Association of $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_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 × 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_2DS_2-VASc and R_2CHADS_2 scores replicated these results. Findings were consistent when excluding patients with baseline atrial fibrillation. In conclusion, $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_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.[1−3] 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.[4,5] Incorporation of renal dysfunction into the $CHADS_2$ score (R_2CHADS_2) has recently been shown to improve discrimination and classification.[3] 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.[6] 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,[7] heart failure,[8] and hypertension.[9] Left atrial (LA) remodeling and dysfunction are known risk factors for the development of AF[10] and for stroke in patients without AF.[11] Therefore, we hypothesized that $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_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.[12] From September 2000 to December 2002, 1,024 outpatient subjects were recruited from 2 Department of Veterans Affairs medical centers (San Francisco Veterans Affairs

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See page 1171 for disclosure information.

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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 enrolment, or were planning to move away from the area within 3 years. On enrolment, 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 $CHADS_2$ score, and 5 with missing data for the calculation of CHA_2DS_2-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 $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 indices. $CHADS_2$ 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). CHA_2DS_2-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. R_2CHADS_2 score was determined by adding 2 points for creatinine clearance <60 ml/min to the $CHADS_2$ 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/m^2). 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-diastolic volume)/LA end-systolic volume.

From the resting echocardiograms, LV mass was calculated using the truncated-ellipse method[15] 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 ($\Delta P = 4v^2$) 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 $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores. Tertiles of $CHADS_2$ were 0 to 1, 2 to 3, and 4 to 6. Tertiles of CHA_2DS_2-VASc and R_2CHADS_2 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 ordinal 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

Table 1
Baseline characteristics by $CHADS_2$ score

Variable	$CHADS_2$ Score			ANOVA/χ^2	Linear Trend
	0–1 (n = 464)	2–3 (n = 407)	4–6 (n = 99)	p Value	p Value
Age (yrs)	63.7 ± 9.7	68.7 ± 11.4	72.0 ± 10.4	0.02	<0.001
Women	89 (19.2)	78 (19.2)	13 (13)	0.34	0.30
White	296 (63.9)	231 (56.8)	52 (53)	0.14	0.01
African-American	67 (14.5)	77 (18.9)	16 (16)		
Hispanic	37 (8.0)	39 (9.6)	10 (10)		
Asian	52 (11.2)	42 (10.3)	17 (17)		
Other	11 (2.4)	18 (4.4)	4 (4)		
Hypertension	239 (51.5)	370 (90.9)	90 (91)	<0.001	<0.001
Diabetes mellitus	26 (5.6)	186 (45.7)	54 (55)	<0.001	<0.001
Hyperlipidemia	284 (61.5)	285 (70.4)	76 (78)	0.001	<0.001
MI	224 (48.3)	236 (58.0)	68 (69)	<0.001	<0.001
Coronary artery bypass graft/percutaneous transluminal coronary angioplasty	255 (55.0)	250 (61.6)	63 (64)	0.08	0.03
Stroke/TIA	0 (0)	52 (12.8)	88 (89)	<0.001	<0.001
Heart failure	12 (2.6)	115 (28.3)	50 (51)	<0.001	<0.001
Peripheral artery disease	31 (6.7)	36 (8.9)	13 (13)	0.09	0.03
Body mass index (kg/m^2)					
<25	138 (29.7)	98 (24.1)	20 (20)	0.03	0.06
25–29.9	188 (40.5)	160 (39.3)	51 (52)		
≥30	138 (29.7)	149 (36.6)	28 (28)		
Smoking					
Never	155 (33.4)	117 (28.8)	29 (29)	0.01	0.92
Past	201 (43.3)	224 (55.0)	51 (52)		
Current	108 (23.3)	66 (16.2)	19 (19)		
Regular alcohol use	158 (34.1)	103 (25.4)	19 (19)	0.002	<0.001
Systolic BP (mm Hg)	129.5 ± 19.1	136.5 ± 21.6	135.6 ± 22.5	<0.001	<0.001
Diastolic BP (mm Hg)	75.0 ± 10.7	74.6 ± 11.4	73.5 ± 12.7	0.47	0.10
Pulse pressure (mm Hg)	54.4 ± 14.8	61.8 ± 16.8	62.0 ± 16.5	<0.001	<0.001
Heart rate (beats/min)	68.0 ± 12.3	68.6 ± 13.0	69.0 ± 12.4	0.68	0.48
AF	18 (3.9)	19 (4.7)	8 (8)	0.20	0.11
Aspirin	326 (72.1)	312 (76.9)	64 (65)	0.035	0.736
β blocker	244 (54.0)	256 (63.1)	61 (62)	0.022	0.018
ACE-I/ARB	179 (39.6)	258 (63.6)	59 (60)	<0.001	<0.001
Statin	269 (59.5)	276 (68.0)	77 (78)	0.001	<0.001
Loop diuretic	36 (7.8)	90 (22.1)	33 (33)	<0.001	<0.001
Thiazide	47 (10.1)	69 (17.0)	14 (14)	0.013	0.024
LAFI	42.8 ± 18.1	37.8 ± 19.1	36.7 ± 19.4	<0.001	<0.001
Left ventricular mass index (g/m^2)	91.7 ± 23.0	102.8 ± 27.9	106.6 ± 28.6	<0.001	<0.001
Left ventricular ejection fraction (%)	62.6 ± 8.5	60.8 ± 10.7	61.5 ± 9.2	0.02	0.04
LA volume index (ml/m^2)	31.3 ± 10.7	35.0 ± 12.9	34.2 ± 13.3	<0.001	<0.001
Diastolic dysfunction					
None	278 (68.5)	204 (55.9)	47 (53)	0.002	<0.001
Impaired relaxation	91 (22.4)	104 (28.5)	29 (33)		
Pseudonormal/restrictive	37 (9.1)	57 (15.6)	12 (14)		
Pulmonary artery systolic pressure (mm Hg)	29.9 ± 7.5	33.7 ± 9.8	33.9 ± 8.7	<0.001	<0.001
Inducible ischemia present	80 (18.2)	111 (30.3)	28 (34)	<0.001	<0.001

