

CMR Quantification of Myocardial Scar Provides Additive Prognostic Information in Nonischemic Cardiomyopathy

Tomas G. Neilan, MD,*†‡ Otavio R. Coelho-Filho, MD,* Stephan B. Danik, MD,†
Ravi V. Shah, MD,*† John A. Dodson, MD,* Daniel J. Verdini, MD,‡
Michifumi Tokuda, MD,* Caroline A. Daly, MD,* Usha B. Tedrow, MD,*
William G. Stevenson, MD,* Michael Jerosch-Herold, PhD,* Brian B. Ghoshhajra, MD,‡
Raymond Y. Kwong, MD, MPH*

Boston, Massachusetts

OBJECTIVES This study sought to determine whether the extent of late gadolinium enhancement (LGE) can provide additive prognostic information in patients with a nonischemic dilated cardiomyopathy (NIDC) with an indication for implantable cardioverter-defibrillator (ICD) therapy for the primary prevention of sudden cardiac death (SCD).

BACKGROUND Data suggest that the presence of LGE is a strong discriminator of events in patients with NIDC. Limited data exist on the role of LGE quantification.

METHODS The extent of LGE and clinical follow-up were assessed in 162 patients with NIDC prior to ICD insertion for primary prevention of SCD. LGE extent was quantified using both the standard deviation-based (2-SD) method and the full-width half-maximum (FWHM) method.

RESULTS We studied 162 patients with NIDC (65% male; mean age: 55 years; left ventricular ejection fraction [LVEF]: $26 \pm 8\%$) and followed up for major adverse cardiac events (MACE), including cardiovascular death and appropriate ICD therapy, for a mean of 29 ± 18 months. Annual MACE rates were substantially higher in patients with LGE (24%) than in those without LGE (2%). By univariate association, the presence and the extent of LGE demonstrated the strongest associations with MACE (LGE presence, hazard ratio [HR]: 14.5 [95% confidence interval (CI): 6.1 to 32.6; $p < 0.001$]; LGE extent, HR: 1.15 per 1% increase in volume of LGE [95% CI: 1.12 to 1.18; $p < 0.0001$]). Multivariate analyses showed that LGE extent was the strongest predictor in the best overall model for MACE, and a 7-fold hazard was observed per 10% LGE extent after adjustments for patient age, sex, and LVEF (adjusted HR: 7.61; $p < 0.0001$). LGE quantitation by 2-SD and FWHM both demonstrated robust prognostic association, with the highest MACE rate observed in patients with LGE involving $>6.1\%$ of LV myocardium.

CONCLUSIONS LGE extent may provide further risk stratification in patients with NIDC with a current indication for ICD implantation for the primary prevention of SCD. Strategic guidance on ICD therapy by cardiac magnetic resonance in patients with NIDC warrants further study. (J Am Coll Cardiol Img 2013;6:944–54) © 2013 by the American College of Cardiology Foundation

Nonischemic dilated cardiomyopathy (NIDC) is characterized by ventricular dilation and impairment of cardiac function in the absence of significant coronary artery disease (1). The annual mortality rate is reported at approximately 7%, with one-third of deaths classified as sudden and likely arrhythmia mediated (2). Implantable cardioverter-defibrillators (ICDs) reduce mortality in patients with NIDC and an ejection fraction (EF) of $\leq 35\%$ (3). However, the majority of patients with NIDC do not benefit from ICD implantation (4,5), and significant procedural risks and expensive downstream healthcare costs exist (6). Therefore, research to develop methods of improved risk stratification beyond conventional measures of cardiac function and functional status would appear to be of significant value (7).

Myocardial fibrosis identified using late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) has been shown to be a predictor of death, ICD therapy, and heart failure hospitalizations in patients with a NIDC (8-11). Outcomes data in patients with NIDC are further supported by mechanistic studies demonstrating that the presence of myocardial scar by LGE-CMR is associated with ventricular arrhythmias (12,13). The presence of LGE provides prognostic information; however, there are limited data on whether quantification of the extent of LGE provides prognostic information beyond identification of the presence of scar. Furthermore, these patients are at risk for the progression of heart failure and arrhythmic events, and an assessment of the differentiating ability of LGE for an arrhythmic versus a heart failure endpoint may be of value. Therefore, we aimed specifically to address whether quantification of LGE provides prognostic information about the risk for heart failure and the risk for arrhythmia in patients with NIDC undergoing ICD implantation for the primary prevention of sudden cardiac death (SCD). We hypothesized that a greater extent of scar would be associated with an increased risk for adverse outcomes.

METHODS

Study population. We performed a prospective observational study in which we collected data on

consecutive patients with NIDC who underwent a CMR study with gadolinium followed by an ICD insertion. CMR studies were performed between 2003 and 2011 at Brigham and Women's Hospital (BWH) and at Massachusetts General Hospital (MGH) in Boston, Massachusetts. Patients were entered into a registry at the time of the CMR study. We then identified all those who had an ICD inserted for the primary prevention of SCD. The diagnosis of NIDC was based on World Health Organization definitions (14). Significant coronary disease was excluded by both clinical history and cardiac investigation. Specifically, the majority of patients in the cohort (156 of 162) underwent coronary angiography to exclude significant coronary artery disease ($>50\%$ luminal narrowing). The remaining 6 patients, ages 18, 20, 22, 22, 24, and 30 years, had undergone recent negative imaging stress testing, and none of the patients had LGE in the distribution typical of myocardial infarction. Other exclusion criteria included an infiltrative cardiomyopathy based either on history or CMR findings and a prior indication for placement of an ICD (such as syncope, cardiac arrest, or sustained ventricular arrhythmias). The protocol was approved by the Human Subjects Review Committee at both hospitals.

