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The CHADS2 Score Predicts Ischemic Stroke in the Absence of Atrial Fibrillation Among Patients with Coronary Heart Disease: Data from the Heart and Soul Study

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Abstract

Background—We sought to evaluate the prognostic performance of the CHADS2 score for prediction of ischemic stroke/TIA in subjects with coronary heart disease (CHD) without atrial fibrillation (AF).

Methods—In 916 non-anticoagulated outpatients with stable CHD and no AF by baseline electrocardiogram, we calculated CHADS2 scores (congestive heart failure, hypertension, age ≥ 75 , diabetes (1 point each), and prior stroke or transient ischemic attack (TIA) (2 points)). The primary outcome was time to ischemic stroke or TIA over a mean follow-up of 6.4 ± 2.3 years.

Results—Over 5821 person-years of follow-up, 40 subjects suffered an ischemic stroke/TIA (rate 0.69 per 100 person-years, 95% CI 0.50-0.94). Compared to subjects with low (0-1) CHADS2 scores, those with intermediate (2-3) and high (4-6) CHADS2 scores had an increased rate of stroke/TIA, even after adjustment for age, tobacco, antiplatelet therapy, statins, and angiotensin inhibitors (CHADS2 score 2-3: HR 2.4, 95% CI 1.1-5.3, $p=0.03$, CHADS2 score 4-6: HR 4.0, 95% CI 1.5-10.6, $p=0.006$). Model discrimination (c-statistic = 0.65) was comparable to CHADS2 model fit in published AF-only cohorts.

Conclusions—The CHADS2 score predicts ischemic stroke/TIA in subjects with stable CHD and no baseline AF. The event rate in non-AF subjects with high CHADS2 scores (5-6) was comparable to published rates in AF patients with moderate CHADS2 scores (1-2), a population known to derive benefit from stroke prevention therapies. These findings should inform efforts to determine whether stroke prevention therapies or screening for silent AF may benefit subjects with stable CHD and high CHADS2 scores.

Keywords

CHADS2; Stroke; Atrial Fibrillation; Coronary Heart Disease; Risk Stratification

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Introduction

The CHADS2 score is a validated clinical prediction tool commonly used to estimate the risk of stroke in atrial fibrillation (AF). The score is derived from the sum of point values of individual stroke risk factors (congestive heart failure (CHF), hypertension, age ≥ 75 , diabetes (1 point each), and prior stroke or transient ischemic attack (TIA) (2 points)).¹ The CHADS2 score is used in clinical practice to guide decisions regarding antiplatelet and anticoagulation therapy. The simplicity of its calculation has facilitated its widespread adoption and endorsement by national and international society guidelines.²⁻⁴

Although the CHADS2 score and other similar risk stratification schemes have proven useful in populations with known AF, the vast majority (85%) of ischemic strokes occur in individuals without known AF.⁵ Patients with coronary heart disease (CHD) are at increased risk for stroke, and each of the component comorbidities of the CHADS2 score has been independently associated with stroke in large cohorts of patients with CHD.⁶⁻⁸ Therefore, we hypothesized that stroke risk may also be well captured by the CHADS2 score in the non-AF CHD population. To test this hypothesis, we evaluated the prognostic performance of the CHADS2 score for prediction of ischemic stroke/TIA in patients with CHD without AF.

Methods

Participants

The Heart and Soul Study is a prospective cohort study designed to investigate psychosocial factors and health outcomes in patients with stable CHD. Details regarding recruitment methods and study design have been published previously.⁹ In brief, between September 2000 to December 2002, 1,024 outpatients with stable CHD were recruited from two Veterans Administration Medical Centers (Palo Alto and San Francisco), one university medical center (University of California, San Francisco), and nine clinics in the Community Health Network of San Francisco. Inclusion criteria were defined as meeting one or more of the following: (1) history of myocardial infarction (MI); (2) evidence of at least 50% stenosis in 1 or more coronary vessels on cardiac catheterization; (3) evidence of exercise-induced ischemia by treadmill electrocardiogram (EKG) or nuclear perfusion stress imaging; or (4) a history of coronary revascularization. Exclusion criteria were defined as one or more of the following: history of MI in the previous 6 months, inability to walk 1 block, or planning to move out of the local area within 3 years.

Of 1,024 study subjects, we excluded participants with atrial fibrillation or flutter on baseline EKG (n=50), warfarin use (n=46), missing data for calculation of the CHADS2 score (n=8), and those lost to follow-up (n=4). The remaining 916 participants are the subjects of this secondary data analysis. This study was approved by the institutional review board and all participants provided written, informed consent.

