CHA$_2$DS$_2$VASc Score as a Predictor of Cardiovascular Events in Ambulatory Patients without Atrial Fibrillation

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Background: New evidence suggests that the CHA$_2$DS$_2$VASc (congestive heart failure, hypertension [HTN], age, diabetes, stroke, vascular disease, and female gender) score may be a reliable tool to predict the risk of thromboembolic events in patients without documented atrial fibrillation (AF).

Methods: We performed a prospective cohort study of outpatients without AF or flutter, who were not using oral anticoagulation. Clinical characteristics were assessed and patients were stratified according to the CHA$_2$DS$_2$VASc score. We evaluated the incidence of major adverse cardiac outcomes and its relation to the CHA$_2$DS$_2$VASc score during the follow-up.

Results: Four hundred sixty-eight patients without AF were enrolled with a mean follow-up of 12 ± 6 months. Age was 64.9 ± 11.3 years. The prevalence of HTN was 88.4%, diabetes 37.6%, heart failure 26.3%, and vascular disease 61.7%. Overall, CHA$_2$DS$_2$VASc score was 3.4 ± 1.4. There were 15 major adverse cardiac outcomes during 12.2 months of follow-up (overall incidence of 3.2 per 100 person-years). We found significant differences in relation to gender, age, previous stroke, and follow-up length in patients with and without adverse outcomes. The CHA$_2$DS$_2$VASc score was higher in those with adverse outcomes (4.2 ± 1.7 vs 3.4 ± 1.4; P = 0.035). Patients with a CHA$_2$DS$_2$VASc ≥6 had a relative risk for adverse outcomes of 4.2 (95% confidence interval: 1.27–13.90).

Conclusions: In our population, CHA$_2$DS$_2$VASc score predicts major adverse cardiac outcomes, including stroke and death, in a cohort of patients without AF. (PACE 2015; 38:1412–1417)

CHA$_2$DS$_2$VASc, stroke, atrial fibrillation, cohort study, risk

Introduction

Risk of thromboembolic events in patients with atrial fibrillation (AF) is variable and dependent on the individual clinical characteristics, covered by the CHA$_2$DS$_2$VASc (congestive heart failure, hypertension [HTN], age, diabetes, stroke, vascular disease, and female gender) score.[1] Each component of the score is associated with an increased risk of adverse cardiac events due to arterial thromboembolic events in patients with AF. Ischemic stroke is one of the main causes of death in the world. According to Centers for Disease Control and Prevention data, stroke affects more than 795,000 people and kills nearly 130,000 people each year in the United States, about one death every 4 minutes, leading to an estimated cost of $34 billion.[2] Measures to detect the population with a higher risk of stroke and the adoption of preventive strategies to reduce new cases are important for any healthcare system.

The Framingham risk score can predict adverse cardiovascular events including stroke, but laboratory data are required to estimate the risk.[3] There is also a score for those with AF.[4] Simpler methods to stratify the probability of stroke are needed. New evidence suggests that patients without documented AF who have an elevated CHA$_2$DS$_2$VASc score are at an increased risk of stroke.[5,6] Based on this hypothesis, we proposed a prospective study to evaluate the ability of the CHA$_2$DS$_2$VASc score in predicting major adverse cardiac outcomes in patients without any previously documented AF.

Methods

Study Design and Population

Prospective cohort study of consecutive patients followed at the outpatient cardiology clinic of our institution between March 2013 and June 2014 was designed to investigate the ability of the CHA_2DS_2VASc in predicting major adverse cardiac outcomes.

Inclusion criteria were as follows: (1) age ≥18 years, (2) absence of any documented AF or atrial flutter (on Holter monitoring, 12-lead electrocardiogram treadmill test, loop monitor, and pacemaker recordings), and (3) absence of the use of any oral anticoagulation (vitamin K antagonist, factor Xa inhibitor, direct thrombin inhibitor).

We excluded patients with mechanical prosthetic heart valves, thrombophilias, recent deep vein thrombosis or pulmonary embolism, and intraventricular thrombus.

