JACC: CARDIOVASCULAR IMAGING
VOL. 8, NO. 7, 2015

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2015.03.008

Incidental LV LGE on CMR Imaging in Atrial Fibrillation Predicts Recurrence After Ablation Therapy

Promporn Suksaranjit, MD,*† Nazem Akoum, MD,*† Eugene G. Kholmovski, PhD,†‡ Gregory J. Stoddard, MS,§ Lowell Chang, MD,*† Kavitha Damal, PhD,§ Krishna Velagapudi, MD,* Allen Rassa, MD,* Erik Bieging, MD,* Shridhar Challa, MD,* Imran Haider, MD,*† Nassir F. Marrouche, MD,*† Christopher J. McGann, MD,*† Brent D. Wilson, MD, PhD*†

ABSTRACT

OBJECTIVES This study sought to evaluate the prognostic significance of left ventricular late gadolinium enhancement (LV-LGE) incidentally found in atrial fibrillation (AF) patients who undergo ablation therapy.

BACKGROUND LV-LGE provides prognostic information in patients with ischemic and nonischemic cardiomyopathies. However, data on the clinical significance of incidental LV-LGE in the AF population are limited.

METHODS A total of 778 patients who were referred for radiofrequency ablation of AF underwent cardiac magnetic resonance examinations between June 2006 and January 2013. Patients with a history of myocardial infarction or ablation therapy were excluded. The presence of LV-LGE was assessed by experienced imaging physicians. Patients were followed for arrhythmia recurrence after the radiofrequency ablation procedure.

RESULTS Of 598 patients included in the study, 60% were men with a mean age of 64 years and a median AF duration of 25 months. LV-LGE was detected in 39 patients (6.5%). There were 240 arrhythmia recurrences observed involving 40% of patients over a median follow-up period of 52 months. On univariate analysis, age (hazard ratio [HR]: 1.02; 95% confidence interval [CI]: 1.00 to 1.03), male sex (HR: 0.63; 95% CI: 0.47 to 0.86), diabetes (HR: 1.53; 95% CI: 1.03 to 2.27), $CHADS_2$ score (HR: 1.19; 95% CI: 1.04 to 1.36), CHA_2DS_2-VASc score (HR: 1.18; 95% CI: 1.08 to 1.30), left atrial (LA) fibrosis (HR: 1.66; 95% CI: 1.41 to 1.96), LV-LGE (HR: 1.83; 95% CI: 1.11 to 3.03), persistent AF (HR: 1.52; 95% CI: 1.11 to 2.09), and LA area (HR: 1.03; 95% CI: 1.01 to 1.05) were significantly associated with arrhythmia recurrence. The recurrence rate was 69% in patients with LV-LGE compared with 38% in patients without LV-LGE ($p < 0.001$). In a multivariate model, LA fibrosis and LV-LGE were independent predictors of arrhythmia recurrence.

CONCLUSIONS In AF patients without history of myocardial infarction, LV-LGE is a significant independent predictor of arrhythmia recurrence after ablation therapy. (J Am Coll Cardiol Img 2015;8:793–800) © 2015 by the American College of Cardiology Foundation.

From the *Division of Cardiovascular Medicine, University of Utah, Salt Lake City, Utah; †Comprehensive Arrhythmia Research & Management Center, Salt Lake City, Utah; ‡Utah Center for Advanced Imaging Research, University of Utah, Salt Lake City, Utah; and the §Division of Epidemiology, University of Utah, Salt Lake City, Utah. Dr. Kholmovski has received a research grant and consulting fees from Marrek Inc. Dr. Marrouche is a consultant for Estech; owner and principal partner with Marrek, MRI-Interventions; and has received grants from Estech, Sanofi, Biotronik, and eCardio. Dr. Wilson has received grant funding for a project on echo contrast from General Electric. All other authors have reported that they have no relationship relevant to the contents of this paper to disclose.

Manuscript received January 16, 2015; revised manuscript received March 11, 2015, accepted March 23, 2015.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CMR = cardiac magnetic resonance

DM = diabetes mellitus

HTN = hypertension

LA = left atrium

LGE = late gadolinium enhancement

LV = left ventricle

MI = myocardial infarction

PAD = peripheral arterial disease

PV = pulmonary vein

SRM = structural remodeling

Atrial fibrillation (AF) is the most common sustained arrhythmia and can result in heart failure (1), stroke (2), and death (3). To achieve rhythm control, catheter ablation is becoming more common due to improved ablation techniques and limited success with anti-arrhythmic drugs.

In a growing number of centers, pre-ablation cardiac magnetic resonance (CMR) is performed to determine if patients are reasonable candidates for ablation therapy (4) and to provide 3-dimensional (3D) left atrial and pulmonary venous anatomy to help guide catheter navigation (5). This CMR study also provides left ventricular function and viability information.

