Relation of CHA_2DS_2VASC Score With Hemorrhagic Stroke and Mortality in Patients Undergoing Fibrinolytic Therapy for ST Elevation Myocardial Infarction

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Hemorrhagic stroke (HS) is a feared complication of Fibrinolytic therapy (FT). Risk assessment scores may help in risk stratification to reduce this complication. Patients (admissions) ≥18 years with a primary diagnosis of ST-elevation myocardial infarction (STEMI) who received systemic thrombolysis were extracted from Nationwide Inpatient Sample database and stratified and compared based on CHA_2DS_2VASC score 0 to 3, 4 to 6, and 7 to 9 as low, intermediate and high risk, respectively. The primary outcomes of interest were HS and mortality. We performed logistic regression analysis with a composite of HS and mortality as the primary end point. Of the 917,307 admissions with a primary diagnosis of STEMI, 39,579 (4.3%) underwent FT. The median score was 3 (interquartile range 1 to 5). The rate of HS significantly increased in the risk category compared with the low and intermediate groups (0.5% and 0.6% vs 4.1%; p <0.001). Mortality increased with increasing risk category (3.8% vs 10.5% vs 20.7%; p <0.001). Compared with the low-risk group patients in the intermediate (odds ratio 2.11 95% confidence interval [CI] 1.56 to 2.85; p <0.001) and high risk groups (odds ratio 3.47 95% CI 1.68 to 7.2; p <0.001) were more likely to experience the composite end point of HS or inpatient mortality. CHA_2DS_2VASC score performed better at predicting mortality (area under curve 0.67, 95% CI 0.64 to 0.7; p = 0.014) than HS (area under curve 0.6 95% CI 0.52 to 0.69; p = 0.021). In conclusion, patients with high CHA_2DS_2VASC score (7 to 9) are at a higher risk of hemorrhagic stroke and death after FT for STEMI. CHA_2DS_2-VASC score performed better at predicting mortality than hemorrhagic stroke in this cohort. **(Am J Cardiol 2019;123:212−217)**

Fibrinolytic therapy (FT) is recommended for the urgent management of ST-elevation myocardial infarction (STEMI) in selected patients who cannot undergo percutaneous coronary intervention (PCI) in a timely manner.[1,2] Hemorrhagic stroke (HS) is a known and feared complication of FT in these patients.[3,4] Advanced age is known to be a risk factor for HS in these patients, and other risk factors have been elucidated as well.[3,5−9] Even so, there are no standard risk scores routinely used in these patients. Souza et al described obesity and the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications score as independent predictors of HS in those receiving FT.[9,10] This score is not being widely used likely because it has not been prospectively validated in this cohort of patients. The CHA_2DS_2VASC score is a risk assessment tool that predicts the risk of stroke in patients with atrial fibrillation.[11−14] It has also been studied as a risk stratification tool in patients without atrial fibrillation related to various conditions and interventions.[15−20] This study was designed to describe the association between CHA_2DS_2VASC score and HS in patients who underwent FT in the setting of STEMI, and to test the reliability of this score as predictor of HS and/or mortality in this cohort.

Methods

Our data was obtained from the Nationwide Inpatient database. The database is a component of the Healthcare Cost and Utilization Project and is the largest publicly available inpatient healthcare database in the United States. It is a deidentified database, therefore analysis from this database was deemed exempt by the Institutional Review Board of our institutions.