CMR protocol. All images were acquired with electrocardiography gating and breath-holding and with the patient in the supine position. Subjects were imaged on either a 1.5-T ($n = 75$) or a 3.0-T ($n = 87$) CMR system (Signa CV/I HDXt platform, General Electric Healthcare, Waukesha, Wisconsin, and Tim Trio, Siemens, Erlangen, Germany, respectively). Both CMR protocols consisted of cine steady-state free precession imaging for cardiac function (BWH: typical repetition time: 3.4 ms; echo time: 1.2 ms; in-plane spatial resolution: 1.6×2 mm; MGH: typical repetition time: 3.5 ms; echo time: 1.4 ms; in-plane resolution: 2.0×2.0 mm) and LGE imaging for myocardial fibrosis (BWH: repetition time: 4.8 ms; echo time: 1.3 ms; inversion time: 200-300 ms; MGH: repetition time: 7.1 ms; echo time: 3.1 ms;

ABBREVIATIONS AND ACRONYMS

CMR	= cardiac magnetic resonance
EF	= ejection fraction
FWHM	= full-width half-maximum
ICD	= implantable cardioverter-defibrillator
LGE	= late gadolinium enhancement
MACE	= major adverse cardiac events
NIDC	= nonischemic dilated cardiomyopathy
SCD	= sudden cardiac death
VT	= ventricular tachycardia

inversion time: 150 to 300 ms). A segmented inversion-recovery pulse sequence for LGE was used starting 10 to 15 min after a cumulative dose of 0.15 mmol/kg of gadolinium diethylenetriaminepenta-acetic acid. Cine imaging and LGE imaging were obtained in 8 to 14 matching short-axis (BWH: 8 mm thick with 0-mm spacing; MGH: 8 mm thick with 2-mm spacing) and 3 radial long-axis planes. To determine whether active myocarditis was playing a role in the reduced EF, a T₂-weighted inversion recovery prepared fast-spin echo sequence was performed using 3 short-axis slices of 12-mm thickness at the base, mid, and apex and a single long-axis slice in a 4-chamber view (15). Qualitatively, the sequence was considered abnormal if there were patchy areas of high T₂ signal intensity indicating focal or regional edema. All images were analyzed with specialized software (Mass Research, University Medical Centre, Leiden, the Netherlands) by researchers blinded to clinical outcome.

Late gadolinium enhancement. 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 was quantified by a semiautomatic detection method using two previously validated methods (16,17). Both methods measured the mass of LGE (in grams), which was then expressed as a percentage of total left ventricular (LV) mass. LGE was quantified using a signal intensity threshold of >2 SD above a remote reference region and also using regions defined as above 50% of maximal signal intensity of the enhanced area (full-width at half maximum [FWHM]). The distribution of LGE was characterized as either midwall, epicardial, focal/involving the right ventricular insertion points, or diffuse. If more than one pattern was present, the distribution was characterized on the basis of the predominant pattern.

Echocardiography. LV mass was derived from the 2-dimensional measurements of intraventricular septal thickness, posterior wall thickness, and LV internal dimensions in diastole, as recommended by the American Society of Echocardiography (18,19). LVEF was measured using the biplane method of discs. Pulmonary artery systolic pressure was estimated from the tricuspid regurgitant velocity plus an estimate of right atrial pressure derived from the inferior vena cava.

Methods of clinical follow-up. We ascertained mortality using the Social Security Death Index and confirmed using electronic chart review. Adjudication of ICD events were performed by 2 cardiac

electrophysiologists (S.B.D., M.T.) blinded to all other clinical data; events were classified as appropriate if they were a result of ventricular tachyarrhythmia according to established criteria (20). Patients were followed up at 3- to 6-month intervals via clinic visits or, if appropriate, transmitted ICD data. Survival analyses were performed for 3 clinical endpoints: 1) the primary endpoint of major adverse cardiac events (MACE), which included a composite of cardiovascular death and a ventricular arrhythmia, terminated by the ICD (either antitachycardia pacing or ICD shock); 2) a secondary endpoint of arrhythmia, defined as a combination of appropriate antitachycardia pacing (ATP) therapy, appropriate ICD shock, and SCD; and 3) a third endpoint, heart failure, defined as heart failure-related death or heart failure hospitalization. The duration of follow-up was determined from the CMR study date to the occurrence of an endpoint. If no endpoint occurred, the patient's data were censored at the date of last clinical follow-up. Complete follow-up was available for all patients.

Statistical analysis. Continuous data are presented as mean \pm SD. Continuous data were compared using an unpaired Student *t* test or Mann-Whitney nonparametric test as appropriate. Nominal data are presented as number and percentages and were compared using a chi-square test. We randomly selected 15 patients with LGE and compared the measurement of LGE volume using both the 2-SD method and the FWHM method. Cohen's kappa was applied to measure inter-reader and intrareader agreement on the volume of LGE using the following grading: 0 to 0.2 (poor), 0.21 to 0.4 (fair), 0.41 to 0.6 (moderate), 0.61 to 0.8 (substantial), and 0.81 to 1.0 (nearly perfect) (21). To test for correlation between the different methods of measuring LGE volume, a Spearman rank correlation coefficient was used. The hazard ratio (HR) for the prediction of events was calculated for each of the outcomes using a Cox regression model. For each outcome of interest, we considered all of the significant variables in the univariate analysis and sought the best overall multivariate models for the composite endpoint, by stepwise-forward selection, with a probability to enter set at $p < 0.05$ and to remove the effect from the regression at $p < 0.05$. We also performed a second multivariate analysis of the associations with established risk factors for adverse outcomes in patients with a cardiomyopathy (age, sex, LVEF, LV end-diastolic volume, and diabetes) and included LGE in this clinical model. Event curves were determined according to the Kaplan-Meier method, and comparisons of