SEE PAGE 801

Left ventricular late gadolinium enhancement (LV-LGE) has prognostic value in patients with ischemic and nonischemic cardiomyopathies (6,7). Recently, incidental LV-LGE found by CMR in AF patients has been associated with mortality (8). However, the relationship between incidental LV-LGE in AF patients and specific cardiovascular outcomes has not been well studied. The goal of this study was to determine whether there is an association of incidental LV-LGE with cardiovascular risk factors and cardiovascular disease processes and to study the relationship between LV-LGE and arrhythmia recurrence after ablation.

METHODS

STUDY POPULATION. We retrospectively collected data on all consecutive patients from June 2006 to January 2013 who were referred for radiofrequency AF ablation and underwent CMR before the procedure. Of the 778 patients, 16 with known coronary artery disease and prior myocardial infarction (MI), 48 with prior AF ablation, and 116 who did not undergo ablation therapy were excluded. The final study population included 598 AF patients who underwent AF ablation. In AF patients with planned ablation therapy, CMR is the primary imaging modality for left atrial (LA) and pulmonary venous (PV) anatomy at our center. Contraindication for CMR included severe renal impairment (glomerular filtration rate <30 ml/min/1.73 m^2), severe claustrophobia, and the presence of a permanent pacemaker or implantable cardioverter-defibrillator. Paroxysmal AF was defined as any AF episode that terminated spontaneously within 7 days after onset (9). Persistent AF was defined as an AF episode that extended beyond 7 days. We defined prior MI by either clinical documentation of MI in the electronic medical record or electrocardiographic evidence per Minnesota codes 1.1.1 to 1.2.8 (10). The patients' $CHADS_2$ and CHA_2DS_2-VASc characteristics were determined by systematic chart review. The study protocol was approved by our Institutional Review Board.

CMR PROTOCOL. All studies were performed either on a 1.5-T Avanto or 3-T Verio scanner (Siemens Medical Solutions, Erlangen, Germany). The CMR protocol consisted of cine steady state free precession imaging for cardiac structure and function, 3D contrast enhanced magnetic resonance angiography for LA and PV anatomy, 2D LGE imaging for viability, and 3D LGE for LA fibrosis. 2D LGE imaging for viability was acquired approximately 12 min after contrast injection (0.1 mmol/kg, MultiHance [Bracco Diagnostics, Inc., Princeton, New Jersey]) using single-shot, electrocardiogram (ECG)-triggered, free-breathing, phase-sensitive inversion recovery sequences in short-axis and horizontal and vertical long-axis orientations covering the whole heart. Scan parameters for 2D LGE imaging were as follows: 3-T - echo time (TE) = 1.1 ms, repetition time (TR) = 2.5 ms, flip angle (FA) = 35°, pixel size = 1.88 × 1.88 × 2.07 mm, slice thickness = 7 mm; 1.5-T - TE = 1.1 ms, TR = 2.5 ms, FA = 45°, pixel size = 1.85 × 1.85 × 2.05 mm, slice thickness = 6 mm.

High-resolution LGE images for assessment of LA fibrosis were acquired 15 min after contrast injection using a 3D respiratory-navigated, ECG-gated, inversion recovery-prepared gradient-recalled pulse sequence. Inversion preparation was applied every heartbeat, and fat saturation was applied immediately before data acquisition. Data acquisition was limited to 15% of the cardiac cycle and was performed during LA diastole. The other scan parameters for assessment of LA LGE at 3-T were as follows: axial imaging volume with field-of-view (FOV) = 400 × 400 × 110 mm, voxel size = 1.25 × 1.25 × 2.5 mm, TR/TE = 3.1/1.4 ms, FA = 14°. Scan parameters for assessment of LA LGE at 1.5-T were as follows: axial imaging volume with FOV = 360 × 360 × 100 mm, voxel size = 1.25 × 1.25 × 2.5 mm, TR/TE = 5.2/2.4 ms, FA = 20°. Typical scan time for the LGE study was 6 to 12 min at 1.5-T and 5 to 9 min at 3-T, depending on patient respiration. LGE images were interpreted by 2 experienced CMR physicians. LV-LGE was considered present only if it was visible in all corresponding myocardial locations on short-axis, horizontal long-axis, and vertical long-axis images. LGE distribution was categorized as subendocardial, mid-myocardial, epicardial, transmural, or adjacent to right ventricular insertion points. Post-processing of LGE images

for LV-LGE was performed with CVI[42] software version 5.0 (Circle Cardiovascular Imaging, Inc., Calgary, Alberta, Canada) and LA fibrosis was performed with custom software (Corview, Marrek, Inc., Salt Lake City, Utah). The amount of LV-LGE and LA fibrosis was quantified using a threshold-based algorithm.

