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The Incidence, Pattern, and Prognostic Value of Left Ventricular Myocardial Scar by Late Gadolinium Enhancement in Patients With Atrial Fibrillation

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Objectives This study sought to identify the frequency, pattern, and prognostic significance of left ventricular (LV) late gadolinium enhancement (LGE) in patients with atrial fibrillation (AF).

Background There are limited data on the presence, pattern, and prognostic significance of LV myocardial fibrosis in patients with AF. LGE during cardiac magnetic resonance imaging is a marker for myocardial fibrosis.

Methods A group of 664 consecutive patients without known prior myocardial infarction who were referred for radiofrequency ablation of AF were studied. Cardiac magnetic resonance imaging was requested to assess pulmonary venous anatomy.

Results Overall, 73% were men, with a mean age of 56 years and a mean LV ejection fraction of 56 ± 10%. LV LGE was found in 88 patients (13%). The endpoint was all-cause mortality, and in this cohort, 68 deaths were observed over a median follow-up period of 42 months. On univariate analysis, age (hazard ratio [HR]: 1.05; 95% confidence interval [CI]: 1.03 to 1.08; chi-square likelihood ratio [LRχ^2]: 15.2; $p = 0.0001$), diabetes (HR: 2.39; 95% CI: 1.41 to 4.09; LRχ^2: 10.3; $p = 0.001$), a history of heart failure (HR: 1.78; 95% CI: 1.09 to 2.91; LRχ^2: 5.37; $p = 0.02$), left atrial dimension (HR: 1.04; 95% CI: 1.01 to 1.08; LRχ^2: 6.47; $p = 0.01$), presence of LGE (HR: 5.08; 95% CI: 3.08 to 8.36; LRχ^2: 28.8; $p < 0.0001$), and LGE extent (HR: 1.15; 95% CI: 1.10 to 1.21; LRχ^2: 35.6; $p < 0.0001$) provided the strongest associations with mortality. The mortality rate was 8.1% per patient-year in patients with LGE compared with 2.3% patients without LGE. In the best overall multivariate model for mortality, age and the extent of LGE were independent predictors of mortality. Indeed, each 1% increase in the extent of LGE was associated with a 15% increased risk for death.

Conclusions In patients with AF, LV LGE is a frequent finding and is a powerful predictor of mortality. (J Am Coll Cardiol 2013;62:2205–14) © 2013 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common clinical cardiac arrhythmia, with estimates suggesting that it affects approximately 1 in 25 adults over the age of 60 years in the

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
CMR = cardiac magnetic resonance
CT = computed tomography
ECG = electrocardiography
EF = ejection fraction
HR = hazard ratio
LGE = late gadolinium enhancement
LRχ^2 = chi-square likelihood ratio
LV = left ventricular
MI = myocardial infarction

United States (1). The occurrence of AF is associated with increases in both cardiovascular and all-cause mortality (2,3). Catheter ablation offers a viable alternative in symptomatic patients who are refractory to pharmacological therapy (4,5), and the use of catheter ablation is increasing (6). The pulmonary veins are the key targets for the ablation of AF (4). For this reason, detailed anatomic imaging of the left atrium and pulmonary veins is routinely performed before the performance of catheter ablation (6,7). Imaging is performed to allow the use of advanced mapping systems during the procedure, to detect anatomical variants, and to minimize complications (8). Multiple different techniques exist for anatomical imaging, including angiography, computed tomography (CT), ultrasound, and cardiac magnetic resonance (CMR) imaging, and there are currently no guidelines and limited clinical data to support an advantage for one imaging modality over another (9). CMR imaging provides accurate and detailed pulmonary vein anatomy before pulmonary vein isolation (10), and CMR imaging may also provide complementary information. Specifically, left ventricular (LV) myocardial fibrosis identified using late gadolinium enhancement (LGE) has been shown to be a predictor of adverse outcomes in broad groups of patients (11–15). However, there are limited data on the presence, pattern, and prognostic significance of LV LGE in patients with AF (16). Therefore, the aim of this study was to determine the incidence, pattern, and prognostic significance of unanticipated LV LGE in patients with AF. We hypothesized that unanticipated LV LGE would be a frequent occurrence and that the presence of LV LGE would be associated with adverse outcomes.

Methods

Study population. We prospectively collected data on all consecutive patients from September 2005 through June 2011 who underwent CMR studies before pulmonary vein isolation. The study indication was specifically for the identification of pulmonary vein anatomy (7). All patients at our institution in whom pulmonary vein isolation is being planned, and without contraindications to the performance of a magnetic resonance study, undergo CMR imaging of the pulmonary venous anatomy. Contraindications to a CMR study included the presence of a permanent pacemaker, severe claustrophobia, and severe impairment of renal function (glomerular filtration rate <30 ml/min/1.73 m^2). Paroxysmal AF was defined as AF that terminated spontaneously <7 days after onset, while persistent AF was defined as that extending beyond 7 days. Hypertension was defined as systolic blood pressure >139 mm Hg or diastolic blood pressure >89 mm Hg on multiple measurements or the use of antihypertensive medication. Heart failure was defined as a clinical history of heart failure or reduced LV ejection fraction (EF). We defined recurrence of AF as AF occurring >3 months after pulmonary vein isolation and confirmed by either electrocardiography (ECG) or cardiac monitoring. We subsequently excluded patients who had prior myocardial infarctions (MIs) by either clinical evidence of MI per electronic medical records or electrocardiographic evidence, defined by Minnesota codes 1.1.1 to 1.2.8 (17). We also obtained LV measurements on echocardiography that was performed at the time of the planned ablation. The Human Subjects Research Review Committee of our institution approved the study protocol.