Measurements

Predictor Variable—The primary predictor was the CHADS2 score. Hypertension was defined as either self-report or systolic blood pressure ≥ 160 mmHg; blood pressure was measured in all participants in the supine position after five minutes of rest. This cutpoint was chosen because it was the criterion used by the Atrial Fibrillation Investigator study (AFI)¹⁰, one of the two classification schemes amalgamated to form the CHADS2 index. Diabetes was defined as self-reported diabetes, receipt of a diabetes medication, or hemoglobin A1c $\geq 7.0\%$. CHF, prior stroke and TIA were determined by self-report.

Outcome Variable—The primary outcome was time to incident TIA or ischemic stroke. Annual follow-up interviews with participants or their proxy were conducted to inquire about interval death or hospitalization. For any reported event, medical records were retrieved and reviewed by two independent and blinded physician adjudicators. If the adjudicators agreed on the outcome classification, their classification was binding. In the event of a disagreement, a third blinded adjudicator was consulted.

Stroke was defined as a new neurologic deficit not known to be secondary to brain trauma, tumor, infection, or other cause, based on the WHO MONICA criteria.^{11, 12} All stroke outcomes were subtyped as hemorrhagic, ischemic, or procedure-related, based on physician diagnosis, which was confirmed by CT/MRI imaging in 84% of cases. Stroke outcomes in this study were restricted to patients with non-procedure-related ischemic strokes. TIA outcomes were based on the clinical judgment of the adjudicators who independently reviewed the medical records (including medical history, physical examination, imaging, laboratory results, and diagnosis of the treating physician), guided by the definition of TIA as a focal neurologic deficit (in the absence of head trauma) lasting more than 30 seconds and no longer than 24 hours, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 minutes and with subsequent complete resolution.

Other Measurements—Age, sex, race, and medical history were determined by self-reported questionnaire. Height and weight were measured to calculate body mass index (BMI). Participants were instructed to bring all medication bottles to the baseline appointment, and study personnel recorded all current medications. Standard 12-lead EKGs were performed on all subjects at the time of enrollment. EKGs were adjudicated by two independent, blinded physicians. In the event of a disagreement, a third adjudicator was consulted. In addition, all EKGs with a paced rhythm were reviewed by a cardiac electrophysiologist to rule out underlying AF.

Statistical Analysis

For descriptive purposes, we divided the primary predictor, the CHADS2 score, into 3 strata of risk: low (0-1), intermediate (2-3) and high (4-6). We compared differences in baseline characteristics between patients with low, intermediate, and high CHADS2 scores using chi-square tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

We calculated cumulative event incidence rates by CHADS2 score. We then used Cox regression to calculate the risk of ischemic stroke or TIA, stratified by CHADS2 score, for comparison with the hazard ratios reported in the original CHADS2 derivation study.¹ We measured cumulative event-free survival by the Kaplan-Meier method and compared unadjusted differences using the log-rank test. We performed Cox regression to assess the ability of the CHADS2 score to independently predict incident stroke/TIA after multivariate adjustment. To avoid model overfitting with the relatively small number of outcome events, we limited adjustment to five covariates based on prior literature and clinical validity: age⁵ and current smoking¹³ (known stroke risk factors), statins¹⁴ and antiplatelet agents¹⁵ (proven stroke prevention therapies), and angiotensin inhibitors^{16, 17} (may prevent left atrial remodeling/AF and improve ventricular function). To assess the potential for residual confounding, we also performed a sensitivity analysis in which all covariates demonstrating an association with the CHADS2 score at $p < 0.05$ were included in the model. The assumption of proportional hazards was found to be valid using log-minus-log curves and the Schoenfeld test^{18, 19}. Finally, to compare discrimination of the CHADS2 score with other similar clinical stroke risk stratification models, we calculated c-statistics for the

CHA₂DS₂-VASc²⁰ and Framingham stroke risk scores.^{21, 22} All analyses were conducted using STATA, version 11.0 (College Station, TX).

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Results

Of the 916 non-anticoagulated participants with no evidence of baseline AF, the mean CHADS₂ score was 1.7 ± 1.2 . The CHADS₂ score was strongly associated with each of the components used to derive the score (age, CHF, hypertension, diabetes, stroke/TIA). Compared with participants with low CHADS₂ scores (0-1), those with high CHADS₂ scores (4-6) also had higher BMIs and were less likely to smoke. They were more likely to have a history of MI, lower left ventricular ejection fractions (LVEF), and higher values of systolic blood pressure, hemoglobin A1c and serum creatinine. Finally, participants with higher CHADS₂ scores were more likely to be using beta blocker, statin, angiotensin inhibitor, antiplatelet and antiarrhythmic medications (Table I).