ABLATION AND FOLLOW-UP PROTOCOLS. The details of the PV isolation, in addition to posterior wall and septal debulking, are described elsewhere (11). In brief, a 10-pole circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, California) and a 3.5-mm ThermoCool ablation catheter (Biosense Webster) were advanced into the LA for mapping and ablation. Radiofrequency energy was delivered with 50 Watts at a catheter tip temperature of 50°C for 5 s, guided by electrogram abolition recorded on the Lasso catheter. Electrical isolation of the pulmonary veins was achieved by placing ablation lesions in a circular fashion in the PV antral region. The additional lesions were placed along the LA posterior wall and septum. The endpoint of interest was atrial arrhythmia recurrence after ablation. Eight day Holter monitoring was performed routinely at 3, 6, and 12 months after ablation and yearly thereafter. In addition, symptom-guided Holter monitoring and 12-lead ECGs were used to determine arrhythmia recurrence. Any sustained atrial arrhythmia for longer than 30 s without antiarrhythmic drug treatment after a 3-month post-ablation blanking period was considered as recurrence, as suggested by Heart Rhythm Society consensus statements (12).

STATISTICAL ANALYSIS. Continuous variables are presented as mean and standard deviations. Categorical data are presented as numbers and percentages. Comparisons between 2 groups were made using the Student *t* test or Mann-Whitney non-parametric test for continuous variables and using the chi-square test or Fisher exact tests for categorical variables, as appropriate. Univariate and multivariate logistic regression models were used to determine predictors of LV-LGE. Spearman's correlation was used to assess the relationship between extent of LV-LGE and atrial fibrosis in AF patients with LV-LGE. A Cox regression model was used to determine the hazard ratio (HR) for arrhythmia recurrence. The best overall multivariate models for LV-LGE were sought by stepwise forward selection with a probability to enter set at $p = 0.05$. Arrhythmia recurrence curves were determined according to Kaplan-Meier methods, and comparison of recurrence rate was performed using a log-rank test. The Harrell concordance C statistic for arrhythmia recurrence outcomes was used to assess the increase in prognostic accuracy resulting from adding LV-LGE to the model with the set of covariates that are risk factors for arrhythmia recurrence after ablation therapy. A p value of <0.05 was considered statistically significant, and all reported p values are 2-tailed. All analyses were performed using STATA version 12 (StataCorp, College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. We included 598 AF patients without history of MI who underwent CMR and first AF ablation. There were 360 men (60%) with a mean age of 64.1 ± 12.0 years and a median AF duration of 25 months (range 6 to 69 months). Two hundred sixty-two patients (44%) had paroxysmal AF, and 336 patients (66%) had persistent AF. There were 81 patients (14%) with diabetes mellitus (DM), 366 patients (61%) with hypertension (HTN), and 54 patients (9%) with heart failure. Patients with LV-LGE were found to have a significantly higher prevalence of DM, dyslipidemia, peripheral arterial disease (PAD), heart failure, and smoking history. $CHADS_2$, CHA_2DS_2-VASc, and LA area were also higher compared with patients without LV-LGE. The clinical demographics of the patients stratified by the presence and absence of LGE are represented in Table 1.

LV-LGE. In our AF patient cohort without history of MI, LV-LGE was found in 39 patients (6.5%) with an average LV-LGE extent of 2.1 ± 2.1%. Of these patients, 34 (89.5%) had a normal LV ejection fraction of ≥55%. The observed pattern of LV-LGE was ischemic in 46% of the patients (subendocardial in

TABLE 1 Baseline Characteristics Stratified by the Presence of LV-LGE

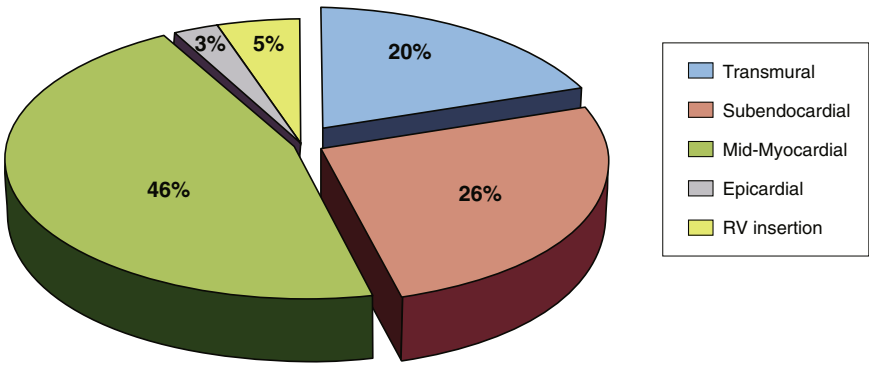
	Overall Cohort (n = 598)	LV-LGE Absent (n = 559)	LV-LGE Present (n = 39)	p Value
Age, yrs	64.1 ± 12.0	63.8 ± 12.0	65.8 ± 11.7	0.313
Male	360 (60.2)	336 (60.1)	24 (61.5)	0.860
Diabetes	81 (13.5)	71 (12.7)	10 (25.6)	0.022
Hypertension	366 (61.2)	337 (60.3)	29 (74.4)	0.082
Smoking history	166 (27.8)	149 (26.7)	17 (43.6)	0.022
Dyslipidemia	172 (28.8)	155 (27.7)	17 (43.6)	0.034
Prior stroke	56 (9.4)	50 (8.9)	6 (15.4)	0.183
PAD	7 (1.2)	5 (0.89)	2 (5.1)	0.017
Heart failure	54 (9.0)	45 (8.1)	9 (23.1)	0.002
Persistent AF	262 (43.8)	247 (44.2)	15 (38.5)	0.487
$CHADS_2$	1.21 ± 1.04	1.17 ± 1.07	1.76 ± 1.04	<0.001
CHA_2DS_2-VASc	2.14 ± 0.06	2.09 ± 1.53	2.85 ± 1.37	0.003
LA fibrosis, %	16.1 ± 10.1	16.0 ± 10.1	17.5 ± 10.1	0.422
LV EF <55%	71 (11.9)	66 (11.8)	5 (12.8)	0.850
LA area, cm^2	28.7 ± 7.7	28.5 ± 7.6	32.2 ± 8.0	0.003

