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Association of Left Atrial Fibrosis Detected by Delayed-Enhancement Magnetic Resonance Imaging and the Risk of Stroke in Patients With Atrial Fibrillation

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Objectives This study tried to determine the association between left atrial (LA) fibrosis, detected using delayed-enhanced magnetic resonance imaging (DE-MRI), and the $CHADS_2$ score (point system based on individual clinical risk factors including congestive heart failure, hypertension, age, diabetes, and prior stroke) variables, specifically stroke.

Background In patients with atrial fibrillation (AF), conventional markers for the risk of stroke base their higher predictive effect on clinical features, particularly previous stroke history, and not individual LA pathophysiological properties. We aimed to determine the association between LA fibrosis, detected using DE-MRI, and the $CHADS_2$ score variables, specifically stroke.

Methods Patients with AF who presented to the AF clinic and received a DE-MRI of the LA were evaluated. Their risk factor profiles, including a $CHADS_2$ score, were catalogued. The degree of LA fibrosis was determined as a percentage of the LA area. Any history of previous strokes, warfarin use, or cerebrovascular disease was recorded.

Results A total of 387 patients, having a mean age of 65 ± 12 years, 36.8% female, were included in this study. A history of previous stroke was present in 36 (9.3%) patients. Those patients with previous strokes had a significantly higher percentage of LA fibrosis (24.4 ± 12.4% vs. 16.2 ± 9.9%, $p < 0.01$). A larger amount of LA fibrosis was also seen in those patients with a higher $CHADS_2$ score (≥2: 18.7 ± 11.4 vs. <2: 14.7 ± 9.2, $p < 0.01$). A logistic regression analysis of all variables except strokes (CHAD score) demonstrated that LA fibrosis independently predicted cerebrovascular events ($p = 0.002$) and significantly increased the predictive performance of the score (area under the curve = 0.77).

Conclusions Our preliminary, multicenter results suggest DE-MRI–based detection of LA fibrosis is independently associated with prior history of strokes. We propose that the amount of DE-MRI–determined LA fibrosis could represent a marker for stroke and a possible therapeutic target with potential applicability for clinical treatment for patients with AF. (J Am Coll Cardiol 2011;57:831–8) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is associated with significant morbidity and mortality, primarily due to the increased risk of ischemic stroke (1). Patients who suffer from this arrhythmia have a 3% to 4% absolute risk of stroke per year; however, this risk varies significantly based on individual clinical features (2). Antithrombotic therapy with the vitamin K antagonist warfarin is highly effective in preventing stroke and improving survival (3,4). However, such therapies are associated with life-threatening hemorrhage and require intensive dosage monitoring (5–7). In an attempt to spare low-risk AF patients from the cost, inconvenience, and risk of warfarin therapy, risk stratification schemes have been developed to tailor anticoagulation therapy to the patient's risk (8,9).

Currently, several risk stratification schemes have been validated and are clinically well established (2,9,10). The

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Abbreviations and Acronyms

AF = atrial fibrillation
DE-MRI = delayed-enhancement magnetic resonance imaging
LA = left atrium/atrial
MRI = magnetic resonance imaging
TI = inversion time
3D = 3-dimensional

$CHADS_2$ index is the most widely used model and was developed using stroke risk data from the National Atrial Fibrillation Registry. It uses a point system based on individual clinical risk factors including congestive heart failure, hypertension, age, diabetes, and prior stroke. This index is a valuable tool when predicting cerebrovascular events in high-risk patients (9,11); however, clinicians rely more heavily on clinical judgment when predicting thromboembolic risk in moderate-risk patients, a substantial portion of the AF population (8). Identification of novel, independent risk factors may supplement existing tools to help guide clinician judgment in better allocating anticoagulation therapeutic strategies, especially with moderate-risk AF patients.

It is well established that AF results in remodeling of the left atrium (LA) structure, including the deposition of highly current-resistant fibrotic tissue. Such deposits correspond to a low voltage response as well as other changes in the electrophysiological properties of the LA substrate (12–14). In spite of this, most AF-thromboembolic risk factors are based on clinical features rather than individual LA pathophysiological properties. In part, this is because analyzing the LA substrate has been challenging. However, new high temporal and spatial resolution magnetic resonance imaging (MRI) allows for improved visualization and characterization of the thin AF wall (15). In addition, by using a novel MRI sequence with delayed-enhancement (DE-MRI), it has become possible to detect and quantify LA structural remodeling as a possible determinant of fibrosis (16). Nevertheless, it has been unclear how the degree of this substrate change seen in AF patients relates to stroke and the current risk stratification schemes.

