CHA_2DS_2-VASc Score as a Predictor of Adverse Outcomes after Ischemic Stroke in Patients without Atrial Fibrillation

Amir Aker MD[1], Ina Volis MD[3], Walid Saliba MD, MPH[2,4], Ibrahim Naoum MD[1], and Barak Zafrir MD[1,4]

Departments of [1]Cardiology, and [2]Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel
[3]Department of Cardiology, Rambam Health Care Campus, Haifa, Israel
[4]Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

ABSTRACT **Background:** Ischemic stroke is associated with increased risk of morbidity and mortality in future vascular events.

Objectives: To investigate whether CHA_2DS_2-VASc scores aid in risk stratification of middle-aged patients without atrial fibrillation (AF) experiencing ischemic stroke.

Methods: We analyzed data of 2628 patients, aged 40–65 years with no known AF who presented with acute ischemic stroke between January 2020 and February 2022. We explored the association between CHA_2DS_2-VASc scores categorized by subgroups (score 2–3, 4–5, or 6–7) with major adverse cardiac and cerebrovascular events (MACCE) including recurrent stroke, myocardial infarction, coronary revascularization, or all-cause death during a median follow-up of 19.9 months.

Results: Mean age was 57 years (30% women); half were defined as low socioeconomic status. Co-morbidities included hypertension, diabetes, obesity, and smoking in 40–60% of the patients. The incidence rate of MACCE per 100 person-years was 6.7, 12.2, and 21.2 in those with score 2–3, 4–5, and 6–7, respectively. In a multivariate cox regression model, compared to patients with score 2–3 (reference group), those with score 4–5 and 6–7 had an adjusted hazard ratio (95% confidence interval [95%CI]) for MACCE of 1.74 (95%CI 1.41–2.14) and 2.87 (95%CI 2.10–3.93), respectively. The discriminative capacity of CHA_2DS_2-VASc score for overall MACCE was modest (area under curve 0.63; 95%CI 0.60–0.66), although better for myocardial infarction 0.69 (95% CI 0.61–0.77).

Conclusions: CHA_2DS_2-VASc score may predict future MACCE in middle-aged patients with ischemic stroke and no history of AF.

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KEY WORDS: atrial fibrillation, CHA_2DS_2-VASc score, cardiovascular events, ischemic stroke

Over 2 million young adults worldwide present with ischemic stroke annually [1]. Epidemiologic data reveals a consistent rise in the incidence of stroke among middle-aged individuals, in contrast to a decreasing incidence among older adults [2]. This concerning trend may be partially attributed to the rising prevalence of traditional modifiable risk factors among younger patients [2,3]. The decline in age of onset is particularly worrisome, as patients who have presented with stroke are at a higher risk of future cardiovascular events, resulting in increased morbidity and mortality. Moreover, they face a threefold higher likelihood of experiencing a recurrent stroke [4]. Stroke in middle-aged individuals carries substantial socioeconomic ramifications leading to a heavy burden of disability, unemployment, and increased healthcare expenses that may affect both clinical prognosis and quality of life [1,3]. This situation underscores the importance of rapid and early identification of predictors for future adverse cardiovascular events after an ischemic stroke. Timely identification of high-risk patients and subsequent intensification of secondary prevention strategies can play a crucial role in altering the course of the disease.

The CHA_2DS_2-VASc score is a well-validated tool, which is routinely used to assess risk for thromboembolic events, particularly stroke, in patients with non-valvular atrial fibrillation (AF) and the need for antithrombotic therapy [5,6]. This simple scoring system also has a significant clinical value for predicting long-term adverse outcomes in patients with stroke [7], peripheral artery disease [8], and acute coronary syndromes [9], even in those without a history of AF [10]. However, there are limited data available on the prognostic value of this scoring system in non-AF younger individuals who have experienced ischemic stroke. Due to the potentially det-

rimental consequences of stroke and considering that the CHA_2DS_2-VASc score is heavily influenced by age, it is important to determine whether its predictive value is maintained in a younger population. In this study, we investigate whether the CHA_2DS_2-VASc score may aid in risk stratification of middle-aged patients without a history of AF presenting with acute ischemic stroke.