Values are mean ± SD or n (%).

AF = atrial fibrillation; EF = ejection fraction; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle; PAD = peripheral arterial disease.

JACC: CARDIOVASCULAR IMAGING, VOL. 8, NO. 7, 2015
JULY 2015:793–800

FIGURE 1 LV-LGE Pattern Distribution in AF Patients

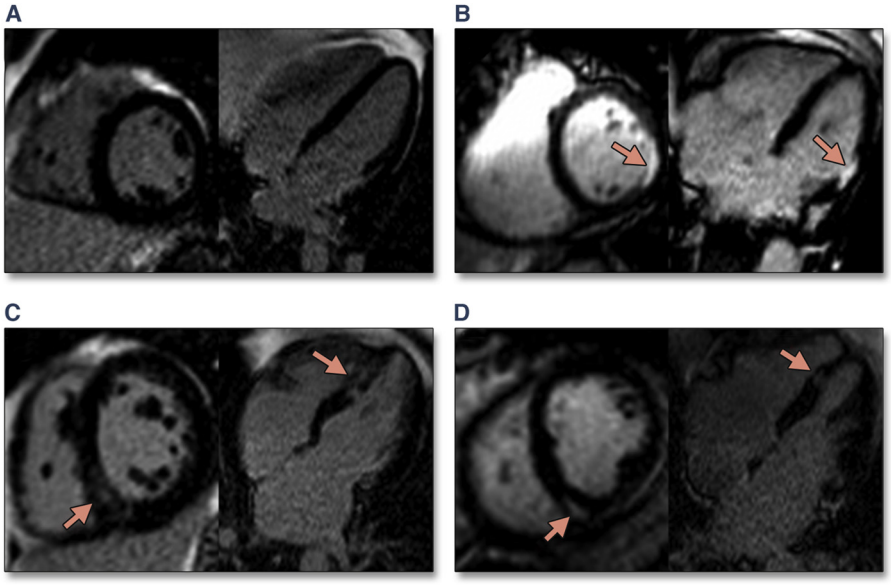


Pie chart showing the left ventricle late gadolinium enhancement (LV-LGE) pattern distribution in the retrospective cohort of atrial fibrillation (AF) patients without a history of myocardial infarction (MI). An ischemic (subendocardial and transmural) pattern was found in almost one-half (46%) of these patients.

10 [26%] and transmural in 8 [20%]) and nonischemic in 54% (mid-myocardial in 18 [46%], epicardial in 1 [3%], and right ventricle [RV] insertional in 2 [5%]) (Figure 1). Examples are shown in Figure 2. In the 18 patients with LV-LGE in an ischemic pattern, there was 1 (6%) who subsequently underwent a revascularization procedure. Of 21 patients with LV-LGE in a nonischemic pattern, 18 (85.7%) had normal LV ejection fraction, 2 (9.5%) were diagnosed with hypertrophic cardiomyopathy, and 1 (4.8%) was diagnosed with dilated cardiomyopathy.

UNIVARIATE AND MULTIVARIATE ASSOCIATIONS WITH LV-LGE. On univariate analysis, DM (odds ratio [OR] = 2.37; 95% confidence interval [CI]: 1.11 to 5.07), dyslipidemia (OR: 2.01; 95% CI: 1.04 to 3.89), PAD (OR: 5.99; 95% CI: 1.12 to 31.92), heart failure

FIGURE 2 Representative LV-LGE Images



LGE **(arrows)** in horizontal long- and short-axis images in AF patients without a history of MI. **(A)** Absence of LGE; **(B)** subendocardial LGE; **(C)** mid-myocardial LGE; **(D)** right ventricular (RV) insertional LGE. Abbreviations as in Figure 1.