In this study, we aim to ascertain the association of LA fibrosis and its association with the $CHADS_2$ score variables and stroke prediction. Furthermore, we provide preliminary evidence that the physiological features of the LA could be used, in addition to clinical features, when identifying stroke risk in patients. Our goal is to provide the groundwork for further prospective studies validating the diagnostic use of LA substrate change, as well as identifying other potentially useful parameters in the development of future risk stratification schemes.

Methods

Study design. A cross-sectional analysis was performed addressing the association between the occurrence of strokes, the accompanying risk factors, and the amount of LA structural remodeling determined by DE-MRI in a patient undergoing pulmonary vein isolation for AF.

Study population. Patients, who presented to the University of Utah in Salt Lake City, Utah, and Clinical Center Coburg, Coburg, Germany, were evaluated prospectively and consecutively enrolled. All patients underwent DE-MRI before pulmonary vein isolation and were included as part of the institutional review board–approved AF research registry at the University of Utah. The patients' clinical, AF, and $CHADS_2$ score characteristics were determined by clinical examination and systematic chart review. Patients with cardiac rhythm devices, renal dysfunction (glomerular filtration rate <60 ml/min), severe claustrophobia, or other contraindications for MRI were excluded from the study. Also, patients with a history of stenotic cerebrovascular disease were excluded from the analysis. A total of 387 patients met these criteria and were included in the final analysis. A history of stroke was documented for 36 individuals (9.3%) within the population. To validate the occurrence of stroke in the included patients, we studied their previous medical records. The clinical demographics of the patients are represented in Table 1.

The study protocol was approved by our institutional review board and was Health Insurance Portability and Accountability Act (HIPAA)–compliant. Patients were classified as having either paroxysmal or persistent AF. Paroxysmal AF was defined as any AF episodes that self-terminated within 7 days. Persistent AF was defined as

Table 1 Clinical Characteristics According to Stroke History

	Stroke (n = 36)	No Stroke (n = 351)	p Value
Age, yrs	64 ± 12	70 ± 7	<0.001
AF type			
Paroxysmal	15 (41.7%)	172 (49%)	NS
Persistent	21 (58.3%)	179 (51%)	NS
Warfarin use	25 (69.4%)	208 (59%)	NS
Female	23 (63.8%)	118 (33.6%)	<0.001
Diabetes mellitus	3 (8.3%)	47 (13.4%)	NS
Hypertension	24 (66.7%)	204 (58%)	NS
Congestive heart failure	2 (5.5%)	36 (10.2%)	NS
Age >75 yrs	8 (22.2%)	65 (18.5%)	NS
Risk score excluding strokes	1.02 ± 0.65	1 ± 0.9	NS
$CHADS_2$ score	3.02 ± 0.65	1 ± 0.9	<0.001
High risk: ≥2	36 (100%)	90 (25.6%)	NS
Moderate risk: 1	—	146 (41.6%)	—
Low risk: 0	—	115 (32.8%)	—
LA structural remodeling, %	24.4 ± 12.4	16.1 ± 9.8	<0.001
LA remodeling stage	2.4 ± 1.1	3.2 ± 0.9	<0.001
Stage I: <8.5% (Q1)	1 (2.8%)	96 (27.3%)	<0.001
Stage II: 8.6%–16% (Q2)	9 (25%)	88 (25.1%)	—
Stage III: 16.1%–21% (Q3)	7 (19.4%)	89 (25.3%)	—
Stage IV: >21.1% (Q4)	19 (52.8%)	78 (22.3%)	—
Time from stroke to DE-MRI scan, days	682 ± 265	—	—

AF = atrial fibrillation; $CHADS_2$ = point system based on individual clinical risk factors including congestive heart failure, hypertension, age, diabetes, and prior stroke; DE = delayed-enhancement; LA = left atria; MRI = magnetic resonance imaging; NS = not significant; Q = quartile.

an episode of AF that lasted longer than 7 days and required medical or electrical cardioversion for termination.