cumulative event rates were performed using the log-rank test. Receiver-operator characteristic (ROC) curves were constructed to determine optimal cutoff (value with the maximal sensitivity and specificity) of LGE extent as measured using both the 2-SD method and the FWHM method to predict MACE. Based on the available literature (8), expecting a 15% difference in the MACE rates between patients with and without LGE, we calculated that we would need 76 subjects in each group (with and without LGE) in order to find a statistically significant difference with a 2-tailed p value <0.05. SAS (SAS Institute Inc., Cary, North Carolina) was used for statistical analysis.

RESULTS

In total, a cohort of 254 patients were identified. From this cohort, 96 patients were excluded due to a prior indication for ICD insertion (n = 45), LGE in a typical infarct pattern (n = 29), or infiltrative cardiomyopathy (n = 22). Of the 29 patients excluded due to LGE in an infarct pattern, 23 underwent negative stress testing prior to the CMR study, and 6 underwent coronary angiography. In the former group of 23 patients, based on the results of the CMR study, coronary angiography was subsequently performed, with significant coronary disease (>50% luminal narrowing) found in 22 patients. Among the 6 patients with prior angiography, all had coronary disease, but of a severity less than the 50% luminal narrowing. Of the 22 patients with an infiltrative cardiomyopathy diagnosed based on the CMR findings, 12 had hemochromatosis, 6 had cardiac sarcoidosis, and 4 had cardiac amyloid. The final cohort consisted of 162 patients who underwent ICD placement, and all were included in the analysis (Tables 1 and 2). There were 106 men and 56 women referred for a CMR study, with a mean LVEF by echocardiography of 26 ± 8%. Median follow-up was 26 months (interquartile range [IQR]: 15 to 43 months; mean: 29 ± 18 months). The CMR study was performed at a median of 13 months (IQR: 9 to 16 months) after onset of heart failure. The majority of patients (56%) were New York Heart Association (NYHA) functional class II; the remainder were functional class III. Among the entire cohort, 98% were prescribed a beta-blocker, 95% either an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, and 41% an aldosterone antagonist. Thirty-eight patients (24%) underwent cardiac resynchronization therapy at the time of ICD

insertion. None of the patients in the entire cohort had qualitative evidence of myocardial edema by T₂ imaging.

Late gadolinium enhancement. LGE was present in 81 patients (50%) (Tables 1 and 2). The LGE pattern was mid-myocardial in 42 patients (52%), epicardial in 21 (26%), focal/insertion points in 16 (20%), and diffuse in 2 (2%). Patients were grouped

Table 1. Baseline Patient Characteristics According to the Presence or Absence of Late Gadolinium Enhancement

	All Patients (n = 162)	LGE Negative (n = 81)	LGE Positive (n = 81)	p Value
Age, yrs	55 ± 14	55 ± 11	55 ± 15	0.56
Male	106 (65)	47 (58)	59 (73)	0.07
Cardiovascular risk factors				
Diabetes	41 (25)	21 (26)	20 (25)	1.00
Hypertension	63 (39)	32 (40)	31 (38)	1.00
Atrial fibrillation	40 (25)	18 (22)	22 (27)	0.59
Family history of DCM	13 (8)	6 (7)	7 (9)	1.00
Alcohol excess	6 (4)	3 (4)	3 (4)	1.00
NYHA functional class				
II	91 (56)	46 (57)	45 (56)	1.00
III	71 (44)	35 (43)	36 (44)	1.00
Heart failure duration, months	13 (9,16)	13 (8-18)	13 (10-16)	0.77
CMR to ICD, months	0.5 (0.25-2.5)	1 (0.5-3)	1 (0.5-2)	0.67
CRT	38 (24)	18 (22)	20 (25)	0.56
BMI, kg/m ²	29 ± 6	29 ± 4	29 ± 7	0.75
SBP, mm Hg	115 ± 18	115 ± 17	115 ± 8	0.48
DBP, mm Hg	71 ± 11	72 ± 10	70 ± 11	0.39
Heart rate, beats/min	74 ± 13	76 ± 13	72 ± 14	0.66
Medication				
ACE/ARB	154 (95)	76 (94)	78 (96)	1.00
Beta-blocker	158 (98)	79 (98)	79 (98)	1.00
Spironolactone	67 (41)	30 (37)	32 (40)	0.87
Diuretics	98 (61)	50 (62)	40 (49)	0.16
Antiarrhythmic	24 (15)	11 (14)	13 (16)	0.83
Coumadin	59 (36)	27 (33)	32 (40)	0.51
Aspirin	59 (36)	28 (35)	31 (38)	0.74
Statin	58 (36)	28 (35)	30 (37)	0.87
QRS duration, ms	117 ± 30	114 ± 33	120 ± 31	0.19
QTc duration, ms	459 ± 30	457 ± 39	461 ± 38	0.69
GFR, ml/min/1.73 m ²	70 ± 20	73 ± 19	67 ± 21	0.11

Values are mean ± SD, n (%), or median (IQR).