The primary outcome of ischemic stroke/TIA occurred in 40 participants during a mean follow-up time of 6.4 ± 2.3 years or 5821 person-years (rate 0.69 per 100 person-years, 95% CI 0.50-0.94). Event rates increased by CHADS₂ score (0: 0.2, 1: 0.4, 2: 0.9, 3: 0.9, 4: 1.1, 5-6: 3.1 per 100 person-years, p for trend = 0.0002) (Table II, Figure 1).

Kaplan-Meier estimates revealed early separation of the event-free survival curves (within the first six months of follow-up), which continued to diverge throughout follow-up (Figure 2). Compared with the reference group of subjects with CHADS₂ scores of 0-1, those with CHADS₂ scores of 2-3 had 2.7 times the rate of stroke/TIA (p=0.01), and those with CHADS₂ scores of 4-6 had 4.6 times the rate (p=0.001). After adjustment for age, smoking, use of statins, antiplatelet agents and angiotensin inhibitors, CHADS₂ score remained independently associated with time to stroke/TIA (CHADS₂ score 2-3: HR 2.4, p=0.03, CHADS₂ score 4-6: HR 4.0, p=0.006). We also performed a sensitivity analysis, in which we created an expanded multivariate model where we also adjusted for serum creatinine, BMI, prior MI, and use of antiarrhythmic agents. After adjustment for these additional covariates, the associations remained significant and similar in magnitude (Table III).

We performed a subgroup analysis limited to only patients with no prior stroke/TIA. In our subgroup analysis, the point estimates for the hazard ratios of patients with CHADS₂ scores 2-3 were similar to those of the main analysis (subgroup analysis: 2.6 (1.1-5.8), p=0.03, compared with main analysis: 2.7(1.3-5.7), p=0.01), and there was no interaction (p = 0.73).

In our cohort, test discrimination of the CHADS₂ score (c-statistic = 0.65) was similar to discrimination when applying other clinical stroke risk stratification models: CHA₂DS₂-VASc²⁰ (0.64), Framingham stroke risk score for patients with no AF (0.63) and new-onset AF (0.64). Because patients with higher CHADS₂ scores had lower LVEFs, we also created

a separate model in which CHF was defined by either self-report or LVEF $\leq 40\%$ and found no appreciable change in the c-statistic (0.65).

Discussion

In 916 patients with coronary heart disease who had no known AF at baseline, we found that the CHADS₂ score was strongly predictive of ischemic stroke/TIA. Compared to participants with low CHADS₂ scores (0-1), those with intermediate CHADS₂ scores (2-3) had an over 2-fold increased rate of stroke and those with high CHADS₂ scores (4-6) had a 4-fold increased rate of stroke. The event rate in non-AF CHD patients with high CHADS₂ scores (5-6) was comparable to the rate in AF patients with moderate CHADS₂ scores (1-2), a population known to derive benefit from stroke prevention therapies such as anticoagulation.¹⁵ This association remained independent after adjustment for a wide range of covariates. Moreover, model discrimination in this non-AF cohort (c-statistic = 0.65) was similar to that which has been observed in external contemporary AF cohorts (c-statistic = 0.56-0.62).²³ These findings indicate the CHADS₂ score may also be useful for risk stratification of patients without known AF. Notably, the discrimination of other, more complex risk stratification schemes (CHA₂DS₂-VASc, Framingham) were no better than CHADS₂ in this population (c-statistic = 0.63-0.64).

Several potential mechanisms may explain these findings. First, patients with high CHADS₂ scores may have a higher risk of developing atrial arrhythmias, which mediates the relationship with stroke outcomes. The strongest support for this comes from the cryptogenic stroke literature. In a study of patients monitored for arrhythmia after suffering an ischemic stroke, higher CHADS₂ scores were noted in patients subsequently found to have occult AF. This association was particularly strong in patients with CHD. These investigators suggested using the CHADS₂ criteria “backwards” to identify a subset of patients with cryptogenic stroke who may benefit from prolonged event monitoring.²⁴ A similar investigation of hypertensive patients admitted for ischemic stroke demonstrated a higher prevalence of CHF, diabetes, CHD, and advanced age in patients found to have silent AF than those in whom monitoring did not reveal AF.²⁵