DE-MRI. DE-MRI was obtained to assess the extent of LA structural remodeling or nonviable tissue using previously described methods (16). Briefly, all studies were performed on either a 1.5-T Avanto or 3-T Verio clinical scanner (Siemens Medical Solutions, Erlangen, Germany) using a total imaging matrix phased-array receiver coil. The scan was acquired, 15 min following contrast agent injection (0.1 mmol/kg, Multihance, Bracco Diagnostic Inc., Princeton, New Jersey), using a 3-dimensional (3D) inversion recovery, respiration navigated, electrocardiogram-gated, gradient echo pulse sequence. We performed a 3D-gated and respiratory-navigated DE scan on the LA in each patient. To achieve the best possible images of the LA, the images of the LA were acquired during the stationary phase, atrial diastole, and within each R-R interval, the views have same slice-selective encoding (same Kz) and different phase encoding (different Ky). Typical acquisition parameters were: free-breathing using navigator gating, a transverse imaging volume with voxel size = 1.25 × 1.25 × 2.5 mm (reconstructed to 0.625 × 0.625 × 1.25 mm), inversion time (TI) = 270 to 310 ms, GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisition) with r = 2 and 46 reference lines. The TI value for the 3D DE scan was chosen from TI scout. The optimal TI was determined in a similar fashion as is used for standard myocardial viability studies with the TI set to null normal left ventricular myocardium. The time between successive radiofrequency pulses (repetition time) and the time between radiofrequency pulse and measurement (echo time) are imaging parameters that determine the strength of the signal; in our study, the repetition time/echo time ratio was 5.4:2.3 ms. Electrocardiogram-gating was used to acquire a small subset of phase encoding views during the diastolic phase of the LA cardiac cycle. The time interval between the R-peak of the electrocardiogram and the start of data acquisition was defined using the cine images of the LA with the sequence optimized for LA diastole in the 2 different patient groups: those in AF and those in regular, sinus rhythm. Data acquisition during LA diastole has been optimized for each of these types of rhythms based on extensive previous patient studies by determining the optimal percent of the R-R interval and acquisition window for data collection for each rhythm (AF and normal sinus rhythm). Fat saturation was used to suppress any fat signal. The echo time of the scan (2.3 ms) was chosen such that fat and water are out of phase and the signal intensity of partial volume fat-tissue voxels was reduced; this allowed improved delineation of the LA wall boundary. Typical scan time for the DE-MRI study was 5 to 10 min depending on subject respiration and heart rate. In addition to the DE-MRI scan, contrast-enhanced MR angiography of the LA and pulmonary veins was performed; this imaging modality provided initial 3D visualization of the LA and was used to assess contrast consistency.

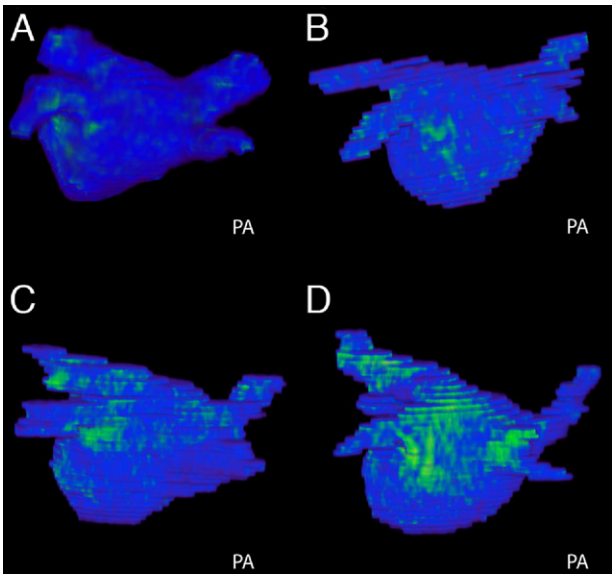

Figure 1 **Staging of DE-MRI LA Structural Remodeling Quartile Distribution**

Delayed-enhancement magnetic resonance images representing posteroanterior views of the left atrium in patients with Stage (quartile) I (**A**: 2.7% enhancement), Stage II (**B:** 10.2% enhancement), Stage III (**C:** 19.4%), and Stage IV (**D:** 38.4% enhancement). Left atrial enhancement is represented as **green** areas. Color Look-Up Table mask has been applied to the rendered images to better differentiate enhanced and nonenhanced tissue. DE-MRI = Delayed-enhancement magnetic resonance imaging; LA = left atrial; PA = posteranterior.

