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Associations between Scar Characteristics by Cardiac Magnetic Resonance and Changes in Left Ventricular Ejection Fraction in Primary Prevention Defibrillator Recipients

Yiyi Zhang, PhD¹, Eliseo Guallar, MD, DrPH¹, Robert G. Weiss, MD², Michael Stillabower, MD³, Gary Gerstenblith, MD², Gordon F. Tomaselli, MD², and Katherine C. Wu, MD²

¹Johns Hopkins University Bloomberg School of Public Health ²School of Medicine, Baltimore, Maryland ³Christiana Care Health Systems Inc., Newark, Delaware

Abstract

BACKGROUND—Left ventricular ejection fraction (LVEF) improves over time in 25%–40% of cardiomyopathy patients with primary prevention implantable cardioverter-defibrillators (ICD). The determinants of LVEF improvement, however, are not well characterized.

OBJECTIVES—We sought to examine the associations of clinical risk factors and cardiac imaging markers with changes in LVEF following ICD implantation.

METHODS—We conducted a retrospective analysis of cardiac magnetic resonance (CMR) images in 202 patients who underwent primary prevention ICD implantation to quantify the amount of heterogeneous myocardial tissue (gray zone [GZ]), dense core and total scar. LVEF was reassessed at least once after ICD implantation.

RESULTS—Over a mean follow-up of 3 years, LVEF decreased in 21.3%, improved in 43.6%, and was unchanged in 35.1% of the patients. Baseline LVEF and myocardial scar characteristics were the strongest determinants of LVEF trajectory with high scar burden and increasing lack of myocardial viability associated with a greater decline in LVEF. There was a trend toward an association between both changes in LVEF and scar extent with subsequent appropriate ICD shock. Changes in LVEF were also strongly associated with heart failure (HF) hospitalizations.

CONCLUSIONS—Scar burden and characteristics were strong determinants, independent of baseline LVEF and other traditional cardiovascular risk factors, of changes in LVEF. Both worsened LVEF and high scar extent were associated with a trend toward increased risk of appropriate shock. These findings suggest that baseline CMR imaging of the myocardial substrate may provide important prognostic information regarding subsequent LV remodeling and adverse events.

Correspondence: Katherine Wu, MD, Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21287, kwu@jhmi.edu.

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Keywords

implantable cardioverter-defibrillator; cardiac magnetic resonance; ejection fraction; gray zone; myocardial scar; appropriate shock

INTRODUCTION

Left ventricular ejection fraction (LVEF) is a key determinant of eligibility for primary prevention implantable cardioverter defibrillator (ICD) placement. However, the trajectory of LVEF in chronic cardiomyopathy patients can vary substantially.¹ While many patients will experience eventual worsening of LVEF, others may exhibit stability and LVEF actually improves in 25%–40% of primary prevention patients after ICD placement, in those with and without cardiac resynchronization therapy (CRT). Recent evidence suggests that improved LVEF is associated with a decrease in all-cause mortality and appropriate ICD shock for ventricular tachyarrhythmia.^{2–6}

Few studies have examined the determinants of LVEF trajectory in ICD recipients, and those that did focused on traditional clinical risk factors.^{4, 7–8} Cardiac magnetic resonance with late gadolinium enhancement (CMR-LGE) can characterize myocardial composition and viability in both ischemic (ICM) and non-ischemic cardiomyopathies (NICM) and predicts adverse outcomes in ICD recipients.⁹ In ICM, tissue heterogeneity by CMR can be quantified as regions of intermediate signal intensity (SI) in the infarct border regions (gray zone [GZ]), reflecting admixtures of scar/fibrosis and viable myocyte bundles and differentiated from dense, non-viable core scar.^{9–12} In NICM, focal scar burden is associated with adverse prognosis.^{13–15} Both types of scar quantification are associated with increased susceptibility to ventricular arrhythmias.^{9–18} It is not established whether and how myocardial tissue characteristics relate to ongoing LV remodeling and changes in LVEF during follow-up, as well as their impact on outcomes in primary prevention ICD patients with and without CRT.

Using data from primary prevention ICD patients with ICM and NICM who underwent pre-implant CMR-LGE imaging, we sought to assess the associations of traditional clinical risk factors and CMR scar characteristics with changes in LVEF during follow-up. We also examined the impact of CMR scar characteristics and patterns of LVEF change on the subsequent risks of appropriate shock and heart failure (HF) hospitalization.