Patient Evaluation

Two physicians independently performed clinical assessment and chart review of all patients using our electronic medical record system. In addition to the initial medical evaluation, we pursued in a proactive fashion the occurrence of major adverse cardiac outcomes during the follow-up. If data were not available in our records, the patient was contacted at least once more, through telephone calls. Patients were excluded from the study if they did not come for the prespecified medical appointment, or if we were not able to establish any form of contact to determine patient status.

CHA_2DS_2VASc Score

The CHA_2DS_2VASc score was calculated for each patient as recommended by the current clinical guidelines.[7] The score ranges from 0 to 9 points. The score takes into account the following clinical characteristics: congestive heart failure or left ventricular dysfunction (1 point), HTN (1 point), age ≥75 years (2 points), diabetes (1 point), stroke (2 points), vascular disease (1 point), age 65–74 years (1 point), and sex category (female; 1 point). The sum of each factor gives us the individual patient's risk score. The risk of thromboembolic complications is around 2% per year for those who scored 2 points and it goes up to 15% per year in the highest strata of the score (9 points).[8]

Congestive heart failure and left ventricular dysfunction were defined as mandated by the current guidelines.[9] We also look for the report, in the electronic medical chart of each patient, of signs and symptoms of either right or left ventricular failure.

HTN was defined according to the Eighth Joint National Committee.[10]

Diabetes was defined according to current recommendations as having a fasting plasma glucose level ≥126 mg/dL, or 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, or a serum A1C ≥6.5%, or a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or a random plasma glucose ≥200 mg/dL.[11] We also searched for the evidence of a prescription for oral hypoglycemic agent or insulin in the patient electronic medical record in those with an unclear diagnosis.

Stroke was defined as a neurological deficit due to an acute focal injury of the central nervous system by a vascular cause.[12]

We defined vascular disease as the presence of any of the following: a history of intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or the lower extremity vessels, abdominal or thoracic surgery, arterial and venous thrombosis, or the presence of a radiologic imaging showing significant atherosclerosis in the aorta or other relevant vascular beds.

Definition of End Points

We defined end points as major adverse cardiac outcomes, the composite of all-cause mortality, stroke, transient ischemic attack (TIA), acute myocardial infarction (AMI), and new onset AF or flutter. A specialist in each field validated each end point (e.g., stroke by a neurologist, AF by a cardiologist, etc.).

Statistical Analysis

Statistical analyses were done using the software Statistical Package for the Social Sciences (SPSS), version 16.0 (IBM Corp., Armonk, NY, USA) and with the software MedCalc, version 7.0 (MedCalc, Ostend, Belgium). Continuous variables were described as means and standard deviations. Categorical variables were described as the absolute frequencies and percentages. Univariate comparisons were made with the χ^2 or the two-sample t-test, as appropriate. *Post hoc* analyses were performed using the Bonferroni test. The diagnostic utility of the CHA_2DS_2VASc score in detecting major adverse cardiac outcomes was determined using receiver-operating characteristic. The results were expressed using the C-statistic. The cumulative occurrence of major adverse cardiac outcomes was analyzed individually and altogether with the Cox proportional hazard regression model. Relative risks (RR, 95% confidence interval [CI]) were reported. Additionally, we measured
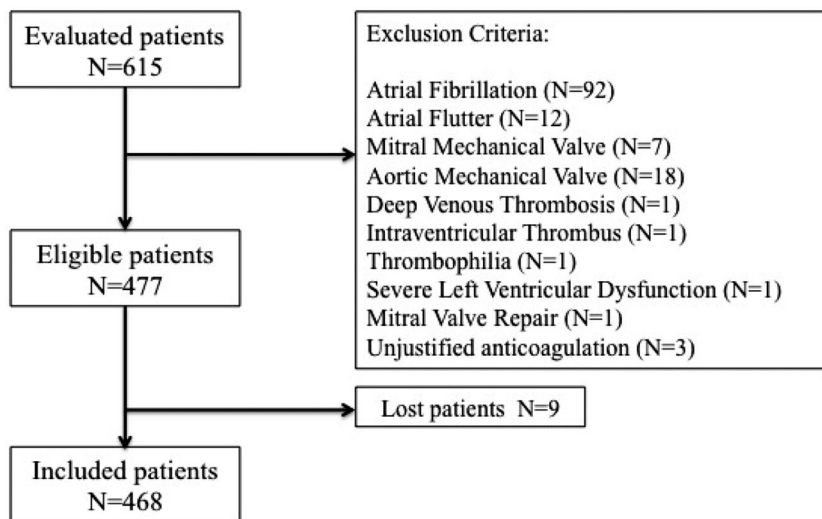
Figure 1. *Patient study selection.*

cumulative event-free major adverse cardiac outcomes survival by the Kaplan-Meier method and compared unadjusted differences using the log-rank test. The significance level was set to $P < 0.05$.