ACE/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI = body mass index; CMR to ICD = time from performance of the cardiac magnetic resonance scan to insertion of implantable cardioverter-defibrillator; CRT = cardiac resynchronization therapy; DCM = dilated congestive cardiomyopathy; DBP = diastolic blood pressure; GFR = glomerular filtration rate using the Modification of Diet in Renal Disease formula done at the time of the CMR; Heart failure duration = time from onset of symptoms to CMR; IQR = interquartile range; LGE Negative = patients without late gadolinium enhancement; LGE Positive = patients with late gadolinium enhancement; NYHA = New York Heart Association; SBP = systolic blood pressure.

Table 2. Imaging Characteristics of the Entire Cohort and Stratified According to the Presence or Absence of LGE

	All Patients (n = 162)	LGE Negative (n = 81)	LGE Positive (n = 81)	p Value
Echocardiography				
LVEF, %	26 ± 8	27 ± 9	24 ± 8	0.40
LVIDd, mm	61 ± 10	60 ± 8	62 ± 12	0.58
Estimated PASP, mm Hg	37 ± 12	34 ± 12	39 ± 13	0.13
CMR				
Field strength, 3.0-T vs. 1.5-T, %	87 ± 54	44 ± 54	43 ± 53	0.99
LVEDV, ml	270 ± 93	267 ± 91	274 ± 97	0.63
LVEDV index, ml/m ²	140 ± 50	136 ± 43	143 ± 51	0.45
LVESV, ml	199 ± 89	191 ± 85	207 ± 94	0.35
LVESV index, ml/m ²	103 ± 47	98 ± 41	109 ± 50	0.31
LVEF, %	28 ± 9	30 ± 7	26 ± 9	0.17
LV mass, g	158 ± 47	156 ± 48	160 ± 52	0.86
LV mass index, g/m ²	81 ± 24	80 ± 24	82 ± 25	0.65
RVEDV, ml	164 ± 62	160 ± 61	168 ± 65	0.81
RVEDV index, ml/m ²	84 ± 31	81 ± 29	87 ± 32	0.34
RVESV, ml	100 ± 55	97 ± 55	103 ± 59	0.31
RVESV index, ml/m ²	51 ± 28	49 ± 26	53 ± 30	0.34
RVEF, %	41 ± 13	44 ± 12	37 ± 13	0.12
LGE				
2-SD, % of LV mass			9 ± 5	
FWHM, % of LV mass			6 ± 4	
Epicardial			21 ± 26	
Mid-myocardial			42 ± 52	
Focal/insertion points*			16 ± 20	
Diffuse			2 ± 2	
Values are mean ± SD. *Predominant location of LGE in anterior or posterior right ventricular insertion points. CMR = cardiac magnetic resonance; FWHM = full-width half-maximum method; LGE = late gadolinium enhancement; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVIDd = left ventricular internal dimension in diastole; PASP = pulmonary artery systolic pressure; RVEDV = right ventricular end diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end systolic volume.				

according to the presence or absence of LGE (Tables 1 and 2). Although glomerular filtration rate, LVEF, and right ventricular EF were lower and estimated pulmonary artery systolic pressure was higher among patients with LGE, these differences were not statistically significant (e.g., LVEF: 26 ± 9% vs. 30 ± 7% in LGE positive vs. LGE negative, respectively; p = 0.17). The volume of LGE as a percentage of the total LV volume was, on average, 50% greater using the 2-SD method in comparison to the FWHM method (9 ± 5% by the 2-SD method vs. 6 ± 4% using the FWHM method; p < 0.001) (Table 2). However, there was a close correlation between the measurement of LGE volume using both methods (r = 0.91; p <

0.001). The kappa coefficients of agreement for the measurement of LGE extent using the 2-SD method were 0.67 (inter-reader) (mean difference in extent of LGE: 0.8%) and 0.65 (intrareader) (mean difference in extent of LGE: 1.1%). The corresponding values using the FWHM method were 0.68 (mean difference in extent of LGE: 0.5%) and 0.70 (mean difference in extent of LGE: 0.5%).

Major adverse cardiac events. There were 51 events among the 162 patients during a mean of 29 ± 18 months of follow-up (median follow-up: 26 months; IQR: 15 to 43 months). Forty-seven of these events were in patients with LGE (event rate: 24%/year), and 4 were in patients without LGE (event rate: 2%/year). Among LGE-positive patients, there were 19 episodes of ATP, 15 appropriate ICD discharges, and 13 cardiovascular deaths. An example of a patient with LGE who underwent ICD placement followed by an appropriate ICD discharge is shown in Figure 1. The 4 adverse events in LGE-negative patients consisted of 2 ATP events, 1 appropriate ICD discharge, and 1 cardiovascular death. The initial event, an ATP event, occurred 13 months after ICD implantation. The appropriate ICD discharge occurred 33 months after insertion, and the cardiovascular death occurred at 64 months after ICD insertion from intractable heart failure. The LGE-negative patients who had events were male, with a mean age of 51 ± 20 years, a mean LV end-diastolic volume of 295 ± 112 ml, a mean LVEF of 22 ± 9%, a mean right ventricular EF of 37 ± 18%, and a mean QRS width of 114 ± 46 ms. The presence of LGE had a sensitivity of 92% (95% confidence interval [CI]: 0.80 to 0.98), a specificity of 69% (95% CI: 0.60 to 0.78), a positive predictive value of 58%, and a negative predictive value of 95% for the occurrence of MACE. The Cox regression analysis revealed that the presence of LGE (HR: 14.5; 95% CI: 6.06 to 32.61; chi-square: 18.75; p < 0.001) and the extent of LGE (by 2-SD: HR: 1.15 for each 1% absolute increase in LGE by volume [95% CI: 1.12 to 1.18; chi-square: 43.26; p < 0.0001]; by FWHM: HR: 1.16 for each 1% increase in LGE extent by volume [95% CI: 1.12 to 1.20; chi-square: 41.6; p < 0.0001]) demonstrated the strongest unadjusted association with MACE (Table 3). We did not find an association between CMR field strength and MACE (HR: 1.03; 95% CI: 0.59 to 1.82; chi-square: 0.01; p = 0.91) (Table 3). In a multivariate model, LGE extent was the strongest covariate selected to form the

