The CHADS2 score predicts ischemic stroke in the absence of atrial fibrillation among subjects with coronary heart disease: Data from the Heart and Soul Study

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

Methods In 916 nonanticoagulated outpatients with stable CHD and no AF by baseline electrocardiogram, we calculated CHADS2 scores (congestive heart failure, hypertension, age ≥75 years, diabetes [1 point each], and prior stroke or 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 5,821 person-years of follow-up, 40 subjects had an ischemic stroke/TIA (rate 0.69/100 person-years, 95% CI 0.50-0.94). Compared with 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 = .03; CHADS2 score 4-6: HR 4.0, 95% CI 1.5-10.6, P = .006). Model discrimination (c-statistic = 0.65) was comparable with 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 with 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. (Am Heart J 2011;162:555-61.)

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 years, diabetes [1 point each], and prior stroke or transient ischemic attack [TIA] [2 points]). 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. Although the CHADS2 score and other similar risk stratification schemes have proven useful in populations with known AF, most (85%) of ischemic strokes occur in individuals without known AF. 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. 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. In brief, between September 2000 and December 2002, 1,024 outpatients with stable CHD were recruited from 2 Veterans Administration medical centers (Palo Alto and San Francisco), 1 university medical center (University of California, San Francisco), and 9 clinics in the Community Health Network of San Francisco. Inclusion criteria were defined as meeting 1 or more of the following: (1) history of myocardial infarction (MI), (2) evidence of at least 50% stenosis in ≥1 coronary vessels on cardiac catheterization, (3) evidence of exercise-induced ischemia by treadmill electrocardiogram (ECG) or nuclear perfusion stress imaging, or (4) a history of coronary revascularization. Exclusion criteria were defined as 1 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 5 years.

Of 1,024 study subjects, we excluded participants with AF or flutter on baseline ECG (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 mm Hg; blood pressure was measured in all participants in the supine position after 5 minutes of rest. This cutpoint was chosen because it was the criterion used by the Atrial Fibrillation Investigator study.10 1 of the 2 classification schemes amalgamated to form the CHADS2 index. Diabetes was defined as self-reported diabetes, receipt of a diabetes medication, or hemoglobin A1c ≥7.0%. Congestive heart failure, prior stroke, and prior 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 proxies were conducted to inquire about interval death or hospitalization. For any reported event, medical records were retrieved and reviewed by 2 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 computed tomography/magnetic resonance 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 >30 seconds and no longer than 24 hours, with rapid evolution of the symptoms to the maximal level of deficit in <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 ECGs were performed on all subjects at the time of enrollment. Electrocardiograms were adjudicated by 2 independent, blinded physicians. In the event of a disagreement, a third adjudicator was consulted. In addition, all ECGs 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). We compared differences in baseline characteristics between patients with low, intermediate, and high CHADS2 scores using χ² tests for categorical variables and 1-way analysis of variance 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 (HRs) 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 multivariable adjustment. To avoid model overfitting with the relatively small number of outcome events, we limited adjustment to 5 covariates based on prior literature and clinical validity: age and current smoking15 (known stroke risk factors), statins14 and antiplatelet agents (proven stroke prevention therapies), and angiotensin inhibitors16,17 (may prevent left atrial [LA] 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 < .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 (STATA Corp, College Station, TX).

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The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the manuscript.

**Results**

Of the 916 nonanticoagulated 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, and 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 fraction (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 β-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 5,821 person-years (rate 0.69/100 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 = .0002) (Table II, Figure 1).

Kaplan-Meier estimates revealed early separation of the event-free survival curves (within the first 6 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 to 1, those with CHADS2 scores of 2 to 3 had 2.7 times the rate of stroke/TIA (\( P = .01 \)), and those with CHADS2 scores of 4 to 6 had 4.6 times the rate (\( P < .001 \)). After adjustment for age, smoking, use of statins, antiplatelet agents, and angiotensin inhibitors, the CHADS2 score remained independently associated with time to stroke/TIA (CHADS2 score 2-3: HR 2.4, \( P = .03 \); CHADS2 score 4-6: HR 4.0, \( P = .006 \)). 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 HRs of patients with CHADS2 scores 2 to 3 were similar to those of the main analysis (subgroup analysis: 2.6 [1.1-5.8], \( P = .03 \), compared with main analysis: 2.7 [1.3-5.7], \( P = .01 \), and there was no interaction (\( P = .73 \)). 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 the Framingham stroke risk score for patients with 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 ≤40% and found no appreciable change in the c-statistic (0.65).

**Discussion**

In 916 patients with CHD who had no known AF at baseline, we found that the CHADS2 score was strongly predictive of ischemic stroke/TIA. Compared with 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. 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). 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).

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

<table>
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<th>CHADS2 score</th>
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<th>Heart &amp; Soul cohort (n = 916)</th>
<th>CHADS2 score</th>
<th>CHADS2 derivation cohort (n = 1733)</th>
<th>Heart &amp; Soul cohort (n = 916)</th>
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<td>0.9</td>
<td>3</td>
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Hazard ratios for the CHADS2 derivation cohort were not published in original study. They are calculated from the data which were presented.


**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.
thrombus formation and stroke. However, even in the absence of AF, patients with heart failure, hypertension, and CHD, and advanced age in patients found to have silent AF than those in whom monitoring did not reveal AF. 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 AF. These investigators suggested using the CHADS2 criteria “backwards” to identify a subset of patients with cryptogenic stroke who may benefit from prolonged event monitoring. 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.

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. However, even in the absence of AF, patients with heart failure, hypertension, and diabetes 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 caused by underlying cardiovascular disease rather than AF itself.

Finally, the CHADS2 risk factors may directly contribute to LA remodeling, a process characterized by dilatation and mechanical dysfunction of the left atrium. These factors may result in blood stasis and confer an increased risk of thromboembolism independent of rhythm. Atrial structural remodeling can be accompanied by wall stretch and electrical remodeling resulting in atrial arrhythmias, with AF being the most common. Diabetes, heart failure, hypertension, and CHD have all been associated with LA remodeling. 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 because 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 because of a greater risk of silent AF or rhythm-independent mechanisms of thromboembolism in this population.

The 2011 American Heart Association/American Stroke Association guidelines for prevention of primary and recurrent stroke recommend risk factor modification of hyperlipidemia, hypertension, and diabetes. 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 most of the 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 mm Hg, hemoglobin A1c 6.0% ± 1.2%). Although stroke prevention guidelines state that opportunistic pulse screening followed by ECG to assess for AF in patients ≥65 years may be useful, this limited ascertainment may be insensitive for sufficient detection of paroxysmal AF.

There are several 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 ECG, it is possible that individuals with known paroxysmal AF who were in sinus rhythm at the time of the baseline ECG 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 ECG could have been misclassified and excluded. However, for paroxysmal AF, any method of AF ascertainment other than continuous ECG 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). Because 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.

Disclosures

None.

References