(OR: 3.43; 95% CI: 1.53 to 7.66), smoking history (OR: 2.13; 95% CI: 1.10 to 4.11), $CHADS_2$ (OR: 1.58; 95% CI: 1.20 to 2.07), CHA_2DS_2-VASc (OR: 1.18; 95% CI: 1.08 to 1.30), and LA area (OR: 1.03; 95% CI: 1.01 to 1.05) provided significant unadjusted associations with LV-LGE. In multivariate models with stepwise selection, PAD (OR: 6.88; 95% CI: 1.19 to 39.72), heart failure (OR: 2.51; 95% CI: 1.05 to 5.98), and LA area (OR: 1.05; 95% CI: 1.01 to 1.10) provided significant adjusted associations with LV-LGE (Table 2). When including only atherosclerotic risk factors in the multivariate model, DM (OR: 2.35; 95% CI: 1.08 to 5.12) and smoking history (OR: 1.98; 95% CI: 1.01 to 3.88) provided significant adjusted associations with LV-LGE (Table 3). When including only embolic risk factors in the multivariate model, CHA_2DS_2-VASc (OR: 1.32; 95% CI: 1.05 to 1.65) and LA area (OR: 1.07; 95% CI: 1.03 to 1.12) provided significant adjusted associations with LV-LGE (Table 4). There is no significant correlation between the extent of LV-LGE and atrial fibrosis (Spearman's rho = -0.32, p = 0.066).

ARRHYTHMIA RECURRENCE. There were 240 arrhythmia recurrences (40%) over a median follow-up period of 52 months. The recurrence rate was significantly higher in patients with incidental LV-LGE than it was in patients without incidental LV-LGE (27 [69%] vs. 213 [38%]; p < 0.001). Median time to recurrence in this cohort was 194 days.

UNIVARIATE AND MULTIVARIATE ASSOCIATIONS WITH ARRHYTHMIA RECURRENCE. On univariate analysis, age (HR: 1.02; 95% CI: 1.00 to 1.03), male sex (HR: 0.63; 95% CI: 0.47 to 0.86), DM (HR: 1.53; 95% CI: 1.03 to 2.27), $CHADS_2$ (HR: 1.19; 95% CI: 1.04 to 1.36), CHA_2DS_2-VASc (HR: 1.18; 95% CI: 1.08 to 1.30), LA fibrosis (HR: 1.66; 95% CI: 1.41 to 1.96), LV-LGE (HR: 1.83; 95% CI: 1.11 to 3.03), persistent AF (HR: 1.52; 95% CI: 1.11 to 2.09), and LA area (HR: 1.03; 95% CI: 1.01 to 1.05) provided significant association with arrhythmia recurrence. In multivariate models, only LA fibrosis (HR: 1.03; 95% CI: 1.02 to 1.05) and LV-LGE (HR: 1.81; 95% CI: 1.12 to 2.91) provided a significant association with arrhythmia recurrence (Table 5). A Kaplan-Meier curve showing a significant difference in arrhythmia recurrence between patients with and without incidental LV-LGE is shown in Figure 3. Harrell's C statistics were significantly improved when adding LV-LGE to LA fibrosis from 0.605 to 0.627 (an improvement of 0.022; 95% CI: 0.004 to 0.400; p = 0.014) and to the model that includes hypertension, AF duration, persistent AF, LV dysfunction, LA size, and fibrosis from 0.649 to 0.663 (an improvement of 0.014; 95% CI: 0.016 to 0.026; p = 0.026) for prediction of the arrhythmia recurrence after ablation therapy.

TABLE 2 Univariate and Multivariate Analyses for Associations With LV-LGE

	Univariate Analyses			Multivariate Analyses (Stepwise Elimination to 4 Variables)		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Age, yrs	1.01	0.99–1.04	0.352			
Male	1.06	0.55–2.07	0.860			
Diabetes	2.37	1.11–5.07	0.026			
Hypertension	1.91	0.91–4.00	0.086			
Dyslipidemia	2.01	1.04–3.89	0.037			
Smoking	2.13	1.10–4.11	0.025			
PAD	5.99	1.12–31.92	0.036	6.88	1.19–39.72	0.031
Heart failure	3.43	1.53–7.66	0.003	2.51	1.05–5.98	0.038
Prior stroke	1.85	0.74–4.63	0.188			
$CHADS_2$	1.58	1.20–2.07	0.001			
CHA_2DS_2-VASc	1.35	1.10–1.65	0.003	1.22	0.98–1.52	0.076
LA fibrosis	1.01	0.98–1.05	0.421			
Persistent AF	0.79	0.41–1.54	0.487			
LV EF <55%	0.91	0.34–2.40	0.850			
LA area	1.06	1.02–1.10	0.004	1.05	1.01–1.10	0.01

CI = confidence interval; other abbreviations as in Table 1.

TABLE 3 Multivariate Analyses of Atherosclerosis Risk Factors for Association With LV-LGE

	Multivariate Analyses (Atherosclerotic Pathway)		
	Odds Ratio	95% CI	p Value
Age, yrs	Removed from the model due to insignificance		
Male	Removed from the model due to insignificance		
Diabetes	2.35	1.08–5.12	0.031
Hypertension	Removed from the model due to insignificance		
Dyslipidemia	1.71	0.87–3.35	0.121
Smoking	1.98	1.01–3.88	0.047
PAD	5.18	0.93–29.00	0.061
Prior stroke	Removed from the model due to insignificance		

Abbreviations as in Tables 1 and 2.

