Association of CHADS$_2$, CHA$_2$DS$_2$-VASc, and R$_2$CHADS$_2$ Scores With Left Atrial Dysfunction in Patients With Coronary Heart Disease (from the Heart and Soul Study)

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The predictive ability of the CHADS$_2$ index to stratify stroke risk may be mechanistically linked to severity of left atrial (LA) dysfunction. This study investigated the association between the CHADS$_2$ score and LA function. We performed resting transthoracic echocardiography in 970 patients with stable coronary heart disease and normal ejection fraction and calculated baseline LA functional index (LAFI) using a validated formula: (LA emptying fraction $\times$ left ventricular outflow tract velocity time integral)/LA end-systolic volume indexed to body surface area. We performed regression analyses to evaluate the association between risk scores and LAFI. Among 970 subjects, mean CHADS$_2$ was 1.7 ± 1.2. Mean LAFI decreased across tertiles of CHADS$_2$ (42.8 ± 18.1, 37.8 ± 19.1, 36.7 ± 19.4, p < 0.001). After adjustment for age, sex, race, systolic blood pressure, hyperlipidemia, myocardial infarction, revascularization, body mass index, smoking, and alcohol use, high CHADS$_2$ remained associated with the lowest quartile of LAFI (odds ratio 2.34, p = 0.001). In multivariable analysis of component co-morbidities, heart failure, age, and creatinine clearance <60 ml/min were strongly associated with LA dysfunction. For every point increase in CHADS$_2$, the LAFI decreased by 4.0%. Secondary analyses using CHA$_2$DS$_2$-VASc and R$_2$CHADS$_2$ scores replicated these results. Findings were consistent when excluding patients with baseline atrial fibrillation. In conclusion, CHADS$_2$, CHA$_2$DS$_2$-VASc, and R$_2$CHADS$_2$ scores are associated with LA dysfunction, even in patients without baseline atrial fibrillation. These findings merit further study to determine the role of LA dysfunction in cardioembolic stroke and the value of LAFI for risk stratification. Published by Elsevier Inc. (Am J Cardiol 2014;113:1166–1172)

Clinical risk stratification schemes for predicting stroke in patients with atrial fibrillation (AF) are derived from clinical databases and incorporate a series of heterogeneous risk factors. The mechanism by which these clinical characteristics are associated with increased stroke risk is not understood. Among several risk stratification indices, the CHADS$_2$ score is the most commonly used for stratifying stroke risk in patients with AF because it is simple to calculate, well validated, and endorsed in practice guidelines. Incorporation of renal dysfunction into the CHADS$_2$ score (R$_2$CHADS$_2$) has recently been shown to improve discrimination and classification. More recently, CHADS$_2$ and other risk scores have been shown to predict stroke risk even in the absence of AF and with discrimination comparable with risk prediction in AF-only cohorts. These findings have raised the issue as to whether the association with stroke may be mediated by silent AF. The CHADS$_2$ index is composed of several clinical factors independently associated with both structural and electrical remodeling of the left atrium, such as older age, ‘heart failure,’ and hypertension. Left atrial (LA) remodeling and dysfunction are known risk factors for the development of AF and for stroke in patients without AF. Therefore, we hypothesized that CHADS$_2$, CHA$_2$DS$_2$-VASc, and R$_2$CHADS$_2$ scores predict LA dysfunction.

Methods

The Heart and Soul Study is a prospective cohort study of psychosocial factors and health outcomes in patients with coronary heart disease (CHD). Details regarding recruitment methods and study design have been previously published. From September 2000 to December 2002, 1,024 outpatient subjects were recruited from 2 Department of Veterans Affairs medical centers (San Francisco Veterans Affairs Medical Center and Palo Alto Veterans Affairs Medical Center). This study was supported by a Department of Veterans Affairs Merit Award, the American Heart Association National Scientist Development Grant, and a Grant IIR 09-092 from the VA Health Services and Development MERIT Award. The content and opinions expressed are solely the responsibility of the authors and do not necessarily represent the views or policies of the Department of Veterans Affairs.
Medical Center and the Veterans Affairs Palo Alto Health Care System), a university medical center (University of California, San Francisco), and 9 public health clinics (Community Health Network of San Francisco). Patients were eligible to participate if they had at least one of the following: a history of myocardial infarction (MI), angiographic evidence of stenosis of 50% or greater in ≥1 coronary vessels, exercise-induced ischemia by treadmill or nuclear testing, history of coronary revascularization, or diagnosis of CHD by an internist or a cardiologist. Subjects were excluded if they were unable to walk 1 block, had an MI within 6 months of study enrollment, or were planning to move away from the area within 3 years. On enrollment, patients completed a medical history interview, health questionnaire, physical examination, and exercise treadmill test with a stress echocardiogram.