Quantitative analysis of LA remodeling. Quantification of LA remodeling was obtained using previously described methods (16). In all DE-MRI images, the epicardial and endocardial LA borders were manually contoured with image display and analysis software in Seg3D (Scientific Computing and Imaging Institute, Salt Lake City, Utah). The relative extent of contrast enhancement within the LA wall was quantified using a threshold-based software algorithm using the pixel intensity distribution of the healthy and nonviable myocardial regions using Marrek, Inc. segmentation and quantification software (Marrek, Inc., Salt Lake City, Utah).

Patients were assigned to 1 of 4 groups based on quartiles (Q) applied to the DE-MRI LA structural remodeling distribution. The quartiles were determined and defined to be the 25th, 50th, and 75th percentile limits of the percentage of LA wall enhancement distribution. Patients with Stage I (Q1) remodeling were defined as those with <8.5% enhancement, Stage II (Q2) as 8.6% to 16%, Stage III (Q3) as 16.1% to 21%, and Stage IV (Q4) as >21.1% (Fig. 1).

Qualitative analysis of LA remodeling. Qualitative confirmation of the percentage of enhancement was performed for all MRI scans using the 3D visualization capabilities of Corview (Marrek, Inc., Salt Lake City, Utah). A maximum intensity projection was used to assess contrast consistency, followed by ray cast volume rendering with an opacity-weighted linear table for analysis of the pre-ablation images.

Statistical analysis. Normal continuous variables are presented as the mean ± SD. A 1-way analysis of variance was used to test for statistical significance; statistical significance was further addressed using the Tukey-Kramer method to correct for multiple comparisons. Categorical variables are presented as the number and percentage of total. Pearson chi-square test was used to assess the statistical significance. Univariate and multivariate logistic regression analyses were performed to evaluate the association between clinical variables and strokes. Differences were considered significant with a p value of less than 0.05. All statistical analysis was performed using JMP Pro (SAS Institute Inc., Cary, North Carolina).

Results

Patient population. A total of 387 patients were included in our analysis. Five patients with a known history of stenotic cerebrovascular disease were excluded from the study. A history of stroke was documented for 36 (9.3%) patients within the population. Patients with a documented history of stroke were older and predominantly women (63.8%). There were no significant differences between the 2 patient groups regarding the type of AF, diabetes, congestive heart failure, and hypertension.

The LA size and volume were included in the steps of model building and were found to be not significant predictors ($p > 0.1$). Once LA fibrosis was determined as a percentage of the LA area, it was included in the model and adjustment for LA dimensions is assumed.

LA fibrosis and stroke. Patients who experienced a prior stroke had a significantly higher percentage of LA fibrosis than those without history of a previous stroke (24.4 ± 12.4% vs. 16.1 ± 9.8%, $p \leq 0.001$) (Fig. 2). Patients with Stage I remodeling experienced very low rates of thromboembolism (2.8%). In comparison, 52.8% of patients with extensive remodeling (Stage IV) had experienced an ischemic event. Figure 3 demonstrates the prevalence of stroke among the various levels of LA structural remodeling. No specific correlation was found between the time of stroke to DE-MRI scan and the amount of LA fibrosis ($r^2 = 0.002$, $p = 0.76$).

LA fibrosis and $CHADS_2$ index. Those AF patients with higher risk factor profiles for stroke ($CHADS_2 \geq 2$) had a significantly larger amount of LA fibrosis when compared to those patients who had either a moderate or low risk profile (Table 2). Analysis of the risk factor profile based on the pre-determined DE-MRI staging system showed that those patients with Stage IV remodeling had a significantly higher $CHADS_2$ score than those patients with a lesser degree of remodeling (Table 3).

LA fibrosis and clinical demographics. Atrial fibrillation patients with more pronounced structural remodeling generally exhibited persistent rather than paroxysmal AF. As expected, warfarin use was more frequent in the moderate- and high-risk groups but was not associated with a lower prevalence of stroke. A total of 233 patients had documented persistent AF, 143 (71.5%) of whom were on warfarin. In the remaining 154 patients with paroxysmal AF, 90 (48.1%) were on warfarin. The large majority of patients who were not on warfarin had documented use of a daily aspirin. Therapeutic ranges of patients on warfarin were unavailable and therefore not reported.