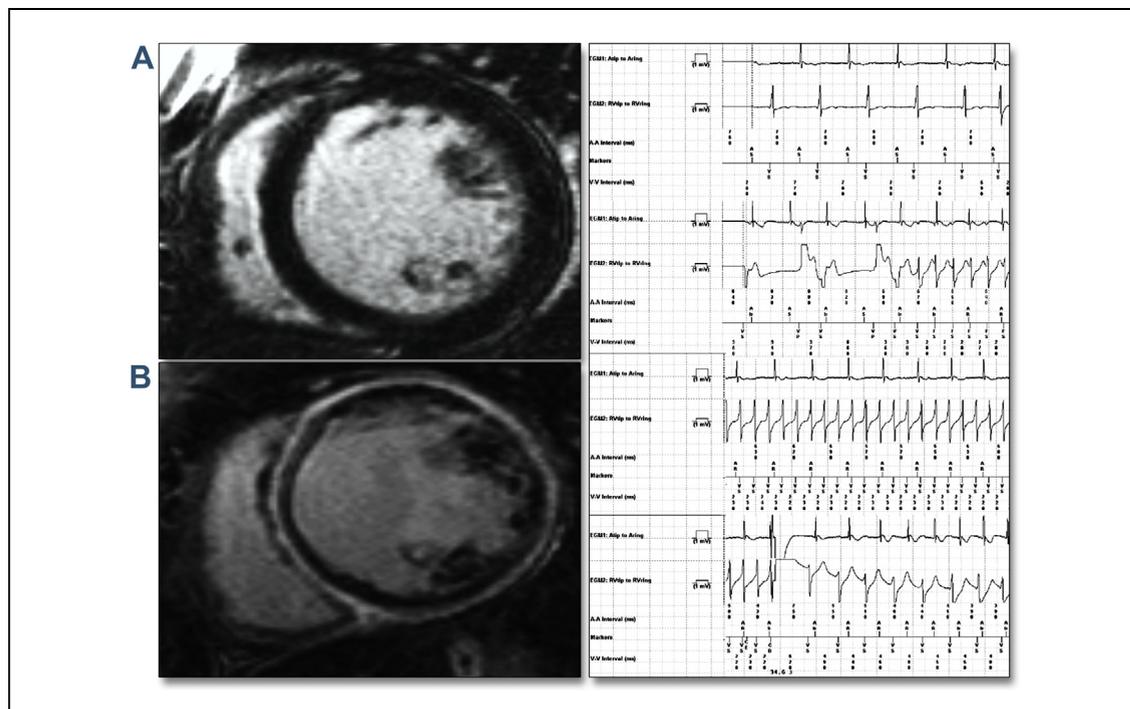


Figure 1. LGE and Adverse Events

Short-axis views of the ventricle after a segmented inversion–recovery pulse sequence for late gadolinium enhancement (LGE) starting 10 to 15 min after the administration of a cumulative dose of 0.15 mmol/kg of gadolinium diethylenetriaminepentaacetic acid in a patient without LGE (**A**) and with mid-myocardial LGE (**B**). The extent of LGE was 18% using the 2-SD method. Telemetry from a dual-chamber implantable cardioverter-defibrillator (ICD) transmission from the patient in (**B**), showing initially sinus rhythm, then some ventricular ectopics, followed by a regular ventricular rhythm with a cycle length of 220 to 230 ms, which triggered a 34-joule defibrillator discharge.

best overall model for the prediction of MACE (Table 4). In a clinical model, in which we tested the association between LGE, age, sex, LVEF, LV end-diastolic volume, and diabetes and MACE, we found that the presence and the extent of LGE were the strongest predictors of adverse events (Table 5).

When the endpoint of arrhythmia was considered, both the presence of LGE (HR: 14; 95% CI: 4.39 to 45.65; chi-square: 19.2; $p < 0.0001$) and the extent of LGE (by 2-SD: HR: 1.17 per each 1% absolute increase in volume of LGE; 95% CI: 1.12 to 1.22; chi-square: 52.1; $p < 0.0001$) were strongly associated with a combined arrhythmic outcome of ATP, ICD discharge, and non-heart failure cardiovascular death. The location of LGE was not associated with the occurrence of an arrhythmic endpoint. There were no other significant univariate associations with an arrhythmic endpoint. When a heart failure endpoint was considered, NYHA functional class II (HR: 12.2; 95% CI: 1.09 to 4.42; chi-square 4.9; $p = 0.03$), systolic blood pressure (HR: 0.97; 95% CI: 0.95 to 0.99; chi-square: 5.9;

$p = 0.01$), glomerular filtration rate (HR: 0.98; 95% CI: 0.97 to 0.99; chi-square: 4.2; $p = 0.03$), estimated pulmonary artery systolic pressure (HR: 1.03; 95% CI: 1.00 to 1.06; chi-square: 4.3; $p = 0.03$), right ventricular EF (HR: 0.97; 95% CI: 0.94 to 0.99; chi-square: 5.8; $p = 0.01$), LGE extent (by FWHM: HR: 1.15; 95% CI: 1.08 to 1.23; chi-square: 20.2; $p < 0.0001$), and LGE location involving the epicardium (HR: 4.88; 95% CI: 1.94 to 12.2; chi-square: 11.4; $p = 0.0007$) demonstrated significant univariate association with the combined endpoint of heart failure hospitalization and heart failure death. The presence of LGE was not associated with this combined heart failure endpoint.