METHODS

PROSE-ICD (Prospective Observational Study of Implantable Cardioverter Defibrillators) is a multicenter prospective study of ICM and NICM patients eligible for primary prevention ICDs.¹⁹ The present analysis comprised 202 patients from the CMR imaging arm of PROSE-ICD with details provided in the Supplement. The study protocol was approved by the Johns Hopkins Hospital Institutional Review Board. All patients gave written informed consent.

Details of the CMR cine and LGE acquisition and analysis protocols are included in the Supplement. CMR variables (GZ, core, and/or total scar) were categorized into tertiles according to cardiomyopathy etiology. Baseline LVEF was determined by CMR and conventional methods (echocardiography, nuclear scintigraphy, or ventriculography). Follow-up LVEFs were predominantly measured by echocardiography (89%). The primary endpoint for the PROSE-ICD study was appropriate ICD shock for ventricular tachyarrhythmias.¹⁹ Hospitalization for HF was a secondary endpoint.

Statistical Analyses

Details of the statistical analyses are provided in the Supplement. Change in LVEF was defined as the difference between the last available LVEF minus the baseline CMR LVEF. Participants were categorized into three LVEF groups: worsened (absolute change in LVEF <−5%), unchanged (absolute change in LVEF −5 to 5%), and improved (absolute change in LVEF >5%). We used linear regression to evaluate the associations of clinical and CMR risk factors with changes in LVEF, stratified by cardiomyopathy etiology. The first model included each individual risk factor and was adjusted for age, sex, race, device type, and baseline LVEF. The second model included simultaneously all risk factors that were statistically significant in the first model and was adjusted for age, sex, race, device type, and baseline LVEF. Cox proportional hazards models were used to estimate the association of LVEF and CMR variables with events.

RESULTS

Baseline characteristics of study participants are shown in Supplemental Table 1. During follow-up, LVEF declined in 21.3%, was unchanged in 35.1%, and improved in 43.6% patients. The mean duration between the first and last available LVEF was 3.0 years. Compared to patients with unchanged or worsened LVEF, those who improved were more likely to be non-ischemic, non-smokers, and CRT-D recipients, with lower baseline LVEF and higher end-systolic volumes (Supplemental Tables 1 & Table 1).

Among ICM patients, median GZ extent was 13.2 grams and median core scar was 18.9 grams. Patients with an improved LVEF had lower GZ extent but similar core scar compared to those with unchanged or worsened LVEF (Table 1). Among NICM patients, scar prevalence was 34.7% with relatively low total scar burden.

Among ICM patients, baseline LVEF, NT-proBNP, GZ, and total scar were individually associated with LVEF changes (Table 2, **Model 1**). These associations remained significant when they were included simultaneously in the same model (Table 2, **Model 2**), with each SD increase in baseline LVEF associated with a −6.9% difference in subsequent change in LVEF (i.e., each SD increase in baseline LVEF was associated with a 6.9% smaller increase in LVEF when follow-up LVEF improved, and associated with a 6.9% greater decrease in LVEF when follow-up LVEF worsened). Similarly, the top tertiles of NT-proBNP and GZ were associated with a −5.0% and a −5.6% difference in the changes in LVEF, respectively, compared with the bottom tertile (Table 2, **Model 2**).

Among NICM patients, baseline LVEF and total scar were associated with LVEF changes in the fully adjusted model (Table 2, **Model 2**). Each SD increase in baseline LVEF was associated with a -7.8% difference in LVEF change, and the top compared with bottom tertile of total scar was associated with a -8.9% difference in LVEF change. These patterns of associations were similar among ICD and CRT-D patients (Supplemental Table 3).

The mean follow-up time for endpoints since the last available LVEF was 1.4 years, during which 23 patients experienced an appropriate shock and 45 had a HF hospitalization (Table 3). There was a non-significant trend toward a lower risk of appropriate shock among patients with a lower baseline scar extent and whose LVEF improved. The hazard ratios for appropriate shock were 1.09 and 0.39 comparing patients with worsened or improved LVEF respectively to those with unchanged LVEF (p -trend=0.08); and 2.89 (p -trend=0.07) comparing the highest vs. lowest tertile of scar extent respectively (Table 3, **Model 1**). When included simultaneously in the same model, the magnitude of the associations was attenuated, but the trend of the associations remained the same (Table 3, **Model 2**). In contrast, LVEF changes, but not scar extent, were strongly associated with HF hospitalization (HR=2.88 and 0.37 comparing patients with worsened or improved LVEF respectively to those with unchanged LVEF, p -trend<0.001).