Of 1,024 study subjects, we excluded 41 with missing data required for the calculation of LA functional index (LAFI), 8 with missing data for the calculation of CHADS2 score, and 5 with missing data for the calculation of CHA2DS2-VASc score. The remaining 970 participants are the subjects of this secondary data analysis. The institutional review board approved this study, and all participants provided written and informed consent.

The primary predictors were the CHADS2, CHA2DS2-VASc, and R2CHADS2 indices. CHADS2 score was determined by assigning 1 point each for the presence of congestive heart failure (CHF), hypertension, age ≥75, and diabetes and by assigning 2 points for history of stroke or transient ischemic attack (TIA). CHA2DS2-VASc score was determined by assigning 1 point each for the presence of CHF, hypertension, age 65 to 74 years, diabetes, and vascular disease (peripheral artery disease or MI) and by assigning 2 points for age ≥75, history of stroke, or TIA. R2CHADS2 score was determined by adding 2 points for creatinine clearance <60 ml/min to the CHADS2 score.

Age, sex, race, and medical history were determined from self-report. Height and weight were measured at baseline, and body mass index was calculated (kg/m²). After 5 minutes in the supine position, systolic blood pressure (BP), diastolic BP, and heart rate were measured. Pulse pressure was calculated from resting BP. Baseline 12-lead electrocardiograms were obtained and read by 2 independent, blinded physicians. In the event of a disagreement, a third-blinded adjudicator was consulted. Hypertension was defined by self-report or systolic BP ≥160 mm Hg on baseline evaluation. Diabetes was defined by self-report, use of diabetes medications, or hemoglobin A1C value ≥7.0%. Histories of CHF, vascular disease, MI, stroke, and TIA were determined by self-report. Creatinine clearance was calculated using the Cockcroft-Gault formula.13

The primary outcome was the LAFI. All subjects underwent resting transthoracic echocardiography at baseline. Echocardiograms were performed by 1 of the 2 trained technicians using a standardized protocol. Studies were performed using an Acuson Sequoia ultrasound system (Siemens Medical Solutions, Mountain View, California). Images were obtained with subjects in the left lateral recumbent and supine positions. Images obtained during held inspiration in the standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views were planimetered with a computerized digitization system to determine end-diastolic and end-systolic left ventricle (LV) volumes by the biplane method of disks. End-diastolic and end-systolic LV volumes were determined from the moments of first mitral valve opening and closing. A single experienced reader blinded to clinical information interpreted all studies. The reproducibility of LAFI by this reader has been previously described with Bland-Altman analyses, which revealed no significant variation (intraobserver reproducibility: mean difference 0.0059, 95% confidence interval 0.015 to −0.012; interobserver reproducibility: mean difference 0.0017, 95% confidence interval 0.025 to −0.013).14

The derivation and validation of the LAFI have been previously published.14 The LAFI was calculated as (LA emptying fraction × LV outflow tract-velocity time integral)/LA end-systolic volume index, where LA emptying fraction was defined as (LA end-systolic volume − LA end-systolic volume)/LA end-systolic volume.