Weighted data on admitted patients ≥18 years with a primary diagnosis of STEMI (International Classification of Disease [ICD] code 410.XX, excluding 410.7X), who received systemic thrombolysis (ICD codes 99.10 and V45.88) were extracted and analyzed. We excluded patients who were transferred out of their admitting hospital because their outcomes were not known and to

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avoid being represented twice. We also excluded patients with missing data on outcome. The CHA_2DS_2-VASC score was computed using Elixhauser co-morbidities as documented by Healthcare Cost and Utilization Project (HCUP) as well as ICD and clinical classification software (CCS) codes as appropriate. The CCS categories are available in the Nationwide Inpatient and have been used to define medical conditions in previous studies.[21–23]

The extracted admissions were stratified into tertiles based on CHA_2DS_2VASC score 0 to 3, 4 to 6, and 7 to 9 as low, intermediate, and high risk, respectively. We compared these groups with regards to their baseline characteristics and inpatient events and outcomes (Tables 1 and 2). We identified co-morbidities including either ICD codes or the CCS when applicable. We identified hospital characteristics based on HCUP documentation.

The primary outcomes of interest were HS and inpatient mortality. Analysis was done using the complex analysis function of SPSS software (IBM, version 24), accounting for the year, strata and clustering per HCUP recommendation. We described continuous variables with means and standard deviation for normally distributed variables and median with interquartile range for variables not normally distributed. Categorical variables were reported as counts with proportions. Pearsons chi-square test was used to compare the groups with respect to categorical variables and the Kruskal-Wallis test for continuous variables. We performed a multivariate logistic regression analysis including all variables in Tables 1 and 2, comparing low risk to both intermediate and high-risk cohorts, with our primary outcome as the dependent variable. A receiver operating characteristic analysis was performed to assess the ability of the CHA_2DS_2VASC score to predict hemorrhagic stroke or

Table 1
Baseline characteristics of patients (admissions) ≥ 18 with a primary diagnosis of STEMI who underwent fibrinolytic therapy stratified by $CHADS_2VA_2SC$ score

Variables	$CHADS_2VA_2SC$ score risk groups			
	0–3 (n = 25,544)	4–6 (n = 9,502)	7–9 (n = 483)	p Value
Age (Years)	56.3 ± 10.0	70.4 ± 11.6	78.6 ± 7.6	< 0.001
Women	3967 (15.5%)	5053b (53.1%)	349c (72.3%)	< 0.001
White	17826 (69.8%)	6631a (69.7%)	358a (74.2%)	0.59
Black	1385 (5.4%)	582b (6.1%)	35a,b (7.3%)	0.432
Hispanic	1745a (6.8%)	735b (7.7%)	35a,b (7.2%)	0.389
Asian	553a (2.2%)	169a (1.8%)	11a (2.2%)	0.584
Native American	267a (1%)	119a (1.2%)	< 11a (1%)	0.513
Other race	788a (3.1%)	287a (3%)	15a (3%)	0.988
Hypertension	13567a (53.1%)	8296b (87.2%)	427b (88.6%)	< 0.001
Diabetes mellitus	4269a (16.7%)	4632b (48.7%)	338c (69.9%)	< 0.001
Congestive heart failure	40a (0.2%)	10a (0.1%)	< 11	0.819
Chronic pulmonary disease	3078a (12%)	1868b (19.6%)	124c (25.7%)	< 0.001
Chronic renal failure	830a (3.3%)	1387b (14.6%)	133c (27.6%)	< 0.001
Obesity (Body mass index ≥ 30 kg/m^2)	3790a (14.8%)	1682b (17.7%)	65a (13.4%)	0.008
Anemia (Blood loss and nutritional deficiency)	1326a (5.2%)	1346b (14.2%)	65b (13.5%)	< 0.001
Valvular disease	< 11	< 11	< 11	0.673
Alcohol abuse	1068a (4.2%)	153b (1.6%)	< 11	< 0.001
Rheumatoid arthritis/collagen vascular diseases	354a (1.4%)	229b (2.4%)	16b (3.2%)	0.005
Coagulopathy	698a (2.7%)	419b (4.4%)	46c (9.5%)	< 0.001
Hypothyroidism	1019a (4%)	1177b (12.4%)	86c (17.7%)	< 0.001
Liver disease	193a (0.8%)	93a (1%)	< 11a (1%)	0.621
Fluid and electrolyte disorders	2867a (11.2%)	1818b (19.1%)	120c (24.9%)	< 0.001
Metastatic cancer	83a (0.3%)	39a (0.4%)	< 11	0.737
Other neurological disorders	573a (2.2%)	452b (4.8%)	39c (8.2%)	< 0.001
Paralysis	148a (0.6%)	102b (1.1%)	10b (2%)	0.028
Peripheral vascular disorders	1230a (4.8%)	1089b (11.5%)	80c (16.5%)	< 0.001
Pulmonary circulation disorders	< 11a	< 11a (0.1%)	< 11	0.439
Current smoker	11879a (46.5%)	2414b (25.4%)	45c (9.4%)	< 0.001
Former smoker	3009a (11.8%)	1714b (18%)	108c (22.4%)	< 0.001
Prior percutaneous coronary intervention	2991a (11.7%)	1554b (16.3%)	74a,b (15.2%)	< 0.001
Prior coronary artery bypass graft surgery	444a (1.7%)	378b (4%)	15b (3.2%)	< 0.001
History of anticoagulation	316a (1.2%)	256b (2.7%)	29c (6%)	< 0.001
Prior stroke/Transient ischemic attack	59a (0.2%)	741b (7.8%)	332c (68.9%)	< 0.001
Carotid artery disease	104a (0.4%)	138b (1.4%)	21c (4.3%)	< 0.001
Atrial fibrillation/flutter	1676a (6.6%)	1503b (15.8%)	118c (24.4%)	< 0.001
Admission to a teaching hospital	14505a (57.1%)	5289a (55.8%)	314b (65%)	0.181
Admission to a rural hospital	2148a (8.5%)	788a (8.3%)	55a (11.3%)	0.542