Results are presented as mean ± SD or n (%).
Hypertension is defined by self-report or systolic BP ≥160 mm Hg on baseline evaluation. Hyperlipidemia is defined by self-report.
ACE-I = angiotensin-converting enzyme inhibitor; ANOVA = analysis of variance; ARB = angiotensin II receptor blocker.

had restrictive filling. For each baseline variable, we tested for trend across risk score tertiles. Linear regression was performed to assess the association among $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 (as tertiles and per point increase) as predictors of LAFI. Logistic regression was performed to assess tertiles of $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 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; StataCorp, College Station, Texas).

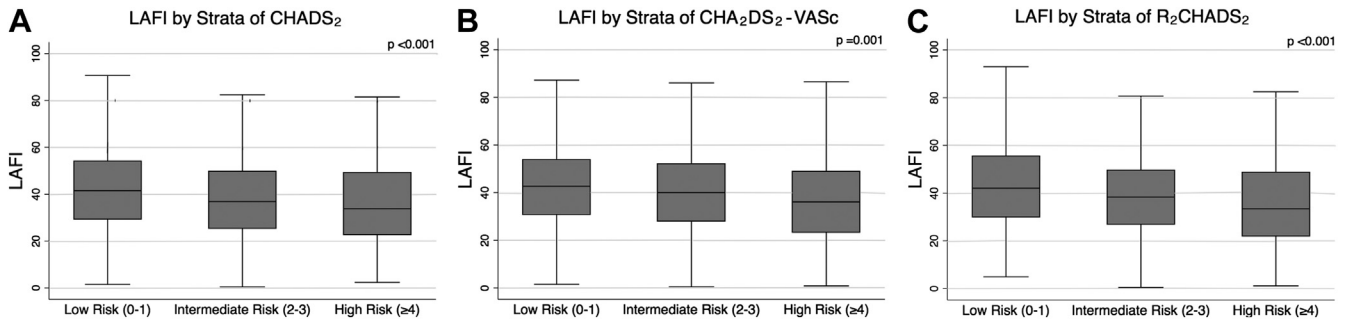

Figure 1. LAFI scores by tertiles of $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores. LAFI score significantly decreased across all strata of (*A*) $CHADS_2$, (*B*) CHA_2DS_2-VASc, and (*C*) R_2CHADS_2 risk scores.