From the resting echocardiograms, LV mass was calculated using the truncated-ellipse method15 and indexed to body surface area. The LV ejection fraction (LVEF) was calculated as (LV end-diastolic volume − LV systolic volume)/LV end-diastolic volume.16 Diastolic dysfunction was separated into 3 categories on the basis of mitral flow ratios of peak velocities at early rapid filling and late filling at atrial contraction (E/A ratio) and systolic or diastolic dominant pulmonary venous flow: (1) impaired relaxation, defined as an E/A ratio of ≤0.75 and systolic dominant pulmonary venous flow, (2) pseudonormal, defined as an E/A of 0.75 to 1.5 and diastolic dominant pulmonary venous flow, and (3) restrictive, defined as an E/A of ≥1.5 and diastolic dominant pulmonary venous flow.17 Pulmonary artery systolic pressure was determined from resting echocardiograms as tricuspid regurgitation gradient + right atrial pressure. The tricuspid regurgitation jet was visualized with color flow mapping, and the tricuspid regurgitation gradient was measured with continuous-wave Doppler. We used the modified Bernoulli equation (ΔP = 4v²) to calculate gradients from velocities. Right atrial pressure was estimated from the size and respiratory variation of flow in the inferior vena cava.

Inducible ischemia was determined from exercise treadmill testing. All participants underwent testing according to a standard Bruce protocol and with continuous 12-lead electrocardiogram monitoring. Subjects underwent transthoracic echocardiography immediately before and after exercise. Inducible ischemia was defined as the presence of ≥1 wall motion abnormality at peak exercise.

Participants were divided into tertiles based on their CHADS2, CHA2DS2-VASc, and R2CHADS2 scores. Tertiles of CHADS2 were 0 to 1, 2 to 3, and 4 to 6. Tertiles of CHA2DS2-VASc and R2CHADS2 were 0 to 1, 2 to 3, and ≥4. Differences in baseline characteristics were compared using chi-square tests for categorical variables and one-way analysis of variance for continuous variables. Diastolic dysfunction was analyzed as an ordi national variable, as we have previously found differences in rates of cardiovascular outcomes in these 3 categories of diastolic dysfunction (no diastolic dysfunction, impaired relaxation, pseudonormal/ restrictive).18 Pseudonormal and restrictive groups were combined for analysis because ≤5% of the study sample
had restrictive filling. For each baseline variable, we tested for trend across risk score tertiles. Linear regression was performed to assess the association among CHADS2, CHA2DS2-VASc, and R2CHADS2 (as tertiles and per point increase) as predictors of LAFI. Logistic regression was performed to assess tertiles of CHADS2, CHA2DS2-VASc, and R2CHADS2 as predictors of reduced LAFI, defined as a binary outcome divided at the median. Although we adjusted multivariate regressions for baseline clinical variables with \( p < 0.10 \), we did not include any binary variables of the component co-morbidities of the risk scores because the risk scores are the primary predictor variables. We did include age as a continuous variable, because age is dichotomized or trichotomized in the risk scores. All analyses were conducted using STATA (version 12.2; Stata-Corp, College Station, Texas).
Results

The cohort consisted of 970 subjects (180 women). Baseline characteristics across tertiles of CHADS2 are listed in Table 1. The mean ($\pm$ SD) CHADS2 score was 1.7 $\pm$ 1.2; 464 (48%) had scores of 0 to 1, 407 (42%) had scores of 2 to 3, and 99 (10%) had scores of 4 to 6. There was no significant difference in sex, race, or AF prevalence across tertiles of CHADS2. Compared with those with low (0 to 1) CHADS2 scores, subjects with intermediate (2 to 3) and high (4) scores were more likely to have higher pulse pressure, a history of hyperlipidemia, MI, coronary artery bypass graft, or percutaneous transluminal coronary angioplasty, and less likely to have normal weight or regular alcohol use. Tertiles of CHADS2 were strongly associated with each component of the CHADS2 index (CHF, hypertension, older age, diabetes, and stroke/TIA). Increase in tertile of CHADS2 was strongly associated with increase in LV mass index, diastolic dysfunction, pulmonary artery systolic pressure, and inducible ischemia.