CMR protocol. All images were acquired with electrocardiographic gating, breath holding, and the patient in a supine position. Subjects were imaged using either a 1.5-T or 3.0-T CMR system (Signa HDxt, GE Healthcare, Waukesha, Wisconsin, or Tim Trio, Siemens Healthcare, Erlangen, Germany, respectively). The CMR protocol consisted of cine steady-state free precession imaging for cardiac function (typical repetition time 3.4 ms, echo time 1.2 ms, in-plane spatial resolution 1.6 $\times$ 2 mm), pulmonary vein anatomy imaging, and LGE imaging (repetition time 4.8 ms, echo time 1.3 ms, inversion time 200 to 300 ms). For LGE imaging, a segmented inversion-recovery pulse sequence was used starting 10 to 15 min after a single bolus dose of 0.15 mmol/kg of gadolinium diethylenetriamine penta-acetic acid (Magnevist, Bayer AG, Leverkusen, Germany). Cine imaging and LV LGE imaging were performed in 8 to 14 matching short-axis (8 mm thick with 0-mm spacing) and 3 radial long-axis planes. This CMR prescription was to ensure that whole-heart coverage was obtained for complete LV and right ventricular assessment. LGE was interpreted as present or absent by the consensus of 2 CMR-trained physicians. LGE was considered present only if confirmed on both short-axis and matching long-axis myocardial locations. LGE extent was quantified using a semiautomatic detection method using a previously validated research tool (Mass Research, Leiden University Medical Center, Leiden, the Netherlands), with the extent of LGE defined using the full width at half maximum criteria (18). The mass of LV LGE was measured in grams and was expressed as a percent of the total LV mass. The distribution of LGE was characterized as subendocardial, transmural, midwall, epicardial, or focal/involving the right ventricular insertion points.

Methods of clinical follow-up. The endpoint of interest was all-cause mortality. We ascertained patient mortality using the Social Security Death Index and reviewed the electronic medical records of all patients. When a patient's electronic medical record provided insufficient follow-up information, the patient's primary provider was contacted regarding clinical events. Complete follow-up was available for all patients.

Statistical analysis. Continuous data are presented as mean ± SD. Continuous data were compared using an unpaired Student *t* test or Mann-Whitney nonparametric test as appropriate. Variables lacking normal distributions and evaluated with nonparametric tests are summarized as medians and quartiles. Nominal data are presented as numbers and percents and were compared using Fisher exact tests or a chi-square test, as appropriate. The hazard ratio (HR) for the prediction of the event was calculated for mortality using a Cox regression model using 3 cohorts: all patients, patients without evidence of MI by clinical history or ECG, and patients without evidence of MI by clinical history, ECG, or LGE imaging. We considered all the significant variables in the univariate analysis and sought the best overall multivariate models for mortality, by stepwise forward selection with a probability to enter the set at $p = 0.01$ and to remove the effect from the regression at $p = 0.01$. Event curves were determined according to the Kaplan-Meier method, and comparisons of mortality rates were performed using the log-rank test. A 2-tailed p value <0.05 was considered significant for all other analyses. SAS was used for statistical analysis (SAS Institute Inc., Cary, North Carolina).

Table 1 Characteristics of All Patients, Patients Without Prior MIs by Clinical History or ECG, and Stratified by the Presence or Absence of LGE

Variable	Entire Cohort (n = 720)	No Prior MI (n = 664)	LGE (n = 88)	No LGE (n = 576)	p Value*
Age (yrs)	56 ± 10	56 ± 11	59 ± 10	55 ± 10	0.007
Men	531 (74%)	484 (73%)	63 (71%)	421 (73%)	0.69
Duration of AF	50 (29–83)	49 (29–84)	54 (34–84)	49 (16–77)	0.71
Paroxysmal AF	250 (35%)	229 (35%)	32 (36%)	197 (34%)	0.72
Persistent AF	472 (66%)	435 (65%)	49 (60%)	386 (67%)	0.72
Prior AF ablation	173 (24%)	160 (24%)	24 (27%)	136 (24%)	0.50
Cardiovascular risk factors					
Diabetes mellitus	106 (15%)	98 (15%)	18 (20%)	80 (14%)	0.11
Hypertension	365 (51%)	324 (49%)	50 (57%)	274 (48%)	0.11
Heart failure	186 (26%)	172 (26%)	32 (36%)	140 (24%)	0.02
Obstructive sleep apnea	142 (20%)	130 (20%)	27 (31%)	103 (18%)	0.009
Valvular heart disease	77 (11%)	70 (11%)	12 (14%)	58 (10%)	0.35
Hyperthyroidism	34 (5%)	32 (5%)	5 (6%)	27 (5%)	0.60
Hypercholesterolemia	240 (33%)	203 (31%)	31 (35%)	172 (30%)	0.32
Excessive alcohol intake	59 (8%)	54 (8%)	5 (6%)	49 (8%)	0.53
Family history of AF	88 (12%)	84 (13%)	10 (11%)	74 (13%)	0.73
Medications					
Aspirin	325 (45%)	291 (44%)	39 (44%)	252 (44%)	0.95
Beta-blockers	491 (68%)	446 (67%)	66 (75%)	380 (66%)	0.11
Calcium-channel blocker	164 (23%)	148 (22%)	19 (22%)	129 (22%)	1.00
ACE inhibitors/ARBs	261 (36%)	234 (35%)	34 (39%)	200 (35%)	0.47
Class I antiarrhythmic agents	157 (22%)	157 (24%)	16 (18%)	141 (24%)	0.22
Class III antiarrhythmic agents	341 (47%)	298 (45%)	45 (51%)	253 (44%)	0.21
Digoxin	64 (9%)	56 (8%)	8 (9%)	48 (8%)	0.38
Spironolactone	19 (3%)	17 (3%)	3 (3%)	14 (2%)	0.48
Diuretic agents	126 (18%)	117 (18%)	20 (23%)	97 (17%)	0.18
Statins	237 (33%)	188 (28%)	30 (34%)	158 (27%)	0.21
BMI (kg/m^2)	29 ± 5	29.5 ± 5	30.6 ± 5	29.2 ± 5	0.03
Systolic blood pressure (mm Hg)	127 ± 17	127 ± 17	126 ± 19	127 ± 17	0.89
Diastolic blood pressure (mm Hg)	75 ± 12	75 ± 12	74 ± 12	75 ± 12	0.56
Heart rate (beats/min)	72 ± 17	72 ± 17	73 ± 19	72 ± 17	0.88
Electrocardiographic parameters					
Sinus rhythm at presentation	459 (64%)	430 (65%)	56 (64%)	374 (65%)	0.81
AV delay (ms)	172 ± 31	172 ± 32	185 ± 33	170 ± 31	0.006
QRS duration (ms)	96 ± 15	96 ± 15	100 ± 18	95 ± 14	0.006
QTc duration (ms)	442 ± 33	441 ± 33	445 ± 28	440 ± 33	0.15
LVH by ECG (Sokolov criteria)	56 (8%)	52 (8%)	8 (9%)	44 (8%)	0.67
GFR ($ml/min/1.73\ m^2$)	83 ± 17	83 ± 17	78 ± 17	84 ± 17	0.001