Alternatively, the CHADS₂ risk factors themselves may increase the risk of stroke or stroke subtypes, independent of cardiac rhythm. In AF, substantial evidence supports induction of a prothrombotic state, endothelial dysfunction, and blood stasis as underlying mechanisms of thrombus formation and stroke.²⁶ However, even in the absence of AF, patients with heart failure²⁷, hypertension,²⁸ and diabetes²⁹ have elevated markers of hypercoagulability and endothelial dysfunction. A recent study demonstrated similar levels of platelet activation in both AF and non-AF patients with cardiovascular comorbidities, suggesting that platelet activation in AF may be due to underlying cardiovascular disease rather than AF itself.³⁰

Finally, the CHADS₂ risk factors may directly contribute to left atrial (LA) remodeling, a process characterized by dilatation and mechanical dysfunction of the left atrium.³¹ These factors may result in blood stasis and confer an increased risk of thromboembolism independent of rhythm.³² Atrial structural remodeling can be accompanied by wall stretch and electrical remodeling resulting in atrial arrhythmias, with AF being the most common.^{31,33,34} Diabetes, heart failure, hypertension, and CHD have all been associated with LA remodeling.³⁵⁻³⁷ The CHADS₂ risk factors may therefore contribute to stroke risk via LA remodeling, either by chamber dilatation producing blood stasis, by induction of AF, or both.

Further investigation is warranted to gain a better understanding of the underlying mechanism, as such knowledge may inform more directed screening or stroke prevention

efforts. Our findings of comparable stroke risk in non-AF patients with high CHADS2 scores (5-6) and AF patients with moderate CHADS2 scores (1-2) raise the question of whether high risk, non-AF patients may benefit from stroke prevention therapies such as anticoagulation, either due to a greater risk of silent AF or rhythm-independent mechanisms of thromboembolism in this population.

The 2011 AHA/ASA guidelines for prevention of primary and recurrent stroke recommend risk factor modification of hyperlipidemia, hypertension, and diabetes.^{38,39} For patients with CHD or prior stroke/TIA, the guidelines recommend antiplatelet therapy. Notably, there were stroke events in our cohort despite the fact that the majority of subjects were receiving antiplatelet therapies (84%) and statins (65%) and had achieved excellent risk factor control (low density lipoprotein: 105+/-33 mg/dL, systolic blood pressure: 133 +/-21 mmHg, hemoglobin A1c: 6.0 +/-1.2%). Although stroke prevention guidelines state that opportunistic pulse screening followed by EKG to assess for AF in patients ≥65 may be useful, this limited ascertainment may be insensitive for sufficient detection of paroxysmal AF.^{39, 40}

There are several notable limitations of our study. This study was performed in a cohort of predominantly male patients with stable CHD, which may limit generalizability. The observational nature of the study cannot eliminate the possibility of residual confounding. However, the CHADS2 score remained strongly and independently predictive of stroke/TIA after adjustment for potential confounding variables; more extensive adjustment did not change point estimates or widen confidence intervals. Notably, approximately 6.2% of participants in the study were receiving antiarrhythmic agents, with greater use in those with high CHADS2 scores. If prescribed for atrial rather than ventricular arrhythmias, those with high CHADS2 scores may have had a higher rate of paroxysmal AF at baseline. Adjustment for antiarrhythmic drug use demonstrated no change in point estimates.

Finally, because our criterion for exclusion of subjects with AF was the baseline EKG, it is possible that individuals with known paroxysmal AF who were in sinus rhythm at the time of the baseline EKG could have been misclassified as non-AF participants and included in the analyses. It is also possible that participants without known AF but who had AF on the baseline study EKG could have been misclassified and excluded. However, for paroxysmal AF, any method of AF ascertainment other than continuous EKG monitoring would be subject to similar misclassification.

Conclusions

In summary, we found that the CHADS2 risk score independently predicts stroke/TIA in patients with CHD who have no known history of AF. The event rate in non-AF CHD patients with high CHADS2 scores (5-6) was comparable to published rates in AF patients with moderate CHADS2 scores (1-2). Since most strokes occur in patients without known AF, the CHADS2 score may have a role in identification of high-risk individuals who may benefit from stroke prevention therapies or screening for silent AF.