Extent of LGE and outcome. ROC curves among patients with LGE were generated to determine whether the extent of LGE could help to identify a group at further increased risk for MACE. Analysis of ROC curves revealed a percentage of LGE by volume of $>6.1\%$ using the 2-SD method (area under the curve: 0.92; sensitivity: 90%; specificity: 95%) and $>4.4\%$ using the FWHM method (area

Table 3. Univariate Analysis for Association With MACE

	HR	95% CI	LR Chi-Square	p Value
Age	1.01	0.99–1.03	1.25	0.26
Male	2.03	1.01–4.06	4.01	0.04
Year of study enrollment	1.14	0.96–1.36	2.29	0.13
CRT	0.83	0.43–1.64	0.26	0.61
Diabetes	1.19	0.64–2.22	0.31	0.57
Hypertension	1.23	0.71–2.17	0.56	0.45
NYHA functional class II	0.75	0.44–1.31	0.99	0.32
NYHA functional class III	1.32	0.76–2.30	0.99	0.32
SBP	1.00	0.99–1.02	0.13	0.72
DBP	1.01	0.98–1.04	0.51	0.47
Heart rate	1.01	0.99–1.04	0.51	0.29
Antiarrhythmic drugs	1.55	0.79–3.06	1.65	0.19
QRS duration	1.00	0.99–1.01	0.14	0.70
GFR	0.98	0.97–0.99	5.71	0.02
Echocardiography				
Estimated PASP	0.99	0.96–1.03	0.12	0.73
Cardiac magnetic resonance				
Field strength 3.0-T (vs. 1.5-T)	1.03	0.59–1.82	0.01	0.91
LVEDV	1.00	0.99–1.01	0.97	0.32
LVESV	1.00	0.99–1.00	0.47	0.49
CMR-derived LVEF	1.00	0.97–1.03	0.07	0.78
CMR-derived LV mass index	1.00	0.99–1.01	0.48	0.48
RVEDV	1.00	0.99–1.01	2.19	0.13
RVESV	1.00	0.99–1.01	2.24	0.13
RVEF	0.99	0.97–1.02	0.75	0.38
LGE	14.50	6.06–32.61	18.75	<0.001
Extent (2-SD)*	1.15	1.12–1.18	43.26	<0.0001
Extent (FWHM)*	1.16	1.12–1.20	41.57	<0.0001
Epicardial	1.63	0.88–3.04	2.39	0.12
Mid-myocardial	0.92	0.52–1.63	0.08	0.77
Focal/insertion points	0.90	0.79–1.01	3.36	0.08
Diffuse	3.12	0.73–13.29	2.37	0.12

*LGE extent HR is for each 1% absolute increase in LGE volume.
HR = hazard ratio; CI = confidence interval; LR = likelihood ratio; MACE = major adverse cardiac events; other abbreviations as in Tables 1 and 2.

under the curve: 0.93; sensitivity: 86%; specificity: 96%) as the optimal combination of sensitivity and specificity for the prediction of events (Fig. 2). Kaplan-Meier curves were generated for event-free survival among patients by both the presence or absence of LGE and the extent of LGE using the two methods of measurement (Fig. 3). Patients with an LGE extent of >6.1% represented a high-risk

subgroup in which there were 46 events, or a cumulative event rate of over 50%/year.

DISCUSSION

We tested whether the extent of LGE among patients with a NIDC who underwent ICD implantation for the primary prevention of SCD could provide additive prognostic information. The extent of LGE provided the strongest independent association, with both a composite endpoint of cardiovascular death and a ventricular arrhythmia or the arrhythmic endpoint. The extent of LGE provided supplementary information beyond conventional risk stratification, identifying one group at an increased risk and one at a decreased risk for adverse events.

These findings are complementary to, and build on, those from previously published reports on the prognostic value of LGE in patients with an NIDC (9–11,22). Wu et al. (10) followed up a similar population of 65 patients with NIDC referred for ICD implantation for a median of 1.4 years. In that study, LGE was identified in 42% of patients with a mean LVEF of 24%, and was associated with an 8-fold higher risk for a composite of CV death, hospitalization for heart failure, and ICD therapy. However, heart failure hospitalizations accounted for the majority of outcomes. Iles et al. (11) performed CMR imaging in 61 patients with NIDC who underwent ICD insertion, and followed them up for a median of 1.6 years. Scar by CMR was identified in 51% and was associated with ICD therapy alone and a composite of death, the need for ICD therapy, and the need for heart transplantation. Indeed, in that study, not a single patient without LGE had an adverse cardiac event. We extend these data, and provide additive information regarding measuring the extent of LGE. Quantification of the extent of LGE using either of two validated clinical methods demonstrated that the extent of LGE provided the strongest association with adverse events.