PATIENTS AND METHODS

STUDY POPULATION

This retrospective cohort analysis study included patients diagnosed with acute ischemic stroke between January 2020 and February 2022. The study population was comprised of middle-aged patients between the ages of 40 and 65 years who did not have a documented history of AF. Patients who developed AF during follow-up period were excluded to reduce the probability of a missed AF diagnosis prior to the stroke event. All patients were members of Clalit Health Services (CHS), the largest health maintenance organization in Israel, which provides inclusive health care for about 4.7 million members. We included only patients for whom we had full access to their electronic data. The study was approved by CHS ethics committee in accordance with the Declaration of Helsinki, which waived the need for individual patient consent due to the retrospective design of the study.

STUDY VARIABLES AND DEFINITIONS

Demographic data, clinical variables, risk factors, and co-morbidities were retrieved from CHS computerized databases. CHA_2DS_2-VASc risk stratification score was calculated for each participant at study entry. The CHA_2DS_2-VASc score includes congestive heart failure (1 point), hypertension (1 point), age 65–74.9 years (1 point), age ≥ 75 years (2 points), diabetes mellitus (1 point), stroke (2 points), vascular disease (1 point), and female sex (1 point) [6]. Since all patients included in the study were below the age of 65 years and were admitted with acute ischemic stroke, the minimum score was 2, the maximum score was 7. The patients were further categorized into three subgroups according to their CHA_2DS_2-VASc score: 2–3, 4–5, and 6–7.

The primary study endpoint was major adverse cardiac and cerebrovascular events (MACCE), which is defined as a composite of myocardial infarction, coronary revascularization for any reason, recurrent ischemic stroke, or all-cause death. Data on MACCE were retrieved from the hospitalization database and were defined by the primary discharge diagnosis with ICD-9 codes for myocardial infarction, coronary revascularization, and ischemic stroke. Data on vital status were retrieved from the Ministry of Interior. Cohort participants were followed until the first occurrence of study outcomes (MACCE) or the end of the follow-up period in February 2023, whichever came first.

STATISTICAL ANALYSIS

Descriptive data are presented in the overall study population and in the three subgroups categorized according to the CHA_2DS_2-VASc risk score (2–3, 4–5, 6–7). Continuous data are reported as means and standard deviation or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as numbers and percentages. One-way ANOVA test was used to compare continuous variables and chi-square to compare categorical variables. For graphical presentation the distribution of study population size and event rates of MACCE per 100 person-years were plotted according to the CHA_2DS_2-VASc score. Kaplan-Meier curves were used to estimate the cumulative incidence of MACCE over time according to the three score subgroups. Log-rank test analysis was performed to compare between score categories. The association of CHA_2DS_2-VASc score components with the risk of MACCE was presented using Forest plots, displaying hazard ratios (HR) with 95% confidence intervals (95%CI). The unadjusted and adjusted HR with 95%CI for developing MACCE during follow-up was calculated for the scoring subgroups with a score of 2–3 defined as the reference group, as well as per 1-unit continuous increase in the risk score. Adjustment was made for variables not incorporated in the CHA_2DS_2-VASc risk score that were associated with the composite outcome event, including age, obesity, smoking, chronic kidney disease, chronic obstructive pulmonary disease (COPD), malignancy, and lipid-lowering drugs.

Discriminatory capacity of CHA_2DS_2-VASc risk score for MACCE and its individual components was assessed by estimating the area under the curve (AUC) of the receiver operator characteristic curves [11]. Study results were considered statistically significant when the 2-sided *P*-value < 0.05. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 25 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

The study population included 2628 patients between the ages of 40 and 65 years who were diagnosed with acute

ischemic stroke. Mean age was 57 ± 6 years and 30% were women. Half of the study population was defined as of low socioeconomic status. The burden of atherosclerotic cardiovascular disease (ASCVD) risk factors was significant, with notably high rates of obesity (43.4%), diabetes (43.5%), hypertension (62.3%), and smoking (63.7%). About 30% of all patients had a known ASCVD prior to admission. Patient risk factors and co-morbidities according to CHA_2DS_2-VASc score subgroups are presented in Table 1.

During a median follow-up period of 19.9 months (IQR 13.6–28.3), MACCE occurred in 450 patients. The components of CHA_2DS_2-VASc scores that were associated with a significant increase in the risk for MACCE included heart failure, hypertension, diabetes, vascular disease, and age above median level (58 years) [Figure 1]. However, male compared to female sex was associated with higher risk of MACCE: HR 1.51, 95%CI 1.21–1.88. The incidence rate of MACCE per 100 person-years increased progressively: 5.9, 7.1, 10.4, 14.3, 18.4, and 58.7, in patients with CHA_2DS_2-VASc score 2 to a maximum risk score of 7, respectively. Kaplan-Meier plot displaying the distribution of time to MACCE stratified by the three risk score subgroups is shown in Figure 2, displaying a graded increment in risk with the increase in CHA_2DS_2-VASc score (log-rank $P < 0.0001$). An increase in the hazard ratio for MACCE was observed with higher CHA_2DS_2-VASc scores. Compared to patients with a score of 2–3 (reference group), the multivariable adjusted HRs (95%CI) for MACCE were 1.74 (1.41–2.14) in patients with a score of 4–5, and 2.87 (2.10–3.93) in those with a score of 6–7 [Table 2], with a relative increase in risk of 37% in the adjusted HR for MACCE per each additional point in the CHA_2DS_2-VASc score, when analyzed as a continuous variable.