DISCUSSION

The purpose of this study was to evaluate the prognostic value of LV-LGE in AF patients who underwent

TABLE 4 Multivariate Analyses of Embolic Risk Factors for Association With LV-LGE

	Multivariate Analyses (Embolic Pathway)		
	Odds Ratio	95% CI	p Value
CHA_2DS_2-VASc	1.32	1.05–1.65	0.017
LA fibrosis	1.00	0.96–1.03	0.850
LA area	1.07	1.03–1.12	0.002
Persistent AF	1.14	0.53–2.45	0.741

Abbreviations as in Tables 1 and 2.

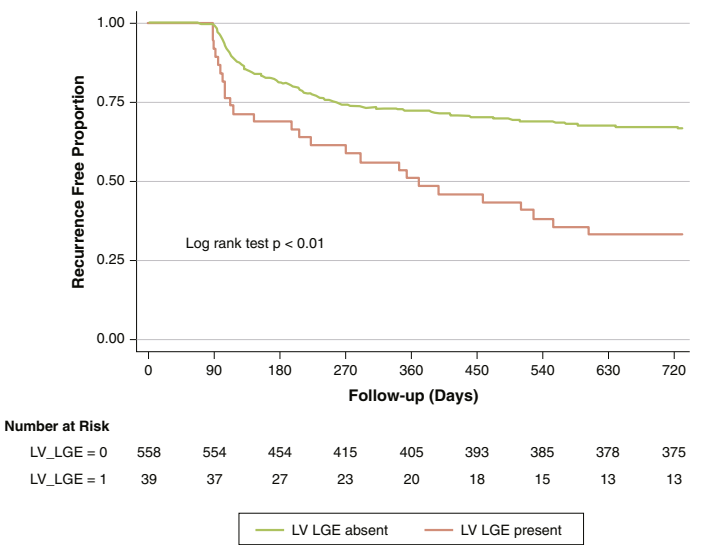
TABLE 5 Univariate and Multivariate Analyses for Associations With Arrhythmia Recurrence

	Univariate Analyses			Multivariate Analyses		
	Hazard Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Age, yrs	1.02	1.00–1.03	0.019	0.99	0.98–1.02	0.990
Male	0.63	0.47–0.86	0.003	0.83	0.50–1.37	0.462
Diabetes	1.53	1.03–2.27	0.035	1.24	0.71–2.16	0.450
Hypertension	1.37	0.99–1.90	0.055	1.38	0.83–2.28	0.210
Dyslipidemia	1.22	0.88–1.69	0.234	1.09	0.79–1.51	0.587
Smoking	1.33	0.97–1.84	0.08	1.25	0.90–1.73	0.185
PAD	1.50	0.48–4.69	0.489	2.72	0.78–9.5	0.117
Heart failure	1.15	0.70–1.90	0.583	0.90	0.46–1.76	0.759
Prior stroke	1.19	0.73–1.93	0.488	0.90	0.57–1.44	0.670
$CHADS_2$	1.19	1.04–1.36	0.009			
CHA_2DS_2-VASc	1.18	1.08–1.30	<0.001	1.01	0.71–1.44	0.949
LA fibrosis (1% increase)	1.66	1.41–1.96	<0.001	1.03	1.02–1.05	<0.001
LV-LGE	1.83	1.11–3.03	0.018	1.81	1.12–2.91	0.015
Persistent AF	1.52	1.11–2.09	0.01	0.75	0.54–1.04	0.089
LV EF <55%	1.03	0.70–1.53	0.878	1.18	0.74–1.88	0.484
LA area	1.03	1.01–1.05	0.003	1.01	0.99–1.03	0.420

Abbreviations as in Tables 1 and 2.

ablation therapy. This study produced several important findings. First, the presence of LV-LGE in AF patients was associated with atherosclerotic and embolic risk factors. An LV-LGE pattern consistent with an ischemic process was detected in 46% of patients with incidentally discovered LV-LGE. The presence of LV-LGE in the remaining patients is presumably due to non-ischemic etiology. Second, the presence of LV-LGE was a significant, independent predictor of arrhythmia recurrence after AF ablation therapy, suggesting that incidental LV-LGE may be an additive risk factor for arrhythmia recurrence.

FIGURE 3 Survival Analysis According to LV-LGE



Kaplan Meier curve showing the difference in arrhythmia-free survival after 2 years of follow-up in patients with and without incidental LV-LGE. Abbreviations as in Figure 1.