Values are mean ± SD, n (%), or median (interquartile range). *LGE-positive versus LGE-negative patients without clinical histories of MI.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; AV = atrioventricular; BMI = body mass index; ECG = electrocardiography; GFR = glomerular filtration rate (using the Modification of Diet in Renal Disease formula done at the time of cardiac magnetic resonance imaging); LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; MI = myocardial infarction; QTc = corrected QT.

Results

In total, 720 consecutive patients were referred for CMR imaging in preparation for pulmonary vein isolation. Of the entire cohort, 56 patients had prior MIs by clinical history or ECG. Cohort characteristics from the entire cohort of 720 patients, the 664 patients without known MI by clinical history or ECG, and this cohort of 664 patients further stratified according to the presence or absence of LGE are presented in Table 1. In brief, in this final study cohort, there were 484 men (73%), with a mean age of 56 ± 11 years (range: 24 to 85 years). Patients presented a median of 49 months after first symptomatic onset of AF (range: 12 months to 12 years); 435 patients (65%) had persistent AF, 229 (35%) had paroxysmal AF, and 430 (65%) were in sinus rhythm at the time of the study. There were 324 patients (49%) with hypertension, 130 (20%) with sleep apnea, 98 (15%) with diabetes, and 172 (26%) with heart failure. In total, 429 patients (69%) were taking class I or class III antiarrhythmic agents.

Imaging characteristics. Imaging characteristics from the entire cohort of 720 patients, the 664 patients without known MI by clinical history or ECG, and this cohort separated according to the presence or absence of LGE are presented in Table 2. By echocardiography, the mean LV EF was 55 ± 10%, the mean LV end-diastolic dimension was 49 ± 5 mm, the mean left atrial dimension was 41 ± 7 mm, and the mean estimated pulmonary artery systolic pressure was 29 ± 7 mm Hg. By CMR imaging, the mean LV end-diastolic volume was 167 ± 42 mL, the mean LV EF was 56 ± 10%, the mean LV mass indexed to body surface area was 71 ± 12 g, the mean right ventricular end-diastolic volume was 163 ± 42 ml, and the mean right ventricular EF was 52 ± 8% (Table 2).

LGE. Among the entire cohort, LGE was detected in 108 patients (15%). Among the entire cohort, the LGE pattern was ischemic in 59% (transmural in 14 [13%] and subendocardial in 50 [46%]) and nonischemic in 41% (midmyocardial in 32 [30%], insertion point in 11 [10%], and epicardial in 1 [1%]) (Table 2). When patients with clinical histories or electrocardiographic evidence of MI were excluded, LGE was detected in 88 (13%) (Table 2). The pattern of LGE was ischemic in 50% (transmural in 6 [7%] and subendocardial in 38 [43%]) and nonischemic in 50% (midmyocardial in 32 [37%], insertion point in 11 [12%], and epicardial in 1 [1%]; representative images are displayed in Fig. 1). The mean extent of LGE was 5.9 ± 3% (median 5.2%; range: 1.2% to 14.6%). Patients were grouped according to the presence or absence of LGE (Tables 1 and 2). There were baseline differences

Table 2 Imaging Characteristics of All Patients, Patients Without Prior MIs by Clinical History or ECG, and Stratified by the Presence or Absence of LGE