DISCUSSION

The main findings of this study of primary prevention ICD candidates are: (1) baseline myocardial scar characteristics and extent are strong determinants of subsequent LVEF trajectory in both ICM and NICM patients; (2) changes in LVEF are strongly associated with the risk of subsequent HF hospitalizations; and (3) both worsened LVEF and high scar extent are associated with a trend toward increased risk of appropriate shock.

LVEF may improve in HF patients as a result of therapies such as pharmacologic therapies and CRT.^{20–24} Among primary prevention ICD patients, 25%–40% improve their LVEF after ICD implantation.^{2–6} Despite the high prevalence of LVEF improvement, little is known regarding the determinants of LVEF changes among primary prevention ICD recipients. In a case-control study of 102 dilated cardiomyopathy patients, shorter QRS duration, female sex, non-ischemic etiology, absence of diabetes, and higher blood pressure were associated with improved LVEF to normal or near-normal with medical therapy.²⁵ In a cohort study of 3,994 HF patients, lower baseline LVEF, female sex, no prior myocardial infarction, non-ischemic etiology, and no digoxin use were associated with improved LVEF.²⁶ In a cohort of incident HF patients, patients with reduced LV function (average LVEF 31.7% with mild LV dilation) increased their LVEF by 6.9% over 5 years.²⁷ Predictors of improved LVEF included female gender, younger age, and lack of coronary artery disease. Consistent with and adding to the previous findings, our study showed that baseline LVEF and cardiomyopathy etiology were important determinants of LVEF changes during follow-up. Improved LVEF tended to occur in those with lower baseline LVEF and non-ischemic etiology, regardless of whether or not they received CRT-D devices. This highlights the dynamic nature of the LVEF trajectory and suggests that some patients, despite a low baseline LVEF, have dysfunctional but sufficiently viable myocardium that can be recruited for partial functional recovery.

Although informative, most of the previous studies only included traditional clinical risk factors and did not evaluate the prognostic significance of some of the newer cardiac imaging markers. CMR has emerged as an imaging technique with high spatial resolution that allows for detailed noninvasive assessment and quantification of scar extent, tissue heterogeneity and viability within the myocardium. A few small-scale studies reported an association between CMR markers of scar and tissue heterogeneity with ongoing LV remodeling. In a study of 51 patients with recent-onset NICM, the extent of CMR myocardial fibrosis was independently associated with the lack of improved LVEF during a 5 month median follow-up.²⁸ In another study of 58 idiopathic dilated cardiomyopathy patients, the absence of CMR myocardial fibrosis was associated with LV reverse remodeling at 2-year follow-up, irrespective of the initial clinical status and of the severity of LV dilatation and dysfunction.²⁹ Similarly, among 44 patients with recent-onset dilated cardiomyopathy, a lower extent of myocardial fibrosis was associated with LV reverse remodeling at 12 months.³⁰ Amongst patients receiving CRT, the majority of studies focused on the relation between scar location and CRT-responsiveness.^{31–33} A recent study of 48 CRT recipients reported an association between higher total scar burden and poor CRT response but did not stratify by ischemic versus non-ischemic etiologies.³⁴

With a much larger and more inclusive cohort of both ischemic and non-ischemic ICD patients, we found that myocardial scar characteristics were the strongest risk factors associated with temporal LVEF changes when compared to other clinical and serum biomarkers. In ICM patients, myocardial scar characteristics, particularly tissue heterogeneity as measured by GZ extent, were strong independent determinants of LVEF changes with smaller scar extents associated with LVEF improvement and higher amounts of scar associated with no change or worsening of LVEF. This association was independent of the baseline LVEF and other traditional cardiovascular risk factors. GZ extent was more strongly associated with LVEF changes than was core scar. This may highlight the differential predictive value of heterogeneous GZ regions compared to that of dense core scar. For a similar extent of core scar and gray zone, core scar would be expected to be fixed and nonviable, and thus, not impact subsequent LVEF as much. In contrast, the heterogeneous GZ regions retain some degree of myocyte viability which may be recruited to improve overall function. Thus, GZ extent can have a stronger impact on subsequent LVEF changes than core scar. However, with a large enough critical mass of GZ, improvement in LVEF would be increasingly less likely.