Age and LA remodeling did not appear to correlate linearly ($r^2 = 0.018$). However, those older than 75 years of age had significantly higher LA fibrosis than younger AF patients did (19.6 ± 11.9% vs. 16.3 ± 9.8%, $p = 0.029$). Further analysis by age groups demonstrated a trend toward larger amounts of structural remodeling (analysis of variance, $p = 0.09$).

Multivariate analysis. Utilizing univariate and multivariate logistic regression analyses that controlled for significantly different comorbidities and known stroke predictors, excluding stroke (CHAD), DE-MRI–quantified LA structural remodeling was independently associated with strokes

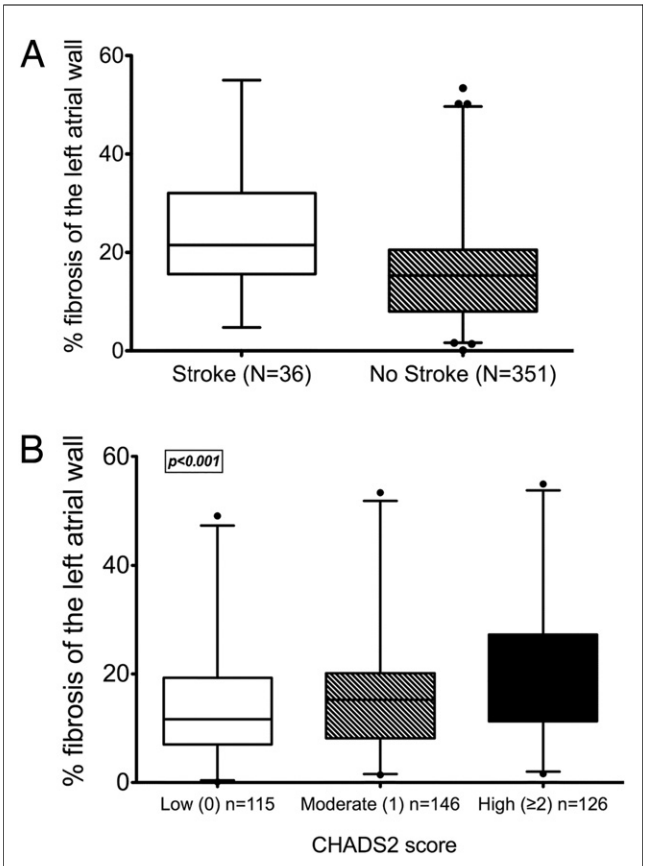

Figure 2 Relationship of LA Structural Remodeling and Stroke

Delayed-enhancement magnetic resonance imaging left atrial structural remodeling according to the history of strokes **(A)** and risk profile **(B).** Patients who experienced a prior stroke had a significantly higher percentage of LA fibrosis compared to those without history of a previous stroke (24.4 ± 12.4% vs. 16.1 ± 9.8%, $p \leq 0.001$). $CHADS_2$ = point system based on individual clinical risk factors including congestive heart failure, hypertension, age, diabetes, and prior stroke; other abbreviation as in Figure 1.