Variable	Entire Cohort (n = 720)	No Prior MI (n = 664)	LGE (n = 88)	No LGE (n = 576)	p Value
Echocardiographic parameters					
LV EF (%)	55 ± 10	55 ± 10	54 ± 13	55 ± 10	0.21
LV diastolic dimension (mm)	49 ± 5	49 ± 5	49 ± 7	49 ± 5	0.62
Estimated PASP (mm Hg)	29 ± 7	29 ± 7	28 ± 7	29 ± 7	0.28
Left atrial dimension (mm)	41 ± 6	41 ± 6	43 ± 6	41 ± 6	0.0004
CMR imaging					
LV EDV (ml)	168 ± 43	167 ± 42	165 ± 42	167 ± 42	0.68
LV ESV (ml)	75 ± 28	74 ± 27	76 ± 30	73 ± 26	0.37
LV EF (%)	56 ± 10	56 ± 10	54 ± 12	57 ± 9	0.006
LV mass (g)	149 ± 33	148 ± 33	154 ± 37	148 ± 33	0.08
LV mass index (g/m^2)	72 ± 12	71 ± 12	74 ± 14	71 ± 12	0.01
RV EDV (ml)	164 ± 42	163 ± 42	154 ± 43	164 ± 42	0.07
RV ESV (ml)	80 ± 26	80 ± 26	75 ± 29	81 ± 25	0.10
RV EF (%)	52 ± 7	52 ± 8	53 ± 8	52 ± 7	0.32
Left atrial dimension (mm)	41 ± 7	41 ± 7	44 ± 8	40 ± 7	<0.0001
LV LGE	108 (15%)	88 (13%)			
LV LGE FWHM (% of LV mass)	6.4 ± 3.5	5.9 ± 3			
LV LGE location					
Subendocardial	50 (46%)		38 (43%)		
Transmural	14 (13%)		6 (7%)		
Epicardial	1 (1%)		1 (1%)		
Midmyocardial	32 (30%)		32 (37%)		
Insertion points	11 (10%)		11 (12%)		

Values are mean ± SD or n (%). *LGE-positive versus LGE-negative patients without clinical histories of MI.

CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; FWHM = full width at half maximum; LV = left ventricular; PASP = pulmonary artery systolic pressure; RV = right ventricular; other abbreviations as in Table 1.

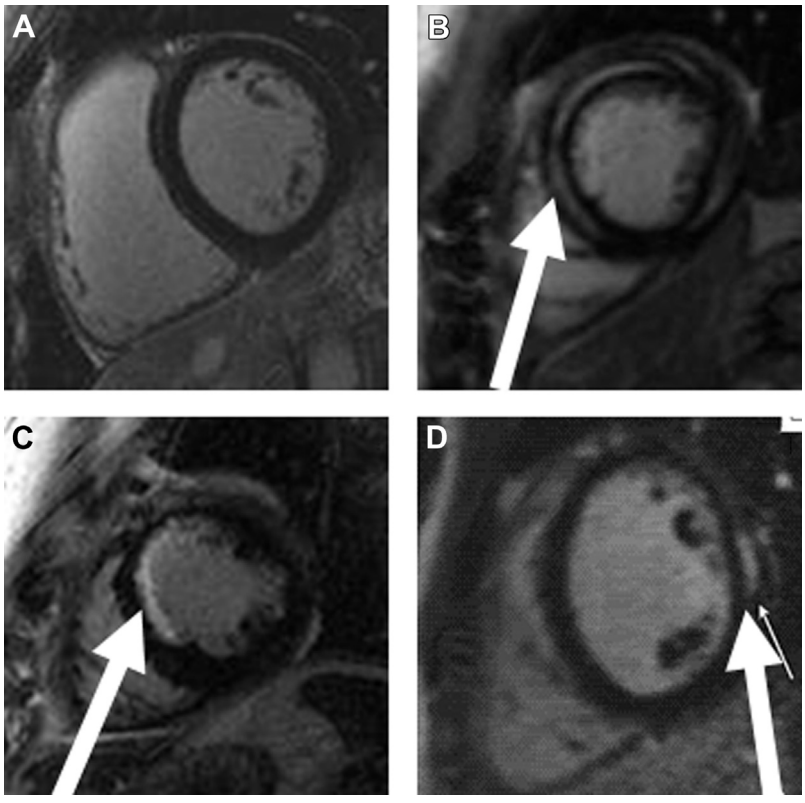

Figure 1 **Representative LGE Images**

Late gadolinium enhancement (LGE) images comparing a normal patient **(A)**; a patient with midmyocardial (LGE), typically seen in dilated cardiomyopathy **(B)**; a patient with a subendocardial MI **(C)**; and a patient with subepicardial LGE **(D)**. Regions of LGE are highlighted using **white arrows**.

among the cohorts with and without LGE. Patients with LGE were on average older and were more likely to have heart failure and sleep apnea. Patients with LGE were also more likely to have lower glomerular filtration rates, lower LV EFs, increased LV mass, increased left atrial dimensions, longer PR intervals, and wider QRS intervals. We performed clinical follow-up in patients with unanticipated LGE. There were 44 patients with LGE in an ischemic distribution. Of these 44 patients, 42 underwent stress testing with imaging, 26 had evidence of ischemia, 21 had evidence of significant coronary artery disease on angiography, and 18 underwent revascularization procedures. Of the patients with LGE in a nonischemic distribution (n = 44), 38 underwent stress testing or angiography. Of these patients, 5 had evidence of significant coronary artery disease, and 2 underwent revascularization procedures. In comparison, 85 of the 576 patients (16%) without LGE underwent subsequent assessment for the presence of obstructive coronary disease ($p < 0.001$). We conclude that, although limited by verification bias, an ischemic pattern of LGE was strongly associated with significant angiographic coronary stenosis and subsequent coronary revascularization.

Mortality. There were 68 deaths over a median of 42 months of follow-up. The mortality rate of the whole cohort was 2.9% per patient-year. There were 46 deaths among 582 patients without LGE (2.3% mortality rate per patient-year), compared with 22 deaths among 88 patients with LGE (8.1% mortality rate per patient-year).