LV-LGE has been validated against histologic findings in animal models and in humans where it has been shown to correlate with myocardial fibrosis (13–17). Although it is not specific (18), the ischemic LGE pattern (subendocardial/transmural) usually represents ischemic heart disease (6,19). On the other hand, nonischemic LGE representing focal myocardial fibrosis can be found in nonischemic cardiomyopathies (15,20) and other cardiac conditions (21–23). In AF populations, the data on incidental LV-LGE patterns and pathophysiology are still limited. In our AF patients without history of MI, LV-LGE was detected in 39 patients (6.5%). In almost one-half of these patients, LV-LGE was seen in an ischemic pattern, which is similar to the findings in the earlier study from Neilan et al. (8). We further found that atherosclerotic and embolic risk factors were independent predictors of LV-LGE. This could be due to unrecognized coronary artery disease or microembolism in AF patients causing an ischemic LV-LGE pattern. However, the mechanism involved in the development of nonischemic LV-LGE patterns in AF patients is still unclear. This could result from LV remodeling associated with chronic AF (24) or aging (25), or from another multifactorial, genetic process. It may also be reflective of the presence of comorbidities and associated myocardial disease.

The prognostic value of LV-LGE has been applied to ischemic and nonischemic cardiomyopathies (6,7) and aortic stenosis (26). Recently, unanticipated LV-LGE in AF patients was shown to be an independent predictor of mortality (8). In our study, we report the prognostic value of incidental LV-LGE for AF ablation outcomes. Patients with LV-LGE had arrhythmia recurrence rates as high as 69% in our cohort. Mechanistically, the presence of fibrosis could render the ventricle less compliant, resulting in impaired relaxation with increased LV filling pressures (27), leading to increased LA pressures and structural remodeling (SRM) (28), which is a substrate for AF. The extent of myocardial fibrosis by LGE has been shown to be correlated with severity of diastolic dysfunction (29). This mechanism is further supported by data from our cohort showing significantly larger LA sizes in patients with LV-LGE. Similar to earlier studies (30), we also showed LA fibrosis as an independent predictor of AF ablation outcome. Interestingly, there was no significant difference between LA fibrosis, a hallmark of SRM, between patients with and without incidental LV-LGE.

Thus, incidental LV-LGE was an additive predictor of arrhythmia recurrence after ablation.

With superior spatial resolution compared to ultrasound (31,32) and the ability to be coregistered with electroanatomical mapping systems (12), CMR and computed tomographic angiography are being used to delineate LA and PV anatomy. To date, there are no guidelines to support the use of CMR as the primary imaging modality to visualize LA and PV anatomy before ablation therapy. Our study emphasizes the advantages of CMR imaging in the AF population, namely the important prognostic information provided by assessment of LA fibrosis and incidental LV-LGE. This information allows clinicians to individualize therapeutic approaches by determining which patients are appropriate for ablation therapy. These findings also provide prognostic value in terms of mortality (8). In situations where CMR is available, it should be considered as the primary imaging modality in arrhythmia patients with no magnetic resonance imaging (MRI) contraindications.

STUDY LIMITATIONS

We do not have data on diastolic LV function to look for association with incidental LV-LGE. However, there are results from a prior study that suggest an association between LV-LGE and diastolic dysfunction (29). Multiple comparisons are made in our analysis without adjustment methods, and there is a possibility that spurious associations may appear statistically significant because of the number of comparisons being performed. However, LV-LGE is our primary predictor of interest for association with arrhythmia recurrence. We consider LV-LGE the only variable that is a confirmatory finding to the primary hypothesis. Because this involves only 1 variable, there is no increased false positive issue for LV-LGE being an independent predictor for arrhythmia recurrence. Although there was significant improvement in the prediction of arrhythmia recurrence after ablation therapy, the absolute changes in predictive accuracy were modest when adding LV-LGE to the current clinical risk factors. This represents the challenge of introducing additional factors, such as LV-LGE, into the risk prediction model. These findings could be further validated with subsequent prospective study. Follow-up and post-ablation monitoring for recurrent arrhythmia was performed using ambulatory ECG monitoring as well as symptom-driven 12-lead ECGs, as recommended by the 2012 HRS/EHRA/ECAS Expert Consensus Statement on catheter and surgical ablation of atrial fibrillation (12). However, this method is known to potentially underrepresent the burden of recurrent atrial arrhythmia and presents a limitation to this and other studies using the same metrics. The etiology of nonischemic LV-LGE in AF remains unclear on the basis of retrospective investigation from our medical record review. Future studies addressing this question are required.

CONCLUSIONS

In this large cohort of AF patients without a history of MI, incidental finding of LV-LGE was shown to be an important, independent predictor of arrhythmia recurrence after ablation therapy. These results further emphasize the role of LGE-MRI in deciding the suitability of ablation therapy for individual AF patients.

ACKNOWLEDGMENTS The authors thank the CMR technologists at the University of Utah for their dedication and expertise.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Brent D. Wilson, Division of Cardiovascular Medicine, 30 North 1900 East, Room 4A100, University of Utah School of Medicine, Salt Lake City, Utah 84132. E-mail: brent.wilson@hsc.utah.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with AF, CMR provides LA and pulmonary venous anatomy as well as LA fibrosis information that can be used for pre-ablation planning. Additionally, left ventricular LV-LGE assessment provides supplementary data that may help further improve patient selection for ablation therapy.