The identification of patients with LVEF improvement has potential clinical implications for risk stratification and management of primary prevention ICD patients. Cumulative evidence suggests that improved LVEF is associated with a decreased risk of mortality and appropriate ICD shock for ventricular tachyarrhythmia, particularly in those whose follow-up LVEF improved to >35%.^{2–6} Consistent with previous findings, our study reported a trend toward an inverse association between LVEF changes and the risk of appropriate shock. These findings underscore that even partial functional improvement in LVEF may reduce subsequent arrhythmic risk while the majority of appropriate ICD firings occur in those in whom LVEF is static or declining despite aggressive HF therapy. GZ extent in ICM and total scar burden in NICM patients were also marginally associated with appropriate shock in our study. CMR markers of tissue heterogeneity and scar were previously

associated with arrhythmia susceptibility and ICD outcomes.^{10, 12–14} Additionally, we found a strong association between LVEF changes and the risk of HF hospitalization, while no clear association with myocardial scar characteristics was observed. This suggests that LVEF changes may lack the specificity for predicting competing adverse outcomes in cardiomyopathy patients, i.e. arrhythmic vs. HF events.

Several limitations of our study should be considered. Although our study included a large cohort of patients with primary prevention ICDs who underwent CMR imaging, it may still be underpowered to detect statistically significant associations with appropriate shock, as relatively few patients had the event. Also, given the sample size, we could not perform multivariable modeling for all possible risk markers but limited the analysis to parameters found to be significant in the initial models. Extensive biomarker profiling of neurohormonal or sympathetic activation, beyond BNP, were unavailable in our study. Because follow-up LVEF measurements were obtained at the discretion of the treating physicians, there were differences in patients who did and did not undergo repeat LVEF assessment. This may limit generalizability of the results. However, baseline LVEFs were similar as well as scar burden and scar characteristics among ICM patients. Since few patients underwent stress test and/or coronary angiography after enrollment, we were unable to examine if interval ischemia influenced LVEF changes. Our CMR methodology did not assess for diffuse fibrosis which can occur in NICM. However, a recent study suggested that diffuse fibrosis may not predict CRT responsiveness.³⁴ Other studies used different SI methodology, which we did not examine here, for measuring GZ and core extents.^{11–12} Given limitations with accurate whole heart quantification of scar characteristics by CMR with in-dwelling ICDs, we were unable to assess the temporal changes in scar burden..

CONCLUSIONS

In this cohort study of patients with primary prevention ICDs, we found that baseline myocardial scar characteristics and extent by CMR were strong determinants of subsequent LVEF trajectory in both ICM and NICM patients. Worsened LVEF, high scar extent, and progressive lack of myocardial viability were associated with a trend toward increased risk of appropriate shock, and LVEF changes with HF hospitalizations. These findings suggest that baseline CMR imaging of scar burden and heterogeneity can provide important prognostic information regarding ongoing and subsequent LV remodeling. They may also have potential implications for the timing of ICD placement with earlier intervention in patients with large scar burden and pattern suggesting lack of viability and evidence of declining LVEF. These findings require additional confirmation in larger populations to better understand the exact mechanisms underlying the associations between myocardial tissue heterogeneity, LVEF changes, and adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline CMR characteristics of participants, by changes in follow-up LVEF*