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Figure 1.
Rate of ischemic stroke/TIA, by CHADS2 score

Figure 2.
Kaplan-Meier curves for survival free of ischemic stroke/TIA, stratified by CHADS2 score

Table I

Baseline characteristics of 916 participants with stable coronary heart disease and no baseline AF, by CHADS2 score

	CHADS2 Score			p-value
	0-1 (n=441)	2-3 (n=389)	4-6 (n=86)	
Demographics				
Age, years	63.5 ± 9.6	69.0 ± 11.1	72.9 ± 9.7	0.007
Male, %	81.2	81.0	87.2	0.38
Caucasian, %	62.5	56.0	52.3	0.07
Body Mass Index, kg/m ²	27.9 ± 4.8	28.9 ± 5.6	28.6 ± 4.6	0.01
Current Smoker, %	24.1	16.2	20.9	0.02
Medical History				
Myocardial Infarction, %	48.1	56.9	69.8	<0.001
Congestive Heart Failure, %	2.3	25.5	46.5	<0.001
Hypertension, %	52.8	92.0	94.2	<0.001
Diabetes, %	5.0	47.8	50.0	<0.001
Prior Stroke/TIA, %	0.0	12.3	88.4	<0.001
Laboratory/Imaging				
SBP, mmHg	130 ± 19	137 ± 22	135 ± 24	<0.001
Hemoglobin A1c, %	5.5	6.4	6.4	<0.001
HDL, mg/dL	47 ± 15	45 ± 14	45 ± 13	0.07
LDL, mg/dL	106 ± 33	103 ± 35	104 ± 33	0.29
Serum Creatinine, mg/dL	1.0 ± 0.4	1.2 ± 0.8	1.3 ± 0.6	<0.001
LVEF, %	62.8	61.0	61.4	0.03
Medication Use				
Antiplatelet Agent*, %	79.1	88.4	83.7	0.002
Beta Blocker, %	53.7	64.0	61.6	0.01
Angiotensin Inhibitor, %	38.1	62.7	57.0	<0.001
Statin, %	59.6	67.6	75.6	0.004
Antiarrhythmics, %	3.6	8.2	10.5	0.005

TIA = transient ischemic attack, SBP = systolic blood pressure, HDL = high density lipoprotein, LDL = low density lipoprotein, LVEF = left ventricular ejection fraction

Values are expressed as mean ± standard deviation or percentage

* Aspirin ± clopidogrel

Table II

Rates and hazard ratios of ischemic stroke/TIA, compared with those of the CHADS2 derivation cohort

CHADS2 Score	Event Rates (per 100 person-years)		Hazard Ratios	
	CHADS2 Derivation Cohort* (n=1733)	Heart & Soul Cohort (n=916)	CHADS2 Score	CHADS2 Derivation Cohort* (n=1733)
0	1.2	0.2	0-1	...
1	2.8	0.4		
2	3.6	0.9	2-3	2.5 (1.4-4.5)
3	6.4	0.9		
4	8.0	1.1	4-6	14.9 (8.0-28.0)
5-6	9.7	3.1		4.6 (1.8-11.8)

* JAMA 2001; 285(22):2864-2870. Note: Hazard ratios for the CHADS2 derivation cohort were not published in original study. They are calculated from the data which was presented.

Association between CHADS2 score and ischemic stroke/TIA in patients with coronary heart disease and no baseline AF

Table III

	CHADS2 score				
	0-1 (10 events among 441 participants)	2-3 (22 events among 389 participants)	4-6 (8 events among 86 participants)		
	HR (95% CI)	p-value	HR (95% CI)	p-value	p-value
Unadjusted	1.0	...	2.7 (1.3-5.7)	0.01	4.6 (1.8-11.8) 0.001
Adjusted for age, tobacco use	1.0	...	2.7 (1.3-5.8)	0.01	4.4 (1.7-11.7) 0.003
Adjusted for above plus use of statins, angiotensin inhibitors	1.0	...	2.3 (1.1-5.1)	0.04	4.0 (1.5-10.6) 0.006
Adjusted for above plus use of antiplatelet agents*	1.0	...	2.4 (1.1-5.3)	0.03	4.0 (1.5-10.6) 0.006
Adjusted for above plus creatinine, BMI, antiarrhythmics, MI	1.0	...	2.2 (1.0-4.9)	0.05	3.2 (1.2-8.8) 0.02

TIA = transient ischemic attack, CHD = coronary heart disease, AF = atrial fibrillation, BMI = body mass index, MI = myocardial infarction
CI = confidence interval; HR = hazard ratio

* Aspirin ± clopidogrel