severe atherosclerosis. Although the SYNTAX score also predicts mortality in NSTEMI patients, we found that the CHA$_2$DS$_2$-VASc score has a stronger predictive value than the SYNTAX score (HR, 1.867 vs. 1.049). In a recent study it was shown that CHA$_2$DS$_2$-VASc score >2 was associated with cardiogenic shock, high Killip class, low LVEF, fatal reinfarction, and in-hospital and long-term mortality in patients with ST-segment elevation MI (26).

In our study, we observed that a higher CHA$_2$DS$_2$-VASc score was independently associated with in-hospital mortality. Moreover, this score and lower ejection fraction (EF) were independent predictors of a high SYNTAX score. The components of CHA$_2$DS$_2$-VASc scores are predictors of in-hospital and long-term cardiovascular outcomes in patients with NSTEMI, and these findings were correlated with our results. Among CHA$_2$DS$_2$-VASc score components, age, gender, hypertension, and diabetes mellitus are well-known risk factors for CAD and thus a co-existence of both diseases may also indicate a higher burden of atherosclerosis. Also, lower EF indicates excessive ischemia and resultant lower left ventricular function. In a previous report, among patients with stable or unstable CAD, adding ACEF (age, creatinine, and EF) score to SYNTAX score rendered a better estimation of major adverse cardiovascular events and mortality (27). Accordingly, using an extended risk score such as CHA$_2$DS$_2$-VASc score in conjunction with the SYNTAX score is reasonable for individual prognosis assessment in unstable CAD populations.

**Study limitations**

This study has some limitations. First, it has a retrospective design and is a single-center register. But the number of recruited patients is considerably high so that some distinctive results may be concluded. Second, the clinical SYNTAX score was not evaluated. Third, we could not obtain all the parameters required for the Global Registry of Acute Coronary Events (GRACE) risk score (such as systolic blood pressure and resting heart rate); therefore we could not calculate the GRACE risk score of the study population. Last, other clinical risk scores applied to the NSTEMI population were not compared.

**Conclusion**

In patients who presented with NSTEMI, both CHA$_2$DS$_2$-VASc and SYNTAX scores are useful in prognosis assessment. There is a significant correlation between SYNTAX and CHA$_2$DS$_2$-VASc scores. Irrespective of AF presence, adding a comprehensive clinical risk score to a solely anatomic score is useful in aiding in clinical decision-making and therapy. This score is easy to calculate and may be very useful in finding high-risk patients for adverse cardiac events and in-hospital mortality.

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**Peer-review:** Externally peer-reviewed.

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