Table 2
Linear regression models of strata of risk scores and left atrial functional index

	Unadjusted		Adjusted*	
	β (SE)	p Value	β (SE)	p Value
$CHADS_2$				
2−3	−4.96 (1.27)	<0.001	−4.10 (1.33)	0.002
4−6	−6.10 (2.07)	0.003	−5.24 (2.17)	0.02
Per point increase	−1.88 (0.49)	<0.001	−1.59 (0.53)	0.003
CHA_2DS_2-VASc				
2−3	−2.40 (1.74)	0.17	−2.66 (1.89)	0.16
≥4	−6.10 (1.81)	0.001	−5.58 (2.35)	0.02
Per point increase	−1.41 (0.38)	<0.001	−1.22 (0.51)	0.02
R_2CHADS_2				
2−3	−5.21 (1.37)	<0.001	−4.57 (1.42)	0.001
≥4	−8.39 (1.54)	<0.001	−6.69 (1.77)	<0.001
Per point increase	−1.85 (0.35)	<0.001	−1.50 (0.40)	<0.001

0 to 1 score category used as reference group for all 3 scoring systems.
SE = standard error.
* Adjusted for age, sex, race, systolic BP, hyperlipidemia, MI, revascularization, body mass index, smoking, and alcohol use.

Table 3
Logistic regression models of strata of risk scores and left atrial functional index category

	Unadjusted		Adjusted*	
	OR (95% CI)	p Value	OR (95% CI)	p Value
$CHADS_2$				
2−3	0.58 (0.45−0.76)	<0.001	0.63 (0.47−0.85)	0.002
4−6	0.50 (0.32−0.78)	0.002	0.57 (0.35−0.92)	0.02
CHA_2DS_2-VASc				
2−3	0.70 (0.48−1.01)	0.06	0.69 (0.45−1.05)	0.08
≥4	0.45 (0.31−0.66)	<0.001	0.46 (0.27−0.77)	0.003
R_2CHADS_2				
2−3	0.64 (0.48−0.86)	0.003	0.68 (0.50−0.94)	0.02
≥4	0.42 (0.30−0.59)	<0.001	0.51 (0.34−0.76)	0.001

LAFI defined as dichotomous outcome divided at median.
0 to 1 score category used as reference group for all 3 scoring systems.
CI = confidence interval.
* Adjusted for age, sex, race, systolic BP, hyperlipidemia, MI, revascularization, body mass index, smoking, and alcohol use.

Results

The cohort consisted of 970 subjects (180 women). Baseline characteristics across tertiles of $CHADS_2$ are listed in Table 1. The mean (±SD) $CHADS_2$ score was 1.7 ± 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 $CHADS_2$. Compared with those with low (0 to 1) $CHADS_2$ 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 $CHADS_2$ were strongly associated with each component of the $CHADS_2$ index (CHF, hypertension, older age, diabetes, and stroke/TIA). Increase in tertile of $CHADS_2$ was strongly associated with increase in LV mass index, diastolic dysfunction, pulmonary artery systolic pressure, and inducible ischemia.

Mean LAFI was 40.1 ± 18.8. LAFI values across tertiles of $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 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 ($CHADS_2$ score 0 to 1: 42.8 ± 18.1, score 2 to 3: 37.8 ± 19.1, score 4 to 6: 36.7 ± 19.4, $p < 0.001$; CHA_2DS_2-VASc score 0 to 1: 43.4 ± 16.4, score 2 to 3: 41.0 ± 18.1, score ≥4: 37.3 ± 20.4, $p = 0.001$; R_2CHADS_2 score 0 to 1: 44.0 ± 17.9, score 2 to 3: 38.8 ± 17.7, score ≥4: 35.6 ± 20.6, $p < 0.001$).

Linear regression analyses of tertiles of $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 as predictors of LAFI are listed in Table 2. When compared with the lowest tertile, intermediate and high tertiles of $CHADS_2$ were strongly associated with lower LAFI after adjustment for age, sex, race, systolic BP, hyperlipidemia, MI, revascularization, body mass index, smoking, and alcohol use (score 2 to 3: beta −4.10, $p = 0.002$, score 4 to 6: beta −5.24, $p = 0.02$). There were similar associations between tertiles of CHA_2DS_2-VASc (score 2 to 3: beta −2.66, $p = 0.16$; score ≥4: beta −5.58, $p = 0.02$) and R_2CHADS_2 (score 2 to 3: beta −4.57, $p = 0.001$; score ≥4: beta −6.69, $p < 0.001$) with LAFI. Linear regression analyses of risk scores as continuous predictors of LAFI are listed in Table 2. For every 1 point increase in $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores, the LAFI decreased by 4.0%, 3.1%, and 3.8%, respectively.