Univariate and multivariate associations with mortality. We tested the associations with mortality among 3 cohorts: all patients, patients without evidence of MI by clinical history or ECG, and patients without evidence of MI by clinical history, ECG, or LGE imaging. Among the entire cohort of all patients, there were 78 deaths. On univariate analysis among all patients (Table 3), age (HR: 1.05; 95% confidence interval [CI]: 1.02 to 1.07; chi-square likelihood ratio [LRχ^2]: 14.9; $p = 0.0001$), diabetes (HR: 2.07; 95% CI: 1.23 to 3.50; LRχ^2: 7.56; $p = 0.006$), hypertension (HR: 1.72; 95% CI: 1.10 to 2.71; LRχ^2: 5.55; $p = 0.02$), heart failure (HR: 1.76; 95% CI: 1.17 to 2.80; LRχ^2: 5.92; $p = 0.01$), left atrial dimension (HR: 1.04; 95% CI: 1.01 to 1.08; LRχ^2: 7.36; $p = 0.007$), the presence of LGE (HR: 6.09; 95% CI: 3.88 to 9.55; LRχ^2: 25.5; $p < 0.0001$), and the extent of LGE (HR: 1.17; 95% CI: 1.10 to 1.24; LRχ^2: 25.8; $p < 0.0001$) provided the strongest

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Table 3 Univariate Analyses for Associations With Mortality Among All Patients

Variable	HR	95% CI	LRχ^2	p Value
Age	1.05	1.02–1.07	14.90	0.0001
Male	0.78	0.47–1.31	0.87	0.35
Duration of AF	1.00	0.99–1.00	0.43	0.51
History of hypertension	1.72	1.10–2.71	5.55	0.02
History of AF ablation	0.80	0.45–1.41	0.59	0.44
History of MI	1.59	0.69–3.67	1.19	0.27
MI on ECG	2.48	1.00–6.17	3.84	0.05
History of diabetes mellitus	2.07	1.23–3.50	7.56	0.006
History of obstructive sleep apnea	0.98	0.56–1.71	0.03	0.95
History of valvular heart disease	1.16	0.74–2.80	1.68	0.28
History of heart failure	1.76	1.17–2.80	5.92	0.01
Beta-blockers	1.49	0.90–2.49	2.39	0.12
ACE inhibitors/ARBs	1.58	1.02–2.46	4.10	0.05
Class I antiarrhythmic agents	0.53	0.29–1.02	3.78	0.08
Class III antiarrhythmic agents	1.51	0.87–2.13	1.91	0.17
Diuretic therapy	1.17	0.67–2.06	1.17	0.57
Statin use	1.73	0.63–2.57	0.51	0.47
Aspirin use	0.75	0.48–1.17	1.59	0.20
Systolic blood pressure	0.99	0.98–1.01	0.86	0.35
Diastolic blood pressure	0.99	0.97–1.01	1.44	0.23
Heart rate	1.01	0.10–1.02	2.56	0.11
BMI	1.04	0.99–1.09	3.12	0.08
Sinus rhythm (at presentation)	0.90	0.56–1.45	0.19	0.66
AV delay	1.02	0.99–1.01	0.28	0.60
QRS duration	1.01	1.00–1.02	4.02	0.05
QTc duration	1.00	1.00–1.01	0.74	0.39
Echocardiographic parameters				
LV EF	0.99	0.97–1.01	1.51	0.22
Estimated PASP	1.00	0.97–1.04	0.05	0.83
LV diastolic dimension	1.01	0.97–1.06	0.23	0.63
Left atrial dimension	1.04	1.02–1.07	4.38	0.04
CMR imaging				
LV EDV	1.00	0.99–1.00	0.02	0.90
LV ESV	1.01	1.00–1.01	1.85	0.17
LV EF	0.98	0.96–1.02	2.99	0.08
LV mass index	1.01	0.99–1.03	0.96	0.39
RV EDV	1.00	0.99–1.00	0.10	0.92
RV ESV	0.99	0.98–1.00	1.27	0.26
RV EF	1.00	0.97–1.03	0.43	0.51
Left atrial dimension	1.04	1.01–1.08	7.36	0.007
LGE				
Presence of LGE	6.09	3.88–9.55	25.50	<0.0001
Midmyocardial LGE	5.41	3.28–8.15	18.70	0.0001
Subendocardial LGE	5.92	3.18–8.60	23.20	<0.0001
Extent of LGE	1.17	1.10–1.24	25.80	<0.0001

CI = confidence interval; HR = hazard ratio; LRχ^2 = chi-square likelihood ratio; other abbreviations as in Tables 1 and 2.

unadjusted associations with mortality among the entire cohort. In a multivariate model among all patients, age (HR: 1.04; 95% CI: 1.01 to 1.06; LRχ^2: 8.81; p = 0.003) and the extent of LGE provided the strongest adjusted associations

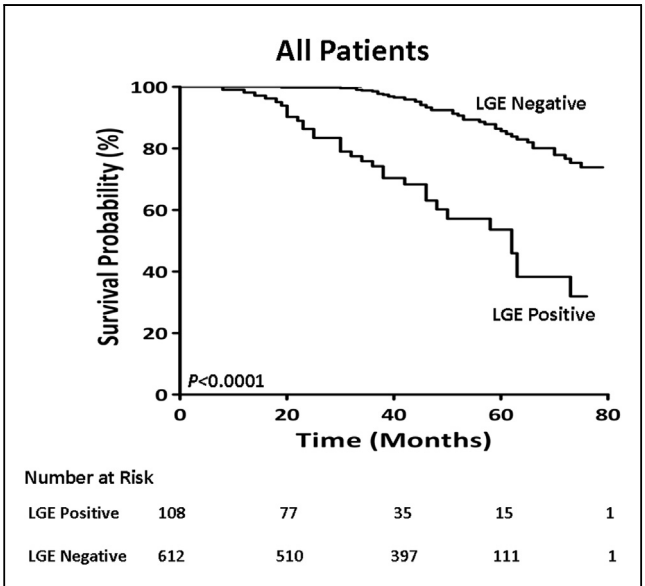

Figure 2 Survival Probability by Presence or Absence of LGE

Kaplan-Meier curves displaying survival probability in cohorts according to the presence or absence of late gadolinium enhancement (LGE). Results were compared using a log-rank test (p < 0.0001).