The discriminatory ability of CHA_2DS_2-VASc score for overall MACCE was modest: AUC 0.63, 95%CI 0.60–0.66, $P < 0.001$. For the individual endpoints, the discriminatory capacity was higher for myocardial infarction: 0.69 (0.61–0.77), $P < 0.001$ and lowest for re-

Table 1. Baseline patient characteristics

		CHA_2DS_2VASc			
Variables	**Overall (n=2628)**	**Score 2-3 (n=1178)**	**Score 4–5 (n=1276)**	**Score 6–7 (n=174)**	***P*-value**
Age, in years	56.8 ± 6.2	55.4 ± 6.6	57.8 ± 5.6	59.1 ± 4.7	< 0.001
Sex (female)	799 (30.4%)	228 (19.4%)	458 (35.9%)	113 (64.9%)	< 0.001
Socioeconomic status (low)	1346 (51.2%)	537 (45.6%)	704 (55.2%)	106 (60.3%)	< 0.001
Diabetes	1144 (43.5%)	107 (9.1%)	866 (67.9%)	171 (98.3%)	< 0.001
Hypertension	1636 (62.3%)	335 (28.4%)	1128 (88.4%)	173 (99.4%)	< 0.001
Obesity	1141 (43.4%)	328 (27.8%)	694 (54.4%)	119 (68.4%)	< 0.001
Smoking	1673 (63.7%)	767 (65.1%)	806 (63.2%)	100 (57.5%)	0.130
Family history of ASCVD	301 (11.5%)	71 (6%)	188 (14.7%)	42 (24.1%)	< 0.001
Chronic kidney disease	189 (7.2%)	189 (7.2%)	40 (3.4%)	110 (8.6%)	< 0.001
Dialysis	28 (1.1%)	5 (0.4%)	15 (1.2%)	8 (4.6%)	< 0.001
COPD	197 (7.5%)	86 (7.3%)	89 (7%)	22 (12.6%)	0.027
Malignancy	241 (9.2%)	104 (8.8%)	123 (9.6%)	14 (8%)	0.682
Heart failure	145 (5.5%)	1 (0.1%)	57 (4.5%)	87 (50%)	< 0.001
Prior ASCVD	802 (30.5%)	83 (7%)	563 (43.3%)	166 (95.4%)	< 0.001
Prior lipid-lowering drugs	1239 (47.1%)	326 (27.7%)	785 (61.5%)	128 (73.6%)	< 0.001

ASCVD = atherosclerotic cardiovascular disease, COPD = chronic obstructive pulmonary disease

Table 2. Occurrence and hazard ratio of MACCE during follow-up, according to CHA_2DS_2VASc score

CHA_2DS_2VASc score	Proportion with event	Rate per 100 person-years	Unadjusted hazard ratio (95%CI)	*P*-value	Multivariable adjusted* hazard ratio (95%CI)	*P*-value
Score 2–3	137/1178 (11.6%)	6.7	Ref.		Ref.	
Score 4–5	254/1276 (19.9%)	12.2	1.93 (1.56–2.39)	< 0.001	1.74 (1.41–2.14)	< 0.001
Score 6–7	59/174 (33.9%)	21.2	3.95 (2.85–5.46)	< 0.001	2.87 (2.10–3.93)	< 0.001
Per 1 unit increase (score 2–7)			1.38 (1.28–1.49)	< 0.001	1.37 (1.26–1.48)	< 0.001

95%CI = 95% confidence interval, MACCE = major adverse cardiac and cerebrovascular events, defined as a composite of myocardial infarction, coronary revascularization for any reason, recurrent ischemic stroke, or all-cause death

*Adjusted to age, obesity, smoking, chronic kidney disease, chronic obstructive pulmonary disease, malignancy, lipid-lowering drugs