Mean LAFI was 40.1 $\pm$ 18.8. LAFI values across tertiles of CHADS2, CHA2DS2-VASc, and R2CHADS2 are shown in Figure 1. Subjects with baseline AF had lower LAFI compared with those without AF (12.4 vs 41.4). Increase in tertile of all 3 risk indices was significantly associated with decrease in mean LAFI (CHADS2 score 0 to 1: 42.8 $\pm$ 18.1, score 2 to 3: 37.8 $\pm$ 19.1, score 4 to 6: 37.0 $\pm$ 19.4, $p<0.001$; CHA2DS2-VASc score 0 to 1: 43.4 $\pm$ 16.4, score 2 to 3: 41.0 $\pm$ 18.1, score 4 to 6: 37.3 $\pm$ 20.4, $p=0.001$; R2CHADS2 score 0 to 1: 44.0 $\pm$ 17.9, score 2 to 3: 38.8 $\pm$ 17.7, score 4: 35.6 $\pm$ 20.6, $p<0.001$).

Linear regression analyses of tertiles of CHADS2, CHA2DS2-VASc, and R2CHADS2 as predictors of LAFI are listed in Table 2. When compared with the lowest tertile, intermediate and high tertiles of CHADS2 were strongly associated with lower LAFI after adjustment for age, sex, race, systolic BP, hyperlipidemia, MI, revascularization, body mass index, smoking, and alcohol use.

Logistic regression analyses of tertiles of CHADS2, CHA2DS2-VASc, and R2CHADS2 as predictors of LAFI as
Table 4
Logistic regression models of risk score components and lowest quartile of left atrial functional index

<table>
<thead>
<tr>
<th>Risk Score Component</th>
<th>Entire Cohort n = 970</th>
<th>Patients Without AF n = 925</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3.00 (2.08–4.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.99 (0.70–1.40)</td>
<td>0.94</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>1.03 (1.01–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.89 (0.63–1.26)</td>
<td>0.52</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1.06 (0.70–1.62)</td>
<td>0.77</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.85 (0.60–1.29)</td>
<td>0.46</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>1.15 (0.84–1.58)</td>
<td>0.39</td>
</tr>
<tr>
<td>LAFI &lt;60 ml/min</td>
<td>1.62 (1.13–2.32)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CI = confidence interval.


dichotomous outcome separated at the median are listed in Table 3. The multivariable models recapitulate the association between LAFI and tertiles of CHADS2 (score 2 to 3: odds ratio [OR] 0.63, p = 0.002; score 4 to 6: OR 0.57, p = 0.02), CHA2DS2-VASc (score 2 to 3: OR 0.69, p = 0.08; score ≥4: OR 0.46, p = 0.003), and R2CHADS2 (score 2 to 3: OR 0.68, p = 0.02; score ≥4: OR 0.51, p = 0.001), using the 0 to 1 score as the reference group for all 3 scoring systems. The associations among higher CHADS2, CHA2DS2-VASc, and R2CHADS2 with lower mean LAFI were consistent in all models when excluding patients with baseline AF. In logistic regression analyses of risk score components listed in Table 4, CHF (OR 3.00, p < 0.001), age (OR 1.03, p < 0.001), and creatinine clearance <60 ml/min (OR 1.62, p = 0.01) were significantly associated with lowest LAFI quartile after multivariate adjustment for all score components.

For the outcome of the highest tertile of risk score, LAFI had slightly better discrimination than LAVI for CHADS2 (c statistic 0.57 vs 0.52, p = 0.04) but was not statistically different for CHA2DS2-VASc (0.58 vs 0.56, p = not significant) or R2CHADS2 (0.60 vs 0.59, p = not significant). There was no significant difference in discrimination between the CHADS2 and CHA2DS2-VASc for lowest LAFI quartile (c statistic 0.60 vs 0.61, p = not significant). R2CHADS2 demonstrated significantly better discrimination than CHADS2 (c statistic 0.63 vs 0.60, p = 0.01). These results were unchanged when excluding subjects with baseline AF.

Discussion

In a cohort of 970 predominantly male outpatients with stable CHD, we found that higher CHADS2 scores were associated with LA dysfunction as measured by the LAFI. Higher CHADS2 predicts lower LAFI independent of age, sex, smoking, or alcohol use. This association was replicated when employing CHA2DS2-VASc and R2CHADS2 indices.