with mortality (HR: 1.16; 95% CI: 1.10 to 1.22; LRχ^2: 24.5; p < 0.0001). A Kaplan-Meier curve showing the difference in mortality between all patients according to the presence or absence of LGE is shown in Figure 2. In a second cohort, we excluded patients with clinical histories of MI or evidence of MI by ECG. In that cohort, on univariate analysis, age (HR: 1.05; 95% CI: 1.03 to 1.08; LRχ^2: 15.2; p = 0.0001), diabetes (HR: 2.39; 95% CI: 1.41 to 4.09; LRχ^2: 10.3; p = 0.001), heart failure (HR: 1.78; 95% CI: 1.09 to 2.91; LRχ^2: 5.37; p = 0.02), left atrial dimension (HR: 1.04; 95% CI: 1.01 to 1.08; LRχ^2: 6.47; p = 0.01), the presence of LGE (HR: 5.08; 95% CI: 3.08 to 8.36; LRχ^2: 28.8; p < 0.0001), and the extent of LGE (HR: 1.15; 95% CI: 1.10 to 1.21; LRχ^2: 35.6; p < 0.0001) provided the strongest associations with mortality (Table 4). In a multivariate model, age (HR: 1.05; 95% CI: 1.02 to 1.08; LRχ^2: 11.1; p = 0.009) and the extent of LGE (HR: 1.15; 95% CI: 1.10 to 1.21; LRχ^2: 32.5; p < 0.0001) again provided the strongest adjusted associations with mortality. A Kaplan-Meier curve showing a significant difference in survival among this cohort, according to the presence or absence of LGE, is presented in Figure 3. In the third cohort, we excluded patients with histories of MI by clinical history, ECG, or an ischemic LGE pattern on CMR (Table 5). In this third cohort, the extent of LGE had the strongest unadjusted association with mortality (HR: 1.24; 95% CI: 1.13 to 1.35; LRχ^2: 22.4; p < 0.0001).

Discussion

We aimed to determine the incidence, pattern, and prognostic significance of myocardial scar in patients with AF

Table 4 Univariate Analyses for Associations With Mortality in Patients Without Prior MIs by History or ECG

Variable	HR	95% CI	LRχ^2	p Value
Age	1.05	1.03–1.08	15.20	0.0001
Male	0.72	0.42–1.24	1.37	0.24
Duration of AF	1.00	0.99–1.00	0.12	0.73
History of hypertension	1.58	0.98–2.56	3.51	0.06
History of AF ablation	0.89	0.49–1.62	0.15	0.70
History of diabetes mellitus	2.39	1.41–4.09	10.30	0.001
History of obstructive sleep apnea	1.52	0.97–2.02	2.08	0.18
History of valvular heart disease	1.51	0.75–3.06	1.36	0.24
History of heart failure	1.78	1.09–2.91	5.37	0.02
History of paroxysmal AF	1.00	0.69–1.46	0.01	0.95
History of persistent AF	1.01	0.69–1.46	0.01	0.98
AF recurrence after PVI	1.39	0.99–1.96	3.67	0.06
Beta-blockers	1.36	0.79–2.32	1.23	0.27
Calcium-channel blockers	1.25	0.71–2.19	0.62	0.43
ACE inhibitors/ARBs	1.22	0.74–2.03	0.60	0.44
Class I antiarrhythmic agents	0.59	0.32–1.08	2.91	0.08
Class III antiarrhythmic agents	1.27	0.77–2.10	0.85	0.36
Diuretic therapy	0.14	0.61–2.05	0.13	0.71
Statin use	0.83	0.19–1.44	1.57	0.23
Systolic blood pressure	0.99	0.98–1.01	0.73	0.39
Diastolic blood pressure	0.99	0.97–1.01	1.39	0.24
Heart rate	1.01	0.99–1.02	2.32	0.12
BMI	1.04	0.99–1.09	2.65	0.10
Sinus rhythm (at presentation)	0.86	0.51–1.44	0.33	0.57
AV delay	1.00	0.99–1.01	0.57	0.45
QRS duration	1.01	1.00–1.03	4.03	0.05
QTc duration	1.01	1.00–1.01	2.17	0.14
Echocardiographic parameters				
LV EF	0.99	0.97–1.02	0.03	0.86
Estimated PASP	1.02	0.98–1.05	0.99	0.32
LV diastolic dimension	1.00	0.96–1.06	0.03	0.85
Left atrial dimension	1.03	1.00–1.07	3.15	0.08
CMR parameters				
LV EDV	1.00	0.99–1.00	0.09	0.76
LV ESV	1.00	0.99–1.01	0.55	0.46
LV EF	0.99	0.97–1.01	0.66	0.41
LV mass	1.00	0.99–1.01	0.03	0.85
LV mass index	1.00	0.98–1.03	0.23	0.63
RV EDV	0.99	0.99–1.00	0.05	0.83
RV ESV	0.99	0.99–1.00	0.08	0.76
RV EF	0.99	0.96–1.02	0.44	0.50
Left atrial dimension	1.04	1.01–1.08	6.47	0.01
LGE				
Presence of LGE	5.08	3.08–8.36	28.80	<0.0001
Midmyocardial LGE	5.91	3.58–11.6	26.70	<0.0001
Subendocardial LGE	3.71	1.95–7.10	15.90	0.0001
Extent of LGE*	1.15	1.10–1.21	35.60	<0.0001

*LGE extent HR is for each 1% absolute increase in LGE volume.
PVI = pulmonary vein isolation; other abbreviations as in Tables 1 to 3.

undergoing pulmonary vein isolation. We performed a full CMR study, including LV LGE imaging, in a large series of consecutive patients with AF. The principal findings of this study were as follows: 1) the incidence of unanticipated LV LGE was 13%; 2) there were 2 relatively even patterns of LV LGE noted in this study, an ischemic pattern and a nonischemic pattern; and 3) the presence of LV LGE had a significant relationship with mortality, even after adjusting for key variables such as sex, diabetes, and heart failure. Similar results were found when we included all patients with and without prior MIs.