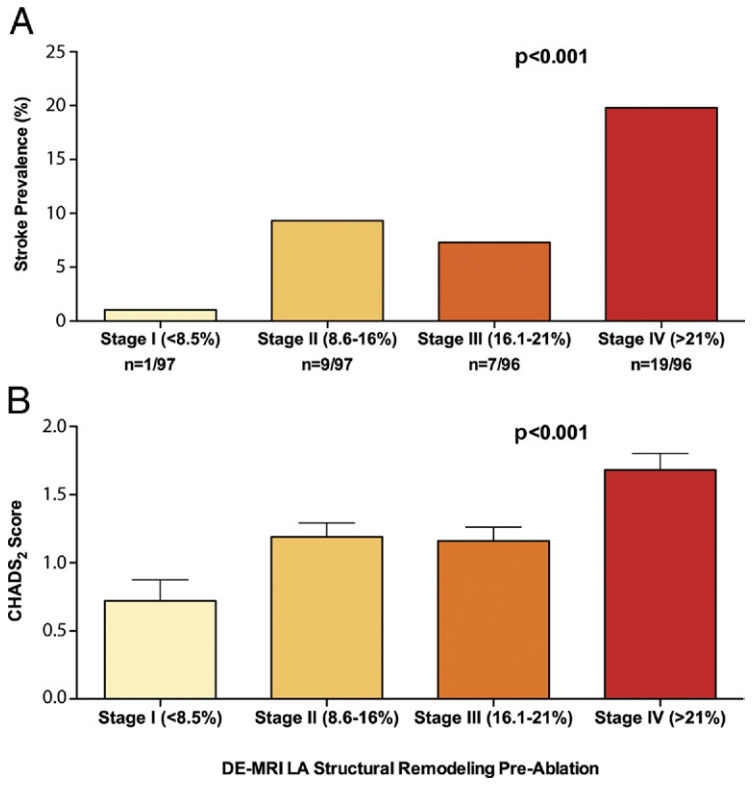

Figure 3 Incidence of Stroke Among the Various Levels of LA Structural Remodeling

History of stroke **(A)** and risk score prevalence for stroke **(B)** according the different delayed-enhancement magnetic resonance imaging left atrial structural remodeling stages (quartiles). Atrial fibrillation patients with higher risk factor profiles for stroke ($CHADS_2$ ≥2) had a significantly larger amount of left atrial fibrosis when compared to those patients who had either a moderate- or low-risk profile (see also Table 2). Abbreviations as in Figures 1 and 2.

Table 2 Characteristics According to Stroke Risk Profile

	Low Risk (n = 115)	Moderate Risk (n = 146)	High Risk (n = 126)	p Value
Age, yrs	59.6 ± 11.3	63.7 ± 11.2	70.8 ± 11.1	<0.001
AF type				
Paroxysmal	60 (52.8%)	77 (52.7%)	50 (39.7%)	0.06
Persistent	55 (47.8%)	69 (47.3%)	76 (60.3%)	0.06
Warfarin use	57 (49.6%)	89 (61%)	87 (69%)	0.008
Female	34 (29.6%)	41 (28.1%)	66 (52.4%)	0.04
Diabetes mellitus	0 (0%)	7 (4.8%)	43 (34%)	<0.001
Hypertension	0 (0%)	115 (78.8%)	113 (89.7%)	<0.001
Congestive heart failure	0 (0%)	7 (4.8%)	31 (24.6%)	<0.001
Age >75 years	0 (0%)	17 (11.6%)	56 (44.4%)	<0.001
Risk score excluding strokes	0 ± 0	1 ± 0	1.93 ± 0.80	<0.001
Stroke	0 ± 0	0 (0%)	36 (23.4%)	NS
Risk score including strokes	0 ± 0	1 ± 0	2.50 ± 0.65	<0.001
LA structural remodeling, %	13.91 ± 8.77	15.99 ± 9.71	20.74 ± 11.32	<0.001
LA remodeling stage	2.16 ± 1.11	2.40 ± 1.07	2.91 ± 1.07	<0.001
Stage I: <8.5% (Q1)	44 (38.3%)	38 (26%)	15 (11.9%)	<0.001
Stage II: 8.6%–16% (Q2)	27 (23.5%)	38 (26%)	32 (25.4%)	—
Stage III: 16.1%–21% (Q3)	25 (21.7%)	43 (29.5%)	28 (22.2%)	—
Stage IV: >21.1% (Q4)	19 (16.5%)	27 (18.5%)	51 (40.5%)	—

Abbreviations as in Table 1.