Characteristic	Overall (n = 202)	Worsened LVEF (n = 43)	Unchanged LVEF (n = 71)	Improved LVEF (n = 88)	P- value $\dagger$
LVEF (%)	27.7±9.7	34.6±7.9	29.0±8.7	23.3±9.1	<0.001
LVEDV (mL)	241.4±76.9	218.7±61.6	246.3±76.8	248.4±82.1	0.09
LVESV (mL)	178.3±75.1	144.9±51.0	178.4±70.9	194.5±83.2	0.002
LV mass (g)	144.8±42.6	132.6±39.2	149.0±43.4	147.4±43.0	0.10
Scar characteristics					
Ischemic cardiomyopathy (n)	104	30	44	30	
GZ (g)	13.2 (7.1, 19.8)	14.5 (8.1, 18.9)	16.7 (9.9, 25.5)	8.5 (4.6, 12.1)	<0.001
Core scar (g)	18.9 (13.4, 25.9)	18.3 (13.5, 23.1)	21.4 (15.7, 29.6)	17.6 (10.7, 25.6)	0.25
Total scar (g)	34.5 (21.5, 44.7)	35.2 (24.1, 42.8)	41.5 (29.1, 52.5)	24.7 (14.7, 32.5)	0.001
Non-ischemic cardiomyopathy (n)	98	13	27	58	
Scar presence	34 (34.7)	5 (38.5)	11 (40.7)	18 (31.0)	0.65
Total scar (g)	0 (0, 4.8)	0 (0, 5.3)	0 (0, 5.4)	0 (0, 3.8)	0.65

* Values are numbers (%), means ± SD, or median (interquartile).

 $\dagger$ P-values represent the comparison across the 3 groups of worsened (absolute decrease in LVEF >5%), unchanged (absolute change in LVEF -5 to 5%), and improved LVEF (absolute increase in LVEF >5%).

LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume.

Table 2

Associations of clinical and imaging risk factors with absolute changes in LVEF, by cardiomyopathy etiology

	Ischemic (n = 104)			Non-ischemic (n = 98)		
	Model 1 [*]	Model 2 [†]	Model 1 [*]	Model 2 [†]	Model 1 [*]	Model 2 [†]
	β coefficient (95% CI)	P-value	β coefficient (95% CI)	P-value	β coefficient (95% CI)	P-value
Age (per 10 years)	1.7 (-0.3, 3.6)	0.09	1.5 (-0.4, 3.4)	0.11	0.2 (-2.4, 2.7)	0.88
Men vs. women	1.3 (-3.2, 5.9)	0.56	1.2 (-3.1, 5.4)	0.59	2.1 (-3.3, 7.6)	0.44
AA vs. non-AA	4.0 (-2.0, 9.9)	0.19	4.9 (-0.4, 10.2)	0.07	0.5 (-5.4, 6.4)	0.87
CRT-D vs. ICD	-0.6 (-5.1, 3.9)	0.79	-0.5 (-4.6, 3.7)	0.83	4.9 (-0.9, 10.6)	0.10
Baseline LVEF (per SD)	-6.4 (-8.3, -4.5)	<0.001	-6.9 (-8.7, -5.2)	<0.001	-5.4 (-7.9, -3.0)	<0.001
NYHA III vs. NYHA I/I	-1.8 (-6.1, 2.6)	0.42			3.7 (-2.4, 9.8)	0.24
Atrial fibrillation	-1.1 (-6.2, 4.1)	0.68			-2.8 (-10.9, 5.2)	0.49
Hypertension	-2.2 (-6.0, 1.6)	0.25			1.7 (-4.5, 7.8)	0.59
Diabetes	-2.2 (-5.9, 1.4)	0.22			5.1 (-5.5, 15.7)	0.34
NT-proBNP						
Tertile 1	Reference		Reference		Reference	
Tertile 2	-4.8 (-8.8, -0.7)	0.02	-4.4 (-8.5, -0.3)	0.03	0.1 (-6.3, 6.6)	0.97
Tertile 3	-6.1 (-10.6, -1.6)	0.01	-5.0 (-9.6, -0.4)	0.03	-3.2 (-10.2, 3.9)	0.37
hsCRP						
Tertile 1	Reference		Reference		Reference	
Tertile 2	-2.6 (-6.9, 1.7)	0.23			-0.8 (-7.2, 5.7)	0.82
Tertile 3	-3.2 (-7.8, 1.4)	0.17			-8.2 (-15.7, -0.7)	0.03
					0.9 (-4.8, 6.6)	0.75
					-5.1 (-13.4, 3.2)	0.23