The Ethics Committee of our institution approved the study protocol. All participants provided a written informed consent. We followed the STROBE statement for cohort studies.[13]

Results

Between March 2013 and June 2014 we screened 615 consecutive patients, 138 of them met at least one of the exclusion criteria. The remaining 477 patients were eligible and were included in the study protocol. Nine patients were lost during follow-up. Four hundred sixty-eight patients were followed by at least one medical visit or telephone contact (six cases) for a period ranging from 6 months to 24 months, with a mean follow-up of 12 ± 4 months. Figure 1 shows the study enrollment.

Associated comorbidities and cardiovascular risk factors were HTN in 414 patients (88.46%), diabetes in 176 (37.6%) patients, heart failure in 128 (26.35%) patients, vascular disease in 289 patients (61.75%), and current or previous smoker status in 165 patients (35.26%).

Mean CHA_2DS_2VASc score was 3.4 ± 1.4. The different scores had a normal distribution. We did not find any patient with a score of 8 points.

Fifteen major adverse cardiac outcomes were identified after an average of 12.2 months of follow-up. There were five deaths from all causes, four ischemic strokes, two TIA, one AMI, and three cases of new onset AF. Overall, incidence of major

adverse cardiovascular end points was 3.2 per 100 person-years.

Patients who presented with any adverse outcome were older (71.1 ± 9.6 years vs 65 ± 11 years; $P = 0.029$), had a greater incidence of previous stroke (20% vs 4.6%; $P = 0.003$), belonged more to the female gender (66.7% vs 48.8%; $P = 0.044$), and had a longer follow-up (15.8 ± 4.5 months vs 12.1 ± 3.99 months; $P < 0.001$).

CHA_2DS_2VASc score was also higher in patients who presented with adverse events (4.2 ± 1.7 vs 3.4 ± 1.4; $P = 0.035$). Table I shows the characteristics of patients stratified into those with and without adverse events.

The C-statistic for the CHA_2DS_2VASc score was 0.62 (95% CI: 0.58–0.67). A score ≥ 6 had a sensitivity of 26.7% and a specificity of 92.1%.

The incidence of major adverse cardiac outcomes in the population of patients with a score ≥ 6 was 9.8 per 100 person-years versus 2.5 per 100 person-years for the population with a score lower than 6. Adopting this score as the cutoff, we obtained a risk relative 4.2 (1.27–13.90) for the occurrence of the combined event in those who scored higher. Table II summarizes the distribution of events on the different CHA_2DS_2VASc categories. Figure 2 shows the event-free survival according to CHA_2DS_2VASc score, analyzed individually and altogether with the Cox proportional hazard regression model.

Patients with a score equal to or greater than 6 had a positive likelihood ratio (LR) of 3.45 for the occurrence of stroke or TIA during follow-up (−LR: 0.78; sensitivity: 28.6 [95% CI: 4.5–70.7]; specificity: 91.7 [95% CI: 88.8–94.1]). The

Table I.