Values in the same row and subtable not sharing the same subscript are significantly different at $p < 0.05$ in the 2-sided test of equality for column proportions. Numbers less than 11 are not reportable per NIS guidelines.

Obesity = BMI ≥ 30 kg/m^2; Anemia: Blood loss anemia, deficiency anemias, Hb < 13.5 g/100 ml (men) or < 12 g/100 ml (women).

Table 2
In-hospital events and outcomes of patients (admissions) ≥ 18 with a primary diagnosis of STEMI who underwent fibrinolytic therapy stratified by $CHADS_2VA_2SC$ score

Variables	$CHADS_2VA_2SC$ score risk groups			
	0−3 (n = 25,544)	4−6 (n = 9,502)	7−9 (n = 483)	p Value
Coronary angiography	24730a (96.8%)	8882b (93.4%)	419c (86.8%)	< 0.001
Percutaneous coronary intervention	21677a (84.9%)	7525b (79.1%)	335c (69.4%)	< 0.001
Coronary artery bypass graft surgery	1477a (5.8%)	626b (6.6%)	10c (2.1%)	0.119
Cardiac arrest	2067a (8.1%)	861b (9.1%)	35a,b (7.3%)	0.395
Cardiogenic shock	1800a (7%)	1188b (12.5%)	75b (15.6%)	< 0.001
Transient ischemic attack/Stroke	294a (1.2%)	189b (2%)	40c (8.3%)	< 0.001
Hemorrhagic stroke	119a (0.5%)	59a (0.6%)	20b (4.1%)	< 0.001
Respiratory failure	1787a (7%)	1399b (14.7%)	100c (20.7%)	< 0.001
Pneumothorax	64a (0.3%)	44b (0.5%)	< 11	0.286
Acute renal failure	1174a (4.6%)	1175b (12.4%)	111c (23%)	< 0.001
Hemorrhage	426a (1.7%)	312b (3.3%)	20b (4.1%)	< 0.001
Pericardial effusion	199a (0.8%)	127b (1.3%)	19c (4%)	0.001
Cardiac tamponade	46a (0.2%)	19a (0.2%)	< 11	0.894
Balloon counterpulsation	1682a (6.6%)	875b (9.2%)	50b (10.3%)	< 0.001
Extracorporeal membrane oxygenation	25a (0.1%)	< 11	< 11	0.375
Percutaneous ventricular assist device	50a (0.2%)	< 11a (0.1%)	< 11	0.644
Blood transfusion	850a (3.3%)	736b (7.7%)	39b (8.1%)	< 0.001
Hemodialysis	84a (0.3%)	196b (2.1%)	25c (5.2%)	< 0.001
Dialysis for acute renal failure	35a (0.1%)	70b (0.7%)	16c (3.2%)	< 0.001
Pericardiocentesis	23a (0.1%)	40b (0.4%)	< 11	0.01
Mortality	968a (3.8%)	997b (10.5%)	100c (20.7%)	< 0.001
Composite outcome (Hemorrhagic stroke and mortality)	982a (3.8%)	1008b (10.6%)	110c (22.8%)	< 0.001
Length of hospital stay (days) (Interquartile range)	3(1%−5%)	3(0%−6%)	4(0%−8%)	< 0.001