One of the primary aims of this study was to determine whether scar imaging by LGE could further assist in the stratification of patients in whom an ICD is currently indicated (23). Identification of low-risk patients is clinically relevant, as it is recognized that a substantial proportion of patients who are currently referred for ICD implantation based on EF do not derive benefit (2). EF is the most widely used measure of LV function, and lower EF is accepted in general to be the strongest predictor of mortality in patients with

Table 4. Multivariate Analysis for Association With MACE

	HR	95% CI	LR Chi-Square	p Value
CMR				
HR	1.04	1.02-1.06	7.8	0.005
LGE	6.21	1.73-22.2	12.5	0.0004
Extent (2-SD)*	1.16	1.07-1.21	39.3	<0.0001

*LGE extent HR is for each 1% absolute increase in LGE volume. Abbreviations as in Tables 1 to 3.

Table 5. Multivariate Clinical Model for Association With MACE

	HR	95% CI	LR Chi-Square	p Value
Age	1.00	0.99-1.03	0.38	0.54
Sex	1.37	0.63-2.94	0.63	0.43
LVEDV	1.00	0.99-1.01	2.67	0.10
LVEF	1.04	0.99-1.08	3.52	0.06
Diabetes	1.11	0.58-2.10	0.09	0.77
LGE	18.9	5.82-61.3	23.9	<0.0001
Extent (2-SD)	5.94	3.92-9.00	32.5	<0.0001

Abbreviations as in Tables 1 to 3.

NIDC (1). However, measurement variability is 5% to 8% (7), and LVEF is recognized to have poor positive predictive value in patients referred for an ICD (7). One of the limitations of studies such as ours is the appropriate definition of *events*. It is clear

from studies such as DEFINITE (Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation) (2) that the ICD therapy rate is far higher than the SCD rate in the control group, suggesting that metrics such as ICD discharge and ATP may overestimate the benefit of ICD insertion (2). Allowing for this likely overestimation, we found that one death occurred among the patients without LGE; that the initial ICD therapy occurred after 1 year of follow-up; and that, cumulatively, there were only 4 total events in the LGE-negative cohort. These data suggest that even in a cohort considered at high risk based on EF, the absence of LGE can be useful in additive risk stratification. These data should support further research into the role of estimation of myocardial scar and risk stratification in patients with NIDC. Also, further work on whether novel CMR-based measures of myocardial fibrosis, such as T1 measurements, could provide further risk stratification seems warranted. Indeed, measurement of myocardial T1 pre- and post-contrast values may provide a more sensitive measure for expansion of the myocardial extracellular matrix (24,25).

Conversely, the extent of LGE also identified a group at substantially elevated risk for events. When we confined our analysis to LGE-positive patients with an LGE of >6.1% using the 2-SD method, we found an overall event rate of 50%/year. Quantification of the extent of LGE may identify a group who may benefit from more advanced electrophysiological therapy, such as VT ablation, or

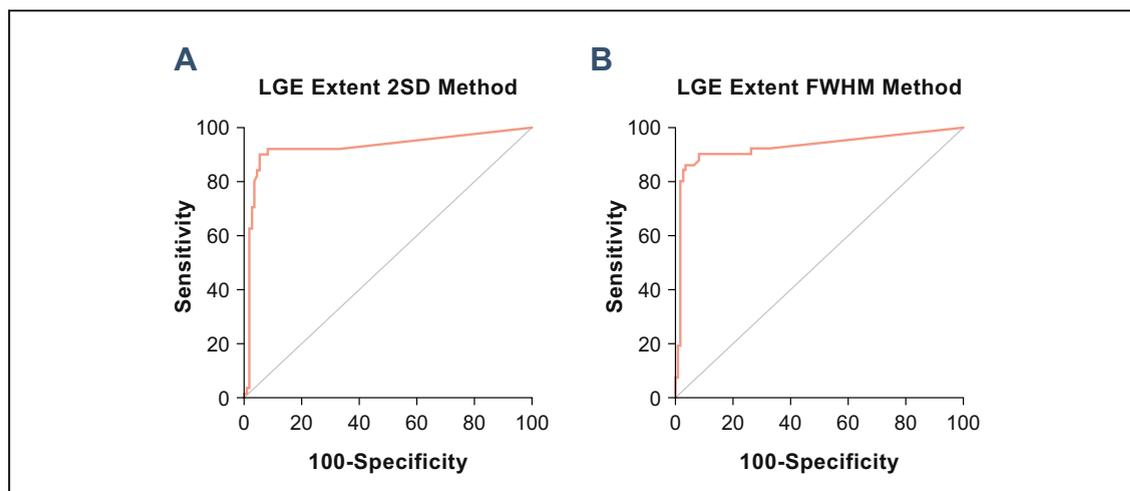
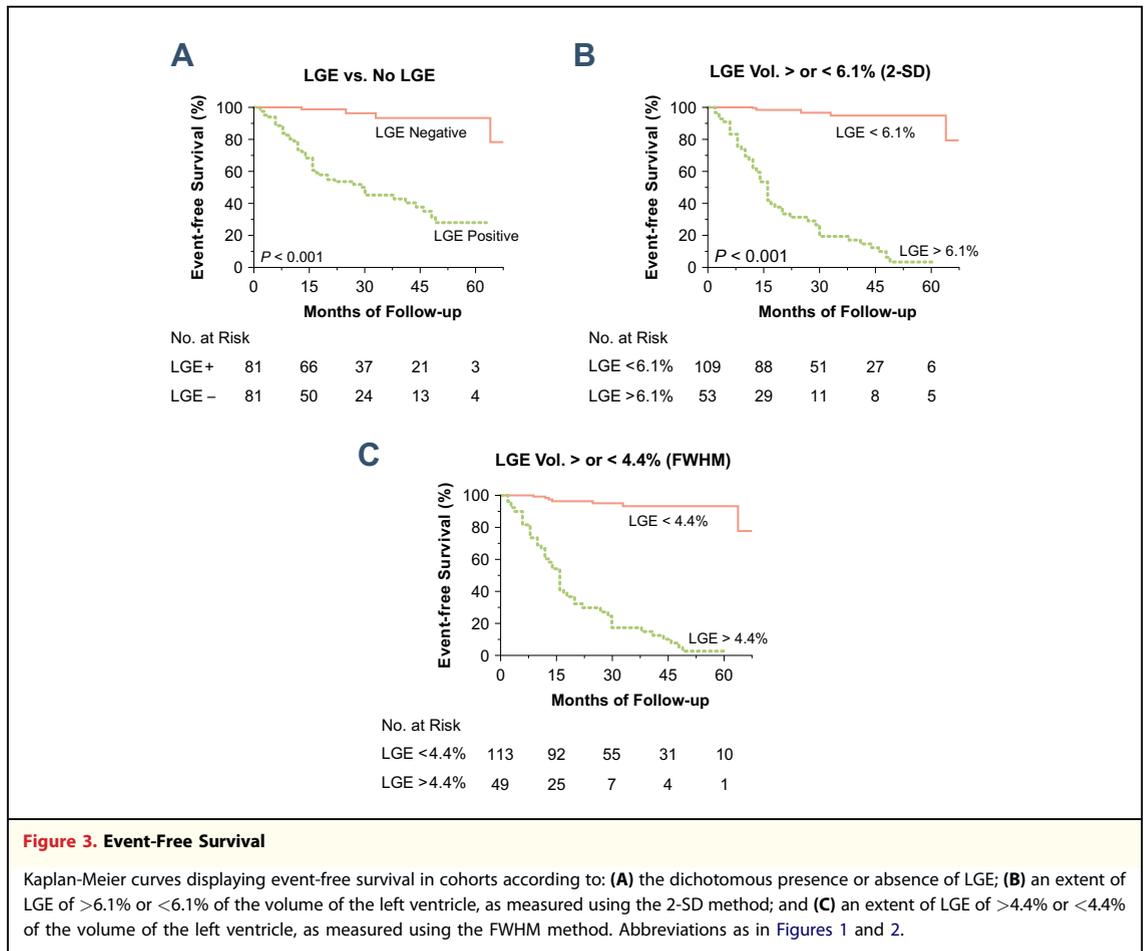