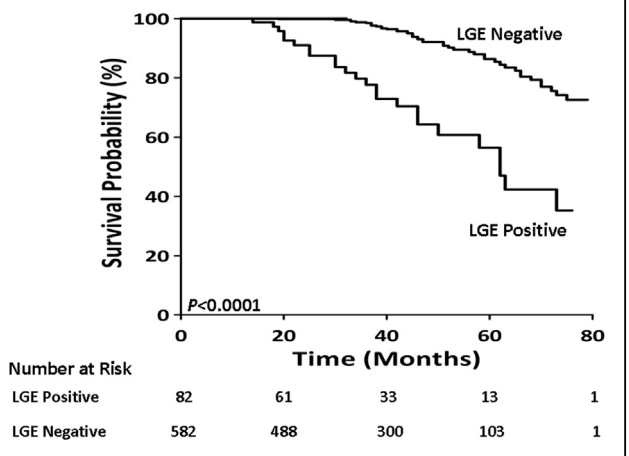

Figure 3 Survival Probability in Patients Without MI

Kaplan-Meier curves displaying survival probability in a subcohort of patients without clinical or electrocardiographic histories of myocardial infarction (MI). Results were compared using a log-rank test ($p < 0.0001$).

The presence of LV LGE provides strong and complementary prognostic information in patients with congenital heart disease (19), MI (14), coronary disease (11), myocarditis (20), aortic stenosis (12), endurance exercise (21), dilated cardiomyopathy (22), and hypertrophic cardiomyopathy (13). However, there are limited data detailing the presence and prognostic significance of LV LGE in patients with AF. In patients with hypertrophic cardiomyopathy, an increased volume of LGE was associated with an increased risk for AF (16,23), but there are no other data supporting myocardial LGE as a predictor of adverse outcomes in patients with AF. In patients with AF, there are robust data showing the associations between age, heart failure, diabetes, prior smoking, a murmur, and LV hypertrophy with mortality in patients with AF (24). Although our results are in a cohort referred for pulmonary vein isolation, there are consistencies between our work and prior data in other AF cohorts. Similar to community data (24), we found in patients referred for ablation that age, diabetes, and heart failure had unadjusted associations with mortality. We also provide additive imaging data and found that imaging provided prognostic information in selected patients with AF. Data are conflicting regarding the role of conventional imaging indexes and outcomes in patients with AF (25,26). In the AFFIRM (Atrial Fibrillation Follow-Up

Table 5 Univariate Analyses for Associations With Mortality in Patients Without Evidence of MI by Clinical History, ECG, or LGE Imaging

Variable	HR	95% CI	LRχ^2	p Value
Age	1.06	1.03–1.09	17.40	<0.0001
Male	0.69	0.40–1.22	1.60	0.21
Duration of AF	0.99	0.99–1.00	0.93	0.33
History of hypertension	1.58	0.94–2.66	2.91	0.09
History of AF ablation	0.76	0.39–1.48	0.64	0.42
History of diabetes mellitus	2.65	1.49–4.69	11.20	0.0008
History of obstructive sleep apnea	1.56	0.94–2.02	2.28	0.16
History of valvular heart disease	1.60	0.76–3.39	1.53	0.22
History of heart failure	2.02	1.19–3.41	6.84	0.009
Beta-blockers	1.43	0.81–2.50	1.56	0.21
Calcium-channel blockers	0.60	0.30–1.23	1.92	0.17
ACE inhibitors/ARBs	1.42	0.85–2.40	1.77	0.18
Class I antiarrhythmic agents	0.57	0.29–1.10	2.80	0.09
Class III antiarrhythmic agents	1.03	0.61–1.75	0.01	0.89
Diuretic therapy	1.23	0.65–2.32	0.39	0.53
Statin use	1.75	1.02–3.03	4.05	0.04
Systolic blood pressure	0.99	0.98–1.01	0.10	0.74
Diastolic blood pressure	1.01	0.98–1.03	0.81	0.37
Heart rate	1.01	0.99–1.02	2.17	0.14
BMI	1.04	0.99–1.10	2.60	0.11
Sinus rhythm (at presentation)	0.95	0.55–1.63	0.04	0.85
AV delay	1.00	0.99–1.00	0.11	0.74
QRS duration	1.01	1.00–1.03	4.81	0.03
QTc duration	1.01	0.99–1.02	3.32	0.07
Echocardiographic parameters				
LV EF	0.99	0.97–1.02	0.34	0.56
Estimated PASP	1.03	0.99–1.06	2.51	0.11
LV diastolic dimension	0.99	0.94–1.04	0.24	0.62
Left atrial dimension	1.02	0.98–1.06	0.84	0.36
CMR parameters				
LV EDV	1.00	0.99–1.01	0.01	0.95
LV ESV	1.00	0.99–1.01	0.25	0.62
LV EF	1.00	0.98–1.03	0.01	0.96
LV mass	1.00	0.99–1.01	0.13	0.72
LV mass index	1.00	0.98–1.02	0.04	0.85
RV EDV	1.00	0.99–1.01	0.26	0.61
RV ESV	1.00	0.99–1.01	0.26	0.61
RV EF	0.98	0.95–1.01	1.78	0.18
Left atrial dimension	1.02	0.98–1.06	0.65	0.42
LGE				
Presence of LGE	4.21	2.18–8.14	18.30	<0.0001
Extent of LGE	1.24	1.13–1.35	22.40	<0.0001

Abbreviations as in Tables 1 to 3.