Values in the same row and subtable not sharing the same subscript are significantly different at p < .05 in the 2-sided test of equality for column proportions. Numbers less than 11 are not reportable per NIS guidelines.

mortality. Associations were considered significant if the p value was less than 0.05.

Results

Of the 917,307 admissions with a primary diagnosis of STEMI, 39,579 (4.3%) underwent FT. We excluded 4,026 patients who were transferred from the admitting hospital or had missing information on disposition. Therefore, 35,539 patients (admissions) were included in our analysis. The mean age was 61.0 ± 12.6, 27.5% were female and the median CHA_2DS_2VASC score was 3 (interquartile range 1 to 5). All the variables of the CHA_2DS_2VASC score increased with increasing risk category. So did the proportion of patients with pulmonary disease, renal disease, anemia, coagulopathy, atrial fibrillation and/or flutter, use of anticoagulation, and history of coronary artery bypass graft surgery. Race was evenly distributed in each group. Anterior STEMI was most common in the high-risk group whereas inferior STEMI was most common in the low and intermediate groups (Figure 1). Rates of coronary angiography, PCI and coronary artery bypass graft also decreased with increasing risk category. Compared with the low risk group, intermediate- and high-risk patients were more likely to undergo intra-aortic balloon counterpulsation, blood transfusion, or hemodialysis. The rate of HS significantly increased in the high-risk category compared with the low and intermediate groups. Mortality increased with each increasing risk category. Compared with the low-risk group, patients in the intermediate (odds ratio [OR] 2.11, 95% confidence interval [CI] 1.56 to 2.85; p < 0.001) and high-risk groups (OR 3.47, 95% CI 1.68 to 7.2; p < 0.001) were more likely to experience the composite end point of HS or inpatient mortality. In the same multivariate model, women (OR 1.61, 95% CI 1.88 to 2.18, p = 0.002) and diabetes (OR 1.4, 95% CI 1.05 to 1.87, p = 0.023) were also independent predictors of the composite end point. CHA_2DS_2VASC score performed better at predicting mortality (area under curve [AUC] 0.67, 95% CI 0.64 to 0.7; p = 0.014) than HS (AUC 0.6, 95% CI 0.52 to 0.69; p = 0.021). Other components that were independent predictors of higher rates of HS and mortality did not accurately predict HS alone (DM: AUC 0.46, 95% CI 0.38 to 0.55, p = 0.378; women: AUC 0.47, 95% CI 0.38 to 0.55, p = 0.446) and performed poorly at predicting mortality (DM: AUC 0.55, 95% CI 0.52 to 0.58, p < 0.001; women: 0.57 95% CI 0.55 to 0.6, p < 0.001)

Discussion

This study suggests that the CHA_2DS_2VASC score performs better at predicting mortality than HS risk in patients who are undergoing FT in the setting of STEMI. In a study describing HS after acute myocardial infarction, Binsell-Gerdin et al determined the major predictors of HS to be age, previous HS, and hypertension.[6] Earlier studies have also included black race, female gender, low-weight, and elevated International Normalized Ratio (INR) as independent risk factors for HS after FT.[24−26] Of these, the