Table 3 Characteristics According to DE-MRI LA Structural Remodeling Stage

	Stage I (Q1) (<8.5%) n = 97	Stage II (Q2) (8.6%–16%) n = 97	Stage III (Q3) (16.1%–21%) n = 96	Stage IV (Q4) (>21.1%) n = 96	p Value
Age, yrs	62.3 ± 12	66.2 ± 12	64.7 ± 11.2	65.9 ± 12.6	NS
AF type					
Paroxysmal	56 (57.7%)	52 (53.6%)	44 (45.8%)	25 (36.1%)	0.01
Persistent	41 (42.3%)	45 (46.7%)	52 (54.2%)	62 (63.9%)	0.01
Warfarin use	53 (54.7%)	62 (63.9%)	58 (60.4%)	60 (61.9%)	NS
Female	29 (70.1%)	34 (35%)	32 (33.3%)	46 (47.4%)	NS
Diabetes mellitus	6 (6.2%)	11 (11.3%)	16 (16.7%)	17 (17.5%)	NS
Hypertension	46 (47.4%)	59 (60.8%)	56 (58.3%)	67 (69.1%)	0.02
Congestive heart failure	3 (3.1%)	8 (8.2%)	9 (9.4%)	18 (18.6%)	0.003
Age >75 years	13 (13.4%)	20 (20.6%)	17 (17.7%)	23 (23.7%)	NS
Strokes	1 (1%)	9 (9.3%)	7 (7.3%)	19 (19.6%)	<0.001
Risk score excluding strokes	0.70 ± 0.73	1.01 ± 0.87	1.02 ± 0.88	1.28 ± 0.95	<0.001
$CHADS_2$ score	0.72 ± 0.77	1.19 ± 1.02	1.16 ± 1	1.68 ± 1.2	<0.001
High risk: ≥2	15 (11.9%)	32 (25.4%)	28 (22.2%)	51 (40.5%)	<0.001
Moderate risk: 1	38 (26%)	38 (26%)	43 (29.5%)	27 (18.5%)	—
Low risk: 0	44 (38.3%)	27 (23.5%)	25 (21.7%)	19 (16.5%)	—
LA structural remodeling, %	6.1 ± 1.9	12.1 ± 2.4	18.5 ± 1.5	30.9 ± 8.8	<0.001

Abbreviations as in Table 1.

(Table 4). Furthermore, patients with Stage I remodeling had a protective odds ratio for strokes and those patients with Stage IV remodeling had nearly 4 times the odds to have a stroke.

In the univariate model, the odds ratios are Q4 versus Q1 = 23.4 ($p < 0.01$), Q3 versus Q1 = 7.5 ($p = 0.02$), Q2 versus Q1 = 9.8 ($p = 0.04$).

Combining clinical with MRI data. When evaluating the conventional clinical predictors of stroke excluding stroke itself (CHAD score), the predictive statistics of the model significantly increased after adding MRI-based LA structural remodeling (area under the curve increased from 0.58 to 0.72). We hypothesized a novel clinical stroke prediction index using numeric allocations for Stage IV remodeling: LA structural remodeling (+2), congestive heart failure (+1), hypertension (+1), age >75 years (+1), and diabetes (+1). In addition, we found that this model's predictive statistics improved the diagnostic performance when compared with clinical variables alone (CHAD) [log odds ratio per unit score = 1.37, $p < 0.001$ vs. 1.03, $p = 0.87$], with the area under the curve of 0.58. When adding the LA fibrosis into the predictive model, the area under the curve increased to 0.72.

Discussion

In our study, we found that AF patients who have suffered an ischemic stroke have significantly higher levels of LA fibrosis as quantified by DE-MRI. In addition, we demonstrated that this LA fibrosis, as a variable of structural atrial remodeling, could be a valuable tool for clinicians to use in conjunction with the $CHADS_2$ index for anticoagulation risk stratification. Further prospective studies are needed;

Table 4 Univariate and Multivariate Logistic Regression Analysis for Strokes

Univariate			Multivariate		
Variable	OR	p Value	Variable	OR	p Value
Persistent vs. paroxysmal AF	1.34	0.40	Persistent vs. paroxysmal AF	1.02	0.98
Warfarin use	0.64	0.22	Warfarin use	0.58	0.14
Female vs. male	3.49	<0.001	Female vs. male	3.11	0.003
Diabetes mellitus	0.58	0.38	Diabetes mellitus	0.43	0.21
Hypertension	1.44	0.32	Hypertension	1.35	0.51
Congestive heart failure	0.51	0.36	Congestive heart failure	0.36	0.19
Age >75 yrs	1.26	0.59	Age >75 yrs	1.18	0.58
LA remodeling stage	2.04	<0.001	LA remodeling stage	2.91	0.027
Stage II (Q2) vs. I (Q1)	9.8	0.018			
Stage III (Q3) vs. I	7.55	0.03			
Stage IV (Q4) vs. I	23.4	<0.001			

Odds ratios (ORs) per unit change.
Abbreviations as in Table 1.

nevertheless, this study provides plausible evidence that LA substrate analysis is an independent risk factor and could possibly be used in addition to standard clinical variables. This could potentially lead to an improvement in the current risk stratification schemes, enhancing our understanding of risks leading to thromboembolic events in AF patients.