Baseline Characteristics

Characteristics	Total 468 (100%)	No Event 453 (96.8%)	Event 15 (3.2%)	P
Female	231 (49.3%)	221 (48.8%)	10 (66.7%)	0.044
Age (years)	64.9 ± 11.3	65 ± 11	71.1 ± 9.6	0.029
Hypertension	414 (88.5%)	402 (88.7%)	12 (80%)	0.660
Diabetes	176 (37.6%)	169 (37.3%)	7 (46.7%)	0.519
HF	128 (27.3%)	124 (27.4%)	4 (26.7%)	0.326
Vascular disease	289 (61.7%)	280 (61.8%)	9 (60%)	0.552
Stroke	24 (5.1%)	21 (4.6%)	3 (20%)	0.003
CHA_2DS_2VASc	3.5 ± 1.4	3.4 ± 1.4	4.2 ± 1.7	0.035
Smoker	57 (12.2%)	55 (12.1%)	2 (13.3%)	0.720
Former smoker	108 (23.1%)	104 (22.9%)	4 (26.7%)	1.000
ASA	392 (83.8%)	380 (83.9%)	12 (80%)	0.498
Clopidogrel	38 (8.1%)	38 (8.4%)	0 (0%)	0.277
β-Blocker	383 (81.8%)	372 (82.1%)	11 (73.3%)	0.641
Antiarrhythmic	26 (5.5)	26 (5.7%)	0 (0%)	0.375
Statin	411 (87.8%)	398 (87.8%)	13 (86.7%)	0.720
Congenital disease	15 (3.2%)	15 (3.3%)	0 (0%)	0.506
Follow-up (months)	12.2 ± 4.1	12.1 ± 4.0	15.8 ± 4.5	<0.001
Uncontrolled hypertension	84 (17.9%)	79 (17.4%)	5 (33.3%)	0.222
Renal or hepatic disease	16 (3.4%)	16 (3.5%)	0 (0%)	0.491
Bleeding	14 (2.9%)	12 (2.6%)	2 (13.3%)	0.313
HASBLED	1.6 ± 0.9	1.6 ± 0.9	2.1 ± 1.3	0.140

Values are presented as mean ± standard deviation or as a percentage.
ASA = acetylsalicylic acid; HASBLED = Hypertension, Abnormal liver or kidney function, Stroke, Bleeding, Labile international normalized ratio values, Age >65 years, and Diabetes; HF = heart failure.

Table II.

Annual Incidence of Events According to CHA_2DS_2VASc Score

CHA_2DS_2VASc	Events	Total of Patients	Follow-Up (Months)	Incidence (Per 100 Person-Years)
0	0	3	14	0.00
1	1	29	11.5	3.6
2	1	88	12.7	1.1
3	3	125	11.9	2.4
4	5	117	12.4	4.1
5	1	66	11.9	1.5
6	2	30	12.2	6.5
7	2	9	12.3	21.6
8	0	0	0	0.0
9	0	1	12	0.0

+LR was 3.35 for the combined end point of stroke, TIA, and death (−LR: 0.79; sensitivity: 27.3 [95% CI: 6.3–60.9]; specificity: 91.9 [95% CI: 89.0–94.2]).

Discussion

This study evaluated the ability of the CHA_2DS_2VASc score in predicting the incidence of major adverse cardiac outcomes in a population of patients with established heart disease and no AF. We observed a high prevalence of cardiovascular diseases and risk factors such as HTN (88% of patients), diabetes (37%), and heart failure (almost one-third of patients). The mean CHA_2DS_2VASc score in our study was higher than the one presented in the original paper, despite the absence of AF in our patients (3.4 ± 1.4 vs 2.9 ± 1.8).[1] The C-statistic for the CHA_2DS_2VASc was not excellent in our population, with substantial differences from recent studies. The validation of CHA_2DS_2VASc in a large Danish cohort of AF patients not receiving oral anticoagulation demonstrated a C-statistic 0.88 (95% CI: 0.87–0.90) in predicting the arterial thromboembolism.[6] Our study showed that patients who scored ≥6 had a positive LR of 3.3 for the occurrence of adverse outcomes during the follow-up.