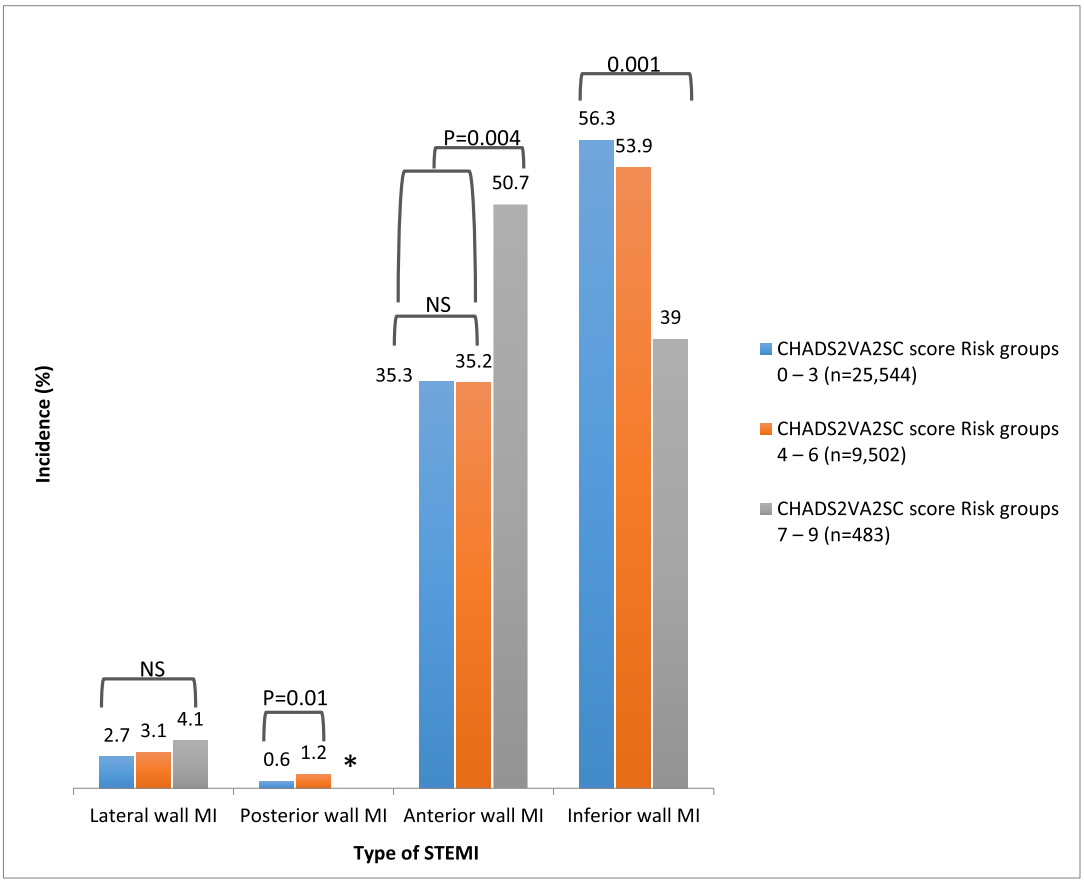

Figure 1. Distribution of STEMI in patients with a primary diagnosis of STEMI who underwent fibrinolytic therapy stratified by $CHADS_2VA_2SC$ score. STEMI = ST elevation myocardial infarction. *=Lower than reportable. Numbers less than 11 are not reportable per NIS guidelines.

CHA_2DS_2VASC score utilizes hypertension, previous stroke, female gender, and age.