Investigation of Rhythm Management) study, heart failure with reduced EF was a stronger predictor of adverse outcomes compared with heart failure with preserved EF (25). However, in unselected patients presenting to emergency departments with AF, there was no difference in outcomes when separated according to EF (26). We also found that the presence or absence of heart failure was a predictor of mortality, while EF was not.

The data on the prognostic value of LGE in a cohort of patients with AF are complementary and additive to prior data in patients with both nonischemic and ischemic patterns of LGE. In this study, these 2 broad, evenly distributed patterns of myocardial scarring were noted. A nonischemic pattern of LGE has been shown to be an independent predictor of mortality in patients with valvular heart disease (12), in patients with hypertrophic cardiomyopathy (27), and in patients with nonischemic cardiomyopathy (28). Similarly, LGE in an ischemic pattern has been shown to be an independent predictor of mortality in asymptomatic patients (15) and symptomatic patients with (29) and without a known prior MI (11). Finally, among all patients referred for CMR scans, combined ischemic and nonischemic patterns of LGE have been shown to predict mortality (30). The mechanisms involved in the development of LV LGE are not clear but are likely different according to LGE pattern. The ischemic pattern of LGE is likely related to silent MI and is similar to data from a large population-based study of volunteers (15). Specifically, Schelbert et al. (15) noted a 17% incidence of unrecognized MI. We believe that the lower percent of unrecognized MI in our population is due to a combination of the 20-year age difference, the percent of patients with diabetes, and baseline use rates of beneficial medications. However, similar to our study, Schelbert et al. (15) noted that the presence of an unrecognized MI was also strongly associated with subsequent mortality. We believe that the nonischemic pattern is likely related to the high percent of patients in our study with heart failure or reduced EFs (22), as more than 25% of our study group had histories of heart failure or reduced EFs.

There is significant variability in pulmonary vein anatomy, and imaging is routinely performed before pulmonary vein isolation in randomized studies of patients undergoing AF ablation (31,32) and in large clinical registries (6) and is supported by guidelines (7,9). However, there are limited data as to whether imaging is required (33), and multiple modalities exist, each with advantages and disadvantages (34). The choice of imaging modality usually depends on local expertise and available equipment and includes magnetic resonance (10), CT, angiography (35), and ultrasound (36). There are comparative data between modalities (37,38), but no study has integrated all imaging modalities, so a complete comparison is lacking. However, cardiac CT and CMR imaging provide superior spatial resolution over ultrasound (39,40) and can also be coregistered with electroanatomical mapping systems (9). Each has advantages and disadvantages. Cardiac CT is widely available and may also provide additive information beyond pulmonary vein anatomy (34); however, CT is associated with radiation exposure (41), and the presence of incidental findings is considerable (42). Magnetic resonance imaging has less availability, lower spatial resolution, and standard

contraindications to its use (7). Allowing for these, both CT and CMR imaging provide equivalent anatomical information (43). In this study, we did not test the ability of one modality over another to provide anatomical information but rather aimed to test whether the accessory information provided by a CMR study would be clinically useful. We found that the additive information provided by a CMR study, the presence of LGE, was an independent predictor of mortality. The CMR study detected infarct and noninfarct patterns of LGE, both of which have been shown to provide additive information in other cohorts (11,22).

Study limitations. This study should be interpreted within the context of the design format. There are data detailing the association between atrial LGE and AF recurrence in patients with AF (44), but the high-resolution sequence required is not part of our standard CMR imaging protocol. We also did not image all patients with AF; we imaged only patients undergoing pulmonary vein isolation. This likely represents a different phenotype from all patients with AF. We wanted to compare this cohort as it relates to all patients with AF. The AFFIRM study enrolled patients with similar LV EFs and a similar percent of patients with heart failure and noted an all-cause mortality rate of 4.7% per year; however, patients were on average 10 years older than in this study (45). The Rate Control Versus Electrical Cardioversion trial also enrolled patients with similar cardiac function, a similar proportion of patients with diabetes, and a higher proportion of patients with heart failure. In that study, the investigators noted a cardiovascular mortality rate of 3% per year (46). These data suggest that our cohort has significant similarities with other populations of patients with AF and that the observed mortality rate is appropriate. Also, we have no data on whether the presence or absence of LV LGE influenced treatment. Although imaging of the pulmonary veins is part of standard clinical and research practice, there are no randomized data supporting pre-ablation imaging on outcomes after ablation of AF. We recorded the medical therapy at the time of discharge after pulmonary vein isolation, and the change in patient-specific antiarrhythmic therapy over time was not included in this analysis. Finally, we did not perform a comparison of available imaging modalities to test their differential effects on outcomes.

Conclusions

Among a large cohort of patients with AF being referred for pulmonary vein isolation, we found a 13% incidence of unanticipated LV LGE. The presence of LV LGE provided strong prognostic information, with each adjusted 1% increase in LV LGE associated with a 15% increased risk for death. Many imaging modalities are available for visualization of the pulmonary vein anatomy before ablation of AF, and these data support the robust and additive prognostic information provided by CMR imaging.

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