	Ischemic (n = 104)			Non-ischemic (n = 98)		
	Model 1 *	Model 2 †	Model 2 ‡	Model 1 *	Model 2 †	Model 2 ‡
	β coefficient (95% CI)	P-value	β coefficient (95% CI)	β coefficient (95% CI)	P-value	P-value
Medications	Reference			Reference		
Aspirin	1.8 (-4.7, 8.3)	0.59		-1.3 (-7.9, 5.3)	0.69	
Beta-blocker	-1.2 (-8.2, 5.8)	0.73		5.1 (-1.7, 11.8)	0.14	
ACE-I/ARB	0.3 (-3.8, 4.3)	0.89		-2.1 (-12.9, 8.8)	0.71	
Spirinolactone	-2.1 (-6.1, 1.9)	0.30		-6.2 (-11.7, -0.7)	0.03	0.29
Diuretics	0.7 (-2.6, 4.1)	0.66		-4.3 (-10.1, 1.5)	0.15	
LVEDV ‡ (per SD)	-1.6 (-3.3, 0.2)	0.08		-4.2 (-7.9, -0.6)	0.02	0.31
LV mass (per SD)	-0.8 (-2.5, 0.9)	0.35		0.3 (-3.4, 4.0)	0.88	
GZ						
Etiology-specific tertile 1	Reference		Reference			
Etiology-specific tertile 2	-3.1 (-7.5, 1.3)	0.16	-3.1 (-7.4, 1.2)			0.16
Etiology-specific tertile 3	-6.6 (-10.6, -2.7)	0.001	-5.6 (-9.8, -1.5)			0.01
Core scar						
Etiology-specific tertile 1	Reference					
Etiology-specific tertile 2	-1.5 (-5.6, 2.7)	0.49				
Etiology-specific tertile 3	-0.8 (-5.6, 4.0)	0.74				
Total scar						
Etiology-specific tertile 1	Reference			Reference		Reference
Etiology-specific tertile 2	-2.1 (-6.7, 2.5)	0.38		-2.8 (-9.3, 3.6)	0.38	0.17
Etiology-specific tertile 3						

	Ischemic (n = 104)			Non-ischemic (n = 98)		
	Model 1 *		Model 2 †	Model 1 *		Model 2 †
	β coefficient (95% CI)	P-value	β coefficient (95% CI) P-value	β coefficient (95% CI) P-value	β coefficient (95% CI) P-value	β coefficient (95% CI) P-value
Etiology-specific tertile 3	-6.6 (-10.6, -2.6)	0.001		-10.1 (-18.3, -1.9)	0.02	-8.9 (-16.8, -1.0) 0.03

* Model 1: Adjusted for age, sex, race, and baseline LVEF.

† Model 2: Model 1 + all risk factors that were statistically significant in Model 1. Due to the high correlation among the 3 CMR scar variables, only the variable presenting the strongest association in model 1 was entered in model 2.

‡ Because of collinearity between EDV and ESV, only EDV, which had the stronger association, was retained in the models.

AA: African-American; LVEDV: left ventricular end-diastolic volume; hsCRP: high sensitivity C-reactive protein.

Table 3

Associations of changes LVEF and CMR characteristic with appropriate shock and HF hospitalization

	Appropriate shock (n=23)		Heart failure hospitalization (n=45)	
	Model 1 *	Model 2 †	Model 1 *	Model 2 †
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Changes in LVEF				
Worsened	1.09(0.38, 3.10)	1.16(0.39, 3.45)	2.78(1.34, 5.79)	2.88(1.33, 6.25)
Unchanged	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Improved	0.39(0.13, 1.23)	0.50(0.16, 1.59)	0.39(0.18, 0.84)	0.37(0.17, 0.82)
<i>P</i> -trend	0.08	0.17	<0.001	<0.001
CMR scar variable ‡				
Etiology-specific tertile 1	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Etiology-specific tertile 2	1.86(0.59, 5.88)	1.69(0.55, 5.21)	1.36(0.64, 2.90)	1.27(0.56, 2.89)
Etiology-specific tertile 3	2.89 (0.92, 9.10)	2.39 (0.79, 7.24)	1.26 (0.54, 2.91)	0.88 (0.37, 2.11)
<i>P</i> -trend	0.07	0.12	0.55	0.82

* Model 1: Adjusted for age, sex, race, device type, atrial fibrillation, cardiomyopathy etiology, and baseline LVEF.

† Model 2: Further included changes in LVEF and CMR scar variable in the same model.

‡ This variable represents gray zone among participants with ischemic cardiomyopathy and total scar among participants with non-ischemic cardiomyopathy, respectively