Figure 2. ROC Curves for LGE Extent Using 2 Methods for the Association of the Composite Outcome of Death and ICD Discharge

Analysis revealed that the percentage of LGE by volume of >6.1% using the 2-SD method (area under the curve: 0.92; sensitivity: 90%; specificity: 95%) (A) and >4.4% using the full-width half-maximum (FWHM) method (area under the curve: 0.93; sensitivity: 86%; specificity: 96%) (B) for prediction of events. ROC = receiver-operating characteristic; other abbreviations as in Figure 1.



involvement of specialist heart failure services. However, the optimum method for measurement of LGE is debated. Although current guidelines recommend using the 2-SD method (26), data suggest that the use of this technique leads to an overestimate of the extent of LGE in comparison to other techniques (27). Additive to this, we found that the extent of LGE using the 2-SD method was 50% greater than that found using the FWHM method. However, there was a strong association between the 2 measures; both methods provided similar additive information in patients with a reduced EF, and the main difference was in the definition of an optimal cutoff value for the prediction of adverse events.

Study limitations. This study should be interpreted within the context of the design format. We specifically studied patients referred for workup of a cardiomyopathy. Referral for a CMR study among this cohort is not standard routine within our institutions. We cannot exclude that clinical features other than the presence of a reduced EF could have

influenced referral for a CMR. However, none of the patients in this study had a prior indication for an ICD, none had an alternative diagnosis other than NIDC, and all had manifested heart failure for a median duration of over a year. Heart failure events that were not captured within the Partners System of hospitals were not independently verified and were documented on the basis of a patient questionnaire and confirmation from the primary providers. We recorded the medical therapy at the time of the CMR study. Patients were enrolled over a long period, and 2 limitations should be noted as a result: both the overall therapy for heart failure evolved and improved over this period and patient-specific therapies such as aldosterone system blockers and diuretics varied over this long period. LGE-determined myocardial fibrosis measures focal or replacement fibrosis and likely underestimates the presence and extent of the myocardial fibrosis that occurs in NIDC (28). Measurement of T1 pre- and post-contrast may further improve the discriminating ability of CMR-derived fibrosis (24,25).

Other data exist for complementary MR and non-MR biomarkers that may further aid risk stratification; these include serum biomarkers, ECG parameters, and measurement of neurohormonal activation, which were not measured in the study (29–31).

CONCLUSIONS

Among patients with NIDC and a reduced EF undergoing ICD implantation for the primary prevention of SCD, the extent of myocardial scar by LGE provides additive risk stratification. This work should promote further research efforts, and specifically a study in a large multicenter, prospectively enrolled cohort to determine whether CMR in

combination with other novel markers can help identify high-risk patients who may benefit from more advanced care or low-risk patients for whom conservative measures may be appropriate.

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Reprint requests and correspondence: Dr. Raymond Y. Kwong, Cardiac Magnetic Resonance Imaging, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. *E-mail:* rykwong@partners.org.

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Key Words: cardiac magnetic resonance ■ implantable cardioverter-defibrillators ■ late gadolinium enhancement ■ nonischemic cardiomyopathy.