Logistic regression analyses of tertiles of $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 as predictors of LAFI as

Table 4
Logistic regression models of risk score components and lowest quartile of left atrial functional index

Risk Score Component	Entire Cohort n = 970		Patients Without AF n = 925	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Heart failure	3.00 (2.08−4.33)	<0.001	2.85 (1.93−4.20)	<0.001
Hypertension	0.99 (0.70−1.40)	0.94	1.13 (0.77−1.66)	0.52
Age (yrs)	1.03 (1.01−1.05)	<0.001	1.02 (1.01−1.04)	0.01
Diabetes mellitus	0.89 (0.63−1.26)	0.52	0.89 (0.62−1.30)	0.56
Stroke	1.06 (0.70−1.62)	0.77	1.05 (0.67−1.64)	0.85
Female sex	0.85 (0.60−1.29)	0.46	1.01 (0.66−1.54)	0.96
Vascular disease	1.15 (0.84−1.58)	0.39	1.21 (0.86−1.71)	0.27
Creatinine clearance <60 ml/min	1.62 (1.13−2.32)	0.01	1.59 (1.08−2.35)	0.02

CI = confidence interval.

a dichotomous outcome separated at the median are listed in Table 3. The multivariate models recapitulate the association between LAFI and tertiles of $CHADS_2$ (score 2 to 3: odds ratio [OR] 0.63, p = 0.002; score 4 to 6: OR 0.57, p = 0.02), CHA_2DS_2-VASc (score 2 to 3: OR 0.69, p = 0.08; score ≥4: OR 0.46, p = 0.003), and R_2CHADS_2 (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 $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 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 $CHADS_2$ (c statistic 0.57 vs 0.52, p = 0.04) but was not statistically different for CHA_2DS_2-VASc (0.58 vs 0.56, p = not significant) or R_2CHADS_2 (0.60 vs 0.59, p = not significant). There was no significant difference in discrimination between the $CHADS_2$ and CHA_2DS_2-VASc for lowest LAFI quartile (c statistic 0.60 vs 0.61, p = not significant). R_2CHADS_2 demonstrated significantly better discrimination than $CHADS_2$ (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 $CHADS_2$ scores were associated with LA dysfunction as measured by the LAFI. Higher $CHADS_2$ predicts lower LAFI independent of age, sex, smoking, or alcohol use. This association was replicated when employing CHA_2DS_2-VASc and R_2CHADS_2 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.[8,9] 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 $CHADS_2$ index predicts risk of stroke in patients without underlying AF.[6] First, for patients in sinus rhythm (SR), the LA dysfunction associated with higher $CHADS_2$ 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.[10] LA structural remodeling is associated with interstitial atrial fibrosis, which can diminish LA function[19] and forms the substrate for electrical reentry.[20] Dilation of the LA is a known risk factor for incident AF[10,21] and has been shown to promote electrical instability through shortening of effective refractory period and atrial conduction.[22,23] Through its association with LA dysfunction, the $CHADS_2$ 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.[24] 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.[11,22] Poor contraction and dilation of the LA appendage (LAA) are associated with LAA thrombosis, even in patients with SR.[25] 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.[26] Several studies have demonstrated that heart failure and hypertension induce atrial extracellular matrix remodeling that increases the risk of AF[27] but is also associated with a prothrombotic state independent of AF.[28] We have previously shown that LAFI has superior discrimination to LAVI and LA emptying fraction for incident HF in patients with preserved EF.[29]

Our findings suggest that the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 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.

$CHADS_2$ was a stronger predictor of LAFI than was CHA_2DS_2-VASc. We believe this is a consequence of overall higher risk scores and upward reclassification when using the CHA_2DS_2-VASc rather than $CHADS_2$ index. The CHA_2DS_2-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 CHA_2DS_2-VASc scores $\geq$4, compared 99 with $CHADS_2$ scores $\geq$4. As a result, upward reclassification with CHA_2DS_2-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 $CHADS_2$ 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 transmitral flow in late diastole obtained by pulsed wave Doppler and its velocity time integral[30] and the fraction of atrial contribution from transmitral flow.[30] 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.[14] It is also easily obtained with small intraobserver and interobserver variabilities.[14]

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.

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