Ntaios et al. published a retrospective study of patients with a prior stroke in which the CHA_2DS_2VASc score proved to be a predictor of
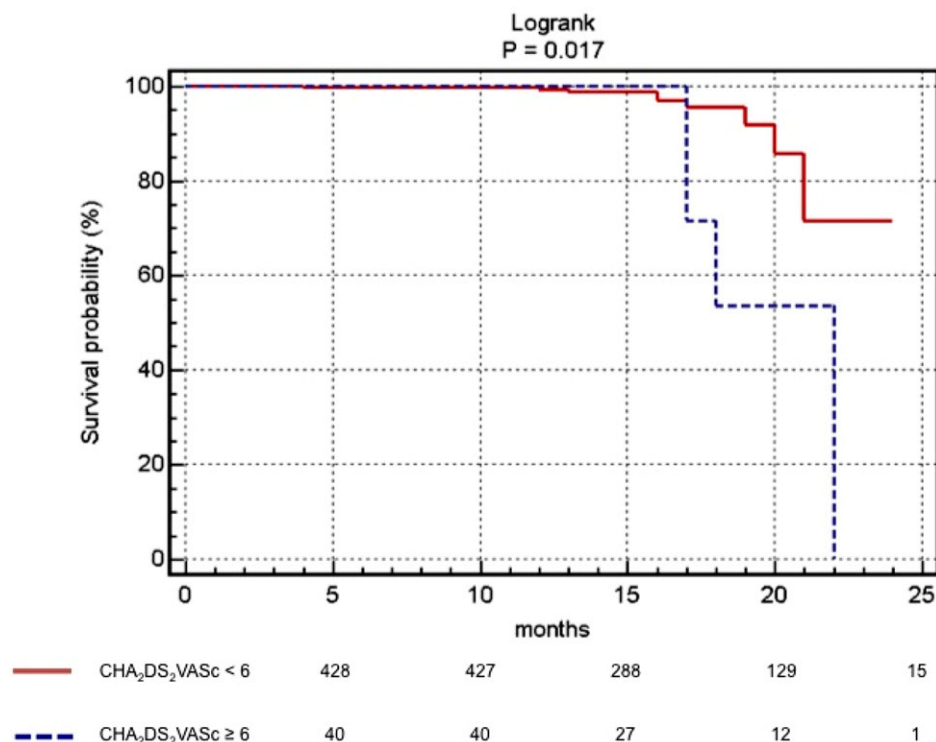
Figure 2. *Event-free survival according to CHA₂DS₂VASc score (P = 0.017).*

adverse outcomes.[5] In our cohort, three of the 15 (20%) patients who developed a major adverse event had a previous history of stroke or TIA. In these three patients, the adverse events were a hemorrhagic stroke, a myocardial infarction, and one death (cause not identified). Tischer et al. demonstrated that the prevalence of AF rises significantly with every increase point in the CHA₂DS₂VASc.[14] In their study, patients with a CHA₂DS₂VASc score greater than 6 had AF more than 30% of cases. The prevalence of thromboembolic events was high, and it was independent of the existence of AF in patients with a CHA₂DS₂VASc score higher than 7. Peguero et al. also showed that the CHA₂DS₂VASc score was able to predict postoperative stroke in patients having cardiac surgery independent of AF.[15] This ability of the CHA₂DS₂VASc score to detect those at increased risk of adverse events, independent of the presence of AF, was also true in our population in an outpatient setting. Subjects with a CHA₂DS₂VASc ≥6 were prone to the occurrence of adverse outcomes. Thus, it is still not clear what should be the strategy in this group of patients regarding the antithrombotic management. For patients in the lowest CHA₂DS₂VASc score strata (2–6 points), we should focus on the early

detection of AF. This arrhythmia carries by itself an increase in the risk of adverse events. One limitation of our study is the possibility of the underdiagnosis of cases of paroxysmal AF, which very often do not cause any clinical symptom.[16,17] It is not possible to state whether the risk conferred by the highest scores are due to the set of comorbidities (that are part of the score itself) or due to a greater chance of developing AF. We believe, however, that the second hypothesis is more reasonable to explain this phenomenon. The observational nature of the study cannot eliminate the possibility of residual confounding. We also did not test the diagnostic ability of the CHADS₂ score. The small sample size, short follow-up, and the small number of events in each CHA₂DS₂VASc strata are also a bias.

In our population, an elevated CHA₂DS₂VASc score was associated with a higher incidence of major adverse cardiac outcomes during follow-up. Larger prospective studies are necessary to better define the increased risk associated with the CHA₂DS₂VASc score in patients without documented AF. Randomized clinical trials are needed to determine which interventions may protect these patients from adverse cardiovascular outcomes, especially stroke.

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