There are several potential explanations for these observations. The overall correlation between stroke risk and LA dysfunction likely reflects the known association between many of the component co-morbidities of these risk scores to structural and electrical remodeling of the atria. However, a key question is whether LA dysfunction mediates the risk of stroke in patients with high stroke risk scores, irrespective of AF. The current findings suggest 2 potential mechanisms to explain our previous work demonstrating that CHADS2 index predicts risk of stroke in patients without underlying AF. First, for patients in sinus rhythm (SR), the LA dysfunction associated with higher CHADS2 scores may increase risk of subsequent AF, which in turn is the final common pathway for cardioembolism. LA remodeling and dysfunction are well-known risk factors for the development of AF. LA structural remodeling is associated with interstitial atrial fibrosis, which can diminish LA function and forms the substrate for electrical reentry. Dilation of the LA is a known risk factor for incident AF and has been shown to promote electrical instability through shortening of effective refractory period and atrial conduction. Through its association with LA dysfunction, the CHADS2 index may identify patients at high risk of progression to AF.

However, previous observations challenge this hypothesis. The TRENDS study evaluated the association of AF burden before stroke in patients with implantable pacemakers or defibrillators who had daily AF burden measurements through their devices. In a small sample of 40 patients with stroke, 29 (73%) did not have AF or atrial tachycardia in the 30 days before stroke. If even some of these strokes were cardioembolic, it suggests that AF is neither necessary nor sufficient for stroke. Therefore, a second explanation is that LA dysfunction, independent of rhythm, may result in atrial hemostasis and confer a prothrombotic diathesis, resulting in thromboembolic stroke in the absence of AF. LA enlargement is associated with risk of stroke after adjustment for other risk factors including AF. Poor contraction and dilation of the LA appendage (LAA) are associated with LAA thrombosis, even in patients with SR. A study of patients with recent neurologic deficits and LAA thrombi found no significant difference in LAA emptying velocities in subjects with SR compared with AF. Several studies have demonstrated that heart failure and hypertension induce atrial extracellular matrix remodeling that increases the risk of AF but is also associated with a prothrombotic state independent of AF.

We have previously shown that LAFI has superior discrimination to LAVI and LA emptying fraction for incident HF in patients with preserved EF.
Our findings suggest that the CHADS2, CHA2DS2-VASc, and R2CHADS2 indices can provide valuable information regarding LA function regardless of underlying rhythm. Therefore these risk stratification schemes may have utility in the identification of patients at high risk for the development of AF as a consequence of structural and electrical remodeling of the atria. They may additionally predict risk of LA thrombus formation as a result of the hemostatic and prothrombotic state conferred by remodeling atria.

CHADS2 was a stronger predictor of LAFI than was CHA2DS2-VASc. We believe this is a consequence of overall higher risk scores and upward reclassification when using the CHA2DS2-VASc rather than CHADS2 index. The CHA2DS2-VASc index is designed to be more sensitive for stroke, rather than to have improved discrimination, which also incorporates specificity. Therefore more patients are reclassified from low to intermediate or high-risk categories. In our study, 348 subjects had CHA2DS2-VASc scores ≥4, compared 99 with CHADS2 scores ≥4. As a result, upward reclassification with CHA2DS2-VASc may have led to a weakened association with LA dysfunction, particularly in the intermediate (score 2 to 3) tertile. Including MI and peripheral artery disease in the multivariate regression of CHADS2, and LAFI did not affect the association.

The LAFI was selected as the measure of LA function for several reasons. It correlates well with traditional parameters of atrial function, such as the peak A wave velocity of transmural flow in late diastole obtained by pulsed wave Doppler and its velocity time integral and the fraction of atrial contribution from transmural flow. Unlike other measures of LA function, the LAFI may be determined in subjects who are not in SR. It is therefore of great utility in monitoring atrial dysfunction in patients with AF and for comparison to patients with SR. It is decreased in subjects with chronic AF and improves with the restoration and maintenance of SR. It is also easily obtained with small intraobserver and interobserver variabilities.

This study has several limitations. The cross-sectional design of this study does not permit us to establish a temporal relationship or causation between clinical stroke risk and LA dysfunction. Because the majority of subjects in our study were men and all had stable CHD, these results may not be generalizable to women or those without underlying CHD. There may have been residual confounding despite our multivariate adjustment.

Disclosures
The authors have no conflicts of interest to disclose.