It has been shown in previous studies that age is a critical indicator of HS risk with STEMI. Patients ages 76 to 85 have approximately twice the risk of stroke after STEMI as compared with patients ages 65 to 75, regardless of fibrinolytic use.[7] Our results show that there is a distinct correlation between age and CHA_2DS_2VASC score (average age by low=>high risk group: 56.3, 70.4, 78.6), confirming that the CHA_2DS_2VASC importantly couples age and risk. In addition to age, there is a skew toward history of hypertension, history of stroke, and female gender in higher risk strata. Because our data set does not include patient body weights, we were unable to directly compare risk strata and the known risk associated with low weight; however, our highest risk group had the lowest incidence of obesity, marking some level of consistency with previous studies. Overall, our results show that the CHA_2DS_2VASC score is consistent with the important risk factors for HS in the setting of FT, and is able to identify a group of patients at much higher risk for HS based on these factors.

Our analysis revealed that the CHA_2DS_2VASC strata have decent prognostic discrimination on overall mortality in patients who underwent FT in the setting of STEMI, with significant differences in overall in-patient mortality between each group. The discriminatory capability of CHA_2DS_2VASC score with regards to mortality is better than with HS, which is unsurprising, given the multitude of prognostic factors that contribute to overall mortality in STEMI patients.

Because mortality in FT patients with HS is very high (60% to 75%), a simple clinical tool to help predict occurrence of HS is useful.[24,25] Our analysis shows no significant difference between low and intermediate CHA_2DS_2VASC groups. However, the high-score group shows elevated risk (4.1%). Compared with the average incidence of HS with PCI, the alternative treatment, this high-risk group has a significantly worse outcome. In a study by Armstrong et al, delayed PCI (average 178 minutes after onset of symptoms) was shown to have an 0.3% risk of HS compared with a 0.5% risk in patients who received immediate FT (average 100 minutes after onset of symptoms) with a revised protocol.[3] Our results are consistent with their results, showing that regardless of CHA_2DS_2VASC group, patients who receive FT are more likely to experience an HS than patients who underwent PCI alone. Moreover, our high-risk group, with 4.1% experiencing the adverse outcome, had a significantly elevated risk of bleed compared with the PCI group. These data support the established fact that it is prudent to transfer these high-risk patients to a hospital with PCI capabilities.

With regards to mortality, we note a much better risk stratification between the three CHA_2DS_2VASC groups. This finding is especially useful in light of the findings by

Armstrong et al.[3] When comparing delayed PCI versus FT, they found that the 30-day mortality associated with FT was 4.6% versus 4.4% in the delayed PCI group, with no statistically significant difference.[3] With this in mind, a low-risk CHA_2DS_2VASC score may favor FT over-delayed PCI, whereas the intermediate- and high-risk CHA_2DS_2-VASC scores may favor delayed PCI over FT due to the increased risk of death.

Admittedly, further studies validating our results with CHA_2DS_2VASC scores in patients with delayed PCI versus immediate FT are needed. However, the CHA_2DS_2VASC score is easily calculated and it may have the potential to be used as an effective early risk-stratification tool for determining the appropriate course of action at hospitals without PCI capabilities.

We analyzed data from the largest inpatient database in the United States. Because this is a retrospective analysis of data, certain limitations are inherent to the nature of the database. The data is limited by data accuracy, as it is an administrative database. Certain patient-specific clinical parameters, such as blood pressure or body weight, were not available, so they could be neither reported nor used in a regression model. This limitation somewhat inhibits our ability to determine the exact efficacy of the CHA_2DS_2VASC score. Finally, the nature of the database also precludes our ability to compare this scoring system to other well-known risk scores like the Thrombolysis in Myocardial Infarction, Global Registry of Acute Coronary Events, or Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs or alcohol (HAS-BLED) risk scores.

In conclusion, patients with high CHA_2DS_2VASC score (7-9) are at a higher risk of HS and death after FT for ST elevation myocardial infarction. The CHA_2DS_2VASC score performed better at predicting mortality than HS in this cohort.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.10.003.

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