TRANSLATIONAL OUTLOOK: Future prospective studies with implementation of LV-LGE into the clinical decision-making strategies for ablation therapy are warranted to validate the incremental prognostic implications of LV-LGE identified on CMR in the AF population.

REFERENCES

1. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920–5.

2. Brand FN, Abbott RN, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation: 30-year follow-up in the Framingham study. JAMA 1985;254:3449–53.

3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.

4. Akoum N, Daccarett M, McGann C, et al. Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. J Cardiovasc Electrophysiol 2011;22:16–22.

5. Kato R, Lickfett L, Meininger G, et al. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. Circulation 2003;107:2004–10.

6. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343:1445–53.

7. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. J Am Coll Cardiol 2006;48:1977–85.

8. Neilan TG, Shah RV, Abbasi SA, et al. The incidence, pattern, and prognostic value of left ventricular myocardial scar by late gadolinium enhancement in patients with atrial fibrillation. J Am Coll Cardiol 2013;62:2205–14.

9. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (Updating the 2006 Guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;57:223–42.

10. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. Circulation 1960;21:1160–75.

11. Segerson N, Daccarett M, Badger T, et al. Magnetic resonance imaging-confirmed ablative debulking of the left atrial posterior wall and septum for treatment of persistent atrial fibrillation: rationale and initial experience. J Cardiovasc Electrophysiol 2009;21:126–32.

12. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm 2012;9:632–96.

13. Kim RJ, Feino DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 1999;100:1992–2002.

14. Mahrholdt H, Goedecke C, Wagner A, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 2004;109:1250–8.

15. Papavassiliu T, Schnabel P, Schroder M, Borggrefe M. CMR scarring in a patient with hypertrophic cardiomyopathy correlates well with histological findings of fibrosis. Eur Heart J 2005;26:2395.

16. Moon JC, Sheppard M, Reed E, Lee P, Elliott PM, Pennell DJ. The histological basis of late gadolinium enhancement cardiovascular magnetic resonance in a patient with Anderson-Fabry disease. J Cardiovasc Magn Reson 2006;8:479–82.

17. Iles LM, Ellims AH, Llewellyn H, et al. Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. Eur Heart J Cardiovasc Imaging 2015;16:14–22.

18. Hunold P, Schlosser T, Vogt FM, et al. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. AJR Am J Roentgenol 2005;184:1420–6.

19. Wu E, Judd RM, Vargas JD, et al. Visualisation of the presence, location and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. Lancet 2001;357:21–8.

20. McCrohon JA, Moon JC, Prasad SK, et al. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. Circulation 2003;108:54–9.

21. Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation 1998;97:1802–9.

22. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:186–93.

23. Smedema JP, Snoep G, van Kroonenburg MP, et al. Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol 2005;45:1683–90.

24. Dosdall DJ, Ranjan R, Higuchi K, et al. Chronic atrial fibrillation causes left ventricular dysfunction in dogs but not goats: experience with dogs, goats, and pigs. Am J Physiol Heart Circ Physiol 2013;305:H725–31.

25. Ling LH, Kistler PM, Ellims AH, et al. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. J Am Coll Cardiol 2012;60:2402–8.

26. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271–9.

27. MacKenna DA, Omens JH, MuCulloch AD, Covell JW. Contribution of collagen matrix to passive left ventricular mechanics in isolated rat hearts. Am J Physiol 1994;266:H1007–18.

28. Pujadas S, Vidal-Perez R, Hidalgo A, et al. Correlation between myocardial fibrosis and the occurrence of atrial fibrillation in hypertrophic cardiomyopathy: a cardiac magnetic resonance imaging study. Eur J Radiol 2010;75:e88–91.

29. Moreo A, Ambrosio G, De Chiara B, et al. Influence of myocardial fibrosis on left ventricular diastolic function: noninvasive assessment by cardiac magnetic resonance and echo. Circ Cardiovasc Imaging 2009;2:437–43.

30. McGann C, Akoum N, Patel A, et al. Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. Circ Arrhythm Electrophysiol 2014;7:23–30.

31. Toffanin G, Scarabeo V, Verlato R, De Conti F, Zampiero AA, Piovesana P. Transoesophageal echocardiographic evaluation of pulmonary vein anatomy in patients undergoing ostial radiofrequency catheter ablation for atrial fibrillation: a comparison with magnetic resonance angiography. J Cardiovasc Med (Hagerstown) 2006;7:748–52.

32. To AC, Gabriel RS, Park M, et al. Role of transesophageal echocardiography compared to computed tomography in evaluation of pulmonary vein ablation for atrial fibrillation (ROTEA study). J Am Soc Echocardiogr 2011;24:1046–55.

KEY WORDS ablation therapy, atrial fibrillation, cardiac magnetic resonance, late gadolinium enhancement