Figure 1. Association of individual components of CHA_2DS_2-VASc scores with the risk of MACCE

Age of study population and male sex do not provide points in the CHA_2DS_2-VASc score

MACCE = major adverse cardiac and cerebrovascular events

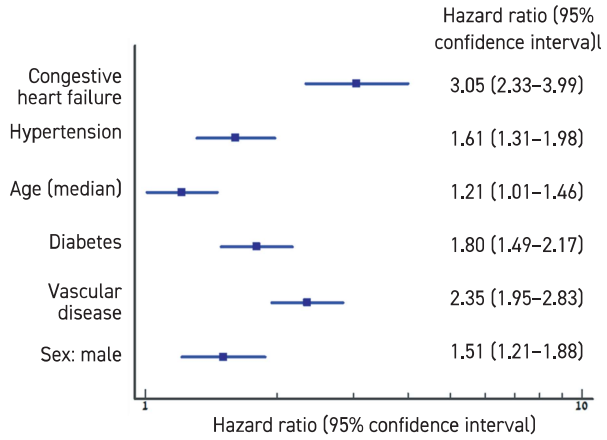
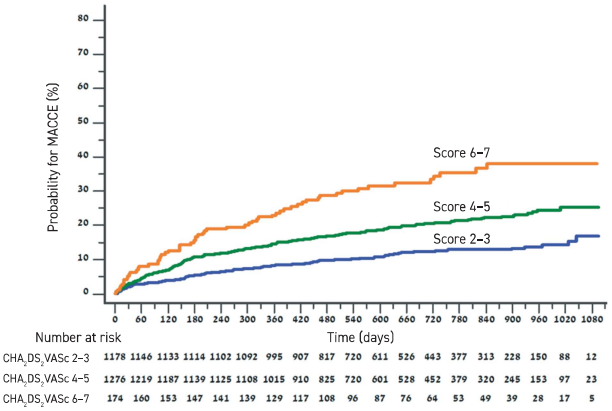


Figure 2. Kaplan-Meier curves presenting the association between categorized CHA_2DS_2VASc score and the cumulative probability for MACCE during follow-up

MACCE = major adverse cardiac and cerebrovascular events



current stroke: 0.60 (0.56–0.65), $P < 0.001$. Replacing the sex coding in the CHA_2DS_2-VASc score (male = 1 point, female = 0) increased the discriminatory capacity to overall MACCE 0.66 (0.63–0.68), myocardial infarction 0.74 (0.68–0.80), and recurrent stroke 0.61 (0.57–0.65), $P < 0.001$ for all analyzes.

DISCUSSION

In the current study we demonstrated that CHA_2DS_2-VASc scores can serve as a mid-term risk stratification tool in adults aged 40 to 65 years who present with acute ischemic stroke and have no history of AF. The utilization of the CHA_2DS_2-VASc score enabled the prediction of a composite adverse cardiac and cerebrovascular outcome, which included recurrent stroke, myocardial infarction, coronary revascularization, or mortality. The discriminative capacity of the scoring system for the composite event was modest, although it was higher for myocardial infarction as an individual endpoint and improved when a point in the risk scoring system was assigned for male sex, rather than to female sex as is customary employed in the CHA_2DS_2-VASc score.

While the global incidence of stroke is declining, there is a concerning upward trend in stroke rates observed among young and middle-aged adults [1,3]. Long-term consequences (physical, psychosocial, and economic) may be devastating, with high rates of recurrent stroke,

disability, and unemployment [3,12]. Considering the detrimental effects of stroke on both quality of life and potential life expectancy, it is crucial to implement risk stratification strategies for optimal secondary prevention among younger and middle-aged individuals who have survived an ischemic stroke. The CHA_2DS_2-VASc score is a clinical risk stratification tool, routinely used to assess the risk of stroke in patients with a non-valvular AF [5]. It is used as a validated scoring system to establish the indication for oral anticoagulation therapy in patients with non-valvular AF [6]. Nevertheless, because each of the components of the risk score is a known and independent cardiovascular risk factor, this scoring system may predict adverse clinical outcomes and mortality in patients with various cardiovascular diseases, regardless of an AF diagnosis [7-10,12-15].

In a recent population-based cohort study with a mean age of 63 years and 4% prevalence of cardiovascular disease, CHA_2DS_2-VASc score was shown to be an independent predictor of all-cause mortality, cardiovascular death, ischemic stroke, and coronary events, irrespective of the presence of AF [12]. Our study further strengthens these results in a younger cohort of middle-aged patients experiencing acute ischemic stroke, demonstrating the predictive role of CHA_2DS_2-VASc scores for a composite outcome of MACCE during mid-term follow-up.