It is important to note that prior stroke was not used as a risk factor, but was rather evaluated more akin to an outcome variable in our cross-sectional study, though it should be noted that MRI was performed after the stroke occurred. Furthermore, significant statistical anomalies in our sample, such as a 3 times higher stroke rate in women, correspond to the analysis of population being evaluated for refractory AF who undergo ablations and cannot be universalized with consideration to selection bias. It is believed that women with AF are evaluated later than men with AF are, having the inclination to have more severe phenotypes of AF and have a larger degree of fibrosis (17–20).

The $CHADS_2$ index is the most accepted, validated risk stratification model; nonetheless, a recent analysis of the current risk stratification schemes by Fang et al. (8) demonstrated its poor ability to predict strokes. In addition, the $CHADS_2$ scheme has been shown to have a poor predictive power for moderate-risk patients, who compose the majority of patients stricken with AF (9). Prior investigators have speculated that additional independent risk factors for AF-related thromboembolism are not included in current risk schemes (8). This has led researchers to evaluate various biomarkers as potential risk factors, including inflammatory and plasma markers for endothelial dysfunction (10,21,22). So far, these additional markers have not been shown to improve the predictive power of the current models.

A systematic review of clinical studies demonstrates that prior stroke, advanced age, hypertension, and diabetes are the only consistent independent risk factors for stroke in AF patients (23). It is important to note that most clinical studies lack rigorous characterization and direct examination of the LA substrate and individual tissue characteristics in AF patients with a history of stroke. Structural and functional parameters in AF patients have largely been based on echocardiographic analysis of left ventricular function and LA size (24,25). Animal models have shown that an increased atrial size is associated with a higher degree of interstitial fibrosis resulting in increased collagen and glycogen deposition within the LA wall (26,27). Fatema et al. (28) evaluated the role of LA volume index as a biomarker for stroke and reported that LA volume enlargement was present in a majority of patients (75%) with first-ever ischemic strokes. This study is consistent with our findings in demonstrating a correlation between LA structural remodeling and ischemic strokes. Of note, it is recognized that most emboli arise from the LA appendage in AF, so the relation and this associated mechanism between LA appendage function and the overall fibrosis in the LA is presumed and not delineated in this study.

Patient age is a consistent, independent risk factor in all studies and is associated with an incremental risk increase for stroke of 1.5% per decade (23). At the present time, it is not entirely clear how aging relates to the underlying pathophysiology related to thromboembolism. Although higher stroke rates may partly be explained by the coexistence of other independent risk factors in the elderly (23), it may also be due to LA structural changes that occur over time, especially within the AF population. Goldman et al. (29) demonstrated that advancing age is independently associated with reduction of LA appendage velocities. Myocardial fibrosis has been shown to increase with age (30), and aging has been shown to be associated with increased LA enlargement and wall thickness (31). Similarly, this study confirms that, although not a linear relationship, elderly AF patients have increased LA enhancement seen on DE-MRI as compared with their younger AF patients. Our data correlating high levels of LA fibrosis and stroke demonstrates the adverse relationship seen in progressive LA substrate remodeling. Therefore, the structural remodeling process accentuated in the elderly may lead to LA substrate and or functional changes resulting in a greater tendency for thromboembolism.

Study limitations. The main limitation of this study was that DE-MRI was not performed at the time of stroke; the time to MRI after the stroke was almost 2 years. We know that LA enhancement as a determinant of fibrosis is a dynamic marker and the level of structural remodeling does not specifically coincide with the time of stroke. It is important to note that the association between structural remodeling and stroke could represent a reverse causality interaction considering that our study results are derived from retrospective data. However, the strength of association among the various stages of LA fibrosis in relationship to the risk factors and stroke is supportive and supports a comprehensive prospective evaluation.

It is also of value to note that the greatest predictive strength of this novel index is evident when applied in conjunction to the standard clinical variables. Therefore, the use of MRI-based LA structural remodeling as a single marker for stroke is not recommended. Also, inclusion of all clinical predictors into the multivariate analysis may have led to model overfitting.

Conclusions

Left atrial structural remodeling as a determinant of AF assessed with DE-MRI is associated with an increased risk of thromboembolism in AF patients. Clinician use of both a $CHADS_2$ index and a quantified measure of AF has the potential to provide a more rigorous risk assessment and improve future risk stratification schemes. Further prospective studies are needed to verify whether AF is a valuable risk parameter and can be incorporated into the existing methodology.

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