Each of the CHA_2DS_2-VASc score components was associated with the risk of MACCE in patients post ischemic stroke. As expected, a history of vascular disease and the presence of heart failure were the strongest predictors of risk for adverse events. In addition, hypertension and diabetes mellitus, which are known risk factors for adverse cardiovascular events, were also associated with higher risk for MACCE. In the INTERSTROKE study, both hypertension and diabetes mellitus were part of 10 risk factors that were associated with 90% of the population attributed risk of stroke [16]. Patients with a higher CHA_2DS_2-VASc score often have additional co-morbidities that may further impact on future risk for cardiovascular events. As such, we observed higher rates of kidney dysfunction and COPD in patients at the highest risk scores. Notably, in the present analysis, men had a higher risk for MACCE than women. This observation is intriguing, considering that the CHA_2DS_2-VASc score assigns 1 point for female sex as a risk factor for thromboembolic events in patients with AF. It was previously suggested that female sex is a risk modifier rather than a risk factor for stroke in patients with AF [17] and that in patients without AF, males may have a higher risk of MACE than females [9]. We observed that a modified CHA_2DS_2-VASc score exhibited a greater discriminatory capacity for MACCE when assigning a point for male sex rather than female sex. This finding concurs with previous studies indicating that at a younger age the incidence rates for stroke are lower in females compared to males [18].

In the present study, the overall discriminatory ability of CHA_2DS_2-VASc score for MACCE was rather modest, although it was significantly higher for myocardial infarction than recurrent stroke. The limited discriminatory capacity of clinical risk scores was previously demonstrated in the literature. In a recent systematic review, the ability of CHA_2DS_2-VASc score to predict ischemic stroke in patients with AF was modest: AUC 0.64, 95%CI 0.63-0.65 [19]. An additional meta-analysis observed that the discrimination power of the CHA_2DS_2-VASc score in predicting ischemic stroke is similar in the presence or absence of AF (overall AUC 0.66, 95%CI 0.63–0.69) [15]. Although the association between the presence of AF and stroke is well-established, the etiology of stroke in AF patients is complex and multifactorial [20]. The components of the CHA_2DS_2-VASc score may be associated with increased incidence of underlying atrial anatomical abnormalities, premature atrial beats, and left atrial size, each of which has individually been associated with a higher burden of stroke, independently of AF. Since the CHA_2DS_2-VASc score is easily calculated and widely used, it may be useful for prospective risk assessment of major adverse cardiovascular and cerebrovascular events in the non-AF population and may possibly guide therapeutic decisions and treatment goals.

Several limitations of this study should be noted. We did not have data on antithrombotic drug therapy. We also lacked information regarding the severity of stroke, such as the National Institutes of Health Stroke Scale, which may impact the risk of mid-term MACCE. In addition, as the study population exclusively consisted of patients diagnosed with acute ischemic stroke, the findings cannot be extrapolated to other populations. Moreover, no information on the etiology of death was available and therefore we could not specifically evaluate the rate of cardiovascular death. Last, the ischemic stroke events occurred during the coronavirus disease 2019 pandemic, which may have influenced the study results.

CONCLUSIONS

CHA_2DS_2-VASc scores may serve as a valuable tool in stratifying the risk of middle-aged patients without AF following an ischemic stroke. Extending the application of the CHA_2DS_2-VASc score to non-AF individuals with stroke could enhance the identification of patients at high

risk for additional cardiovascular and cerebrovascular events. This recognition, in turn, could enable the implementation of more effective secondary prevention measures, ultimately improving clinical outcomes.

Correspondence

Dr. B. Zafrir
Dept. of Cardiology, Carmel Medical Center, Haifa 3436212, Israel
Phone: (972-4) 825-0801
Email: barakzmd@gmail.com

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Capsule

The many functions of autoantibodies

Autoantibodies are usually known for their role in mediating autoimmune diseases, but evidence has increasingly indicated that they can have protective as well as pathological roles in human health. In a perspective, **Jaycox** and colleagues discussed how autoantibodies may confer an underappreciated level of heterogeneity in human biology, which could have diverse impacts in, for example, cancer, neurodegeneration, and infectious diseases. They also highlighted the need for autoantibody-wide association studies reminiscent of such studies in genetics. By better understanding the diverse functions of autoantibodies, new biomedical paradigms might be revealed that could help guide drug development.

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