JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 70, NO. 10, 2017
ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2017.07.712

Outcomes of Cardiac Resynchronization Therapy With or Without Defibrillation in Patients With Nonischemic Cardiomyopathy

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ABSTRACT

BACKGROUND Recent studies have cast doubt on the benefit of cardiac resynchronization therapy (CRT) with defibrillation (CRT-D) versus pacing (CRT-P) for patients with nonischemic cardiomyopathy (NICM). Left ventricular myocardial scar portends poor clinical outcomes.

OBJECTIVES The aim of this study was to determine whether CRT-D is superior to CRT-P in patients with NICM either with (+) or without (−) left ventricular midwall fibrosis (MWF), detected by cardiac magnetic resonance.

METHODS Clinical events were quantified in patients with NICM who were +MWF (n = 68) or −MWF (n = 184) who underwent cardiac magnetic resonance prior to CRT device implantation.

RESULTS In the total study population, +MWF emerged as an independent predictor of total mortality (adjusted hazard ratio [aHR]: 2.31; 95% confidence interval [CI]: 1.45 to 3.68), total mortality or heart failure hospitalization (aHR: 2.02; 95% CI: 1.32 to 3.09), total mortality or hospitalization for major adverse cardiac events (aHR: 2.02; 95% CI: 1.32 to 3.07), death from pump failure (aHR: 1.95; 95% CI: 1.11 to 3.41), and sudden cardiac death (aHR: 3.75; 95% CI: 1.26 to 11.2) over a maximum follow-up period of 14 years (median 3.8 years [interquartile range: 2.0 to 6.1 years] for +MWF and 4.6 years [interquartile range: 2.4 to 8.3 years] for −MWF). In separate analyses of +MWF and −MWF, total mortality (aHR: 0.23; 95% CI: 0.07 to 0.75), total mortality or heart failure hospitalization (aHR: 0.32; 95% CI: 0.12 to 0.82), and total mortality or hospitalization for major adverse cardiac events (aHR: 0.30; 95% CI: 0.12 to 0.78) were lower after CRT-D than after CRT-P in +MWF but not in −MWF.

CONCLUSIONS In patients with NICM, CRT-D was superior to CRT-P in +MWF but not −MWF. These findings have implications for the choice of device therapy in patients with NICM. (J Am Coll Cardiol 2017;70:1216–27)

Cardiac resynchronization therapy (CRT) is a standard treatment for patients with heart failure (HF), impaired left ventricular (LV) systolic function, and a prolonged QRS duration (1,2). Although CRT-pacing (CRT-P) prevents pump failure by correcting LV dyssynchrony, the addition of defibrillation (CRT-D) leads to a greater treatment effect by preventing sudden cardiac death (SCD) from ventricular arrhythmias (2,3).

It is well recognized that the clinical outcome of CRT is influenced by the underlying etiology of HF. Nonischemic cardiomyopathy (NICM) is associated with a better LV reverse remodeling response (4) and better clinical outcomes after CRT (5). Because NICM

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Manuscript received April 17, 2017; revised manuscript received July 3, 2017, accepted July 5, 2017.

is associated with a lower background risk for ventricular arrhythmias than ischemic cardiomyopathy, the benefit of CRT-D over CRT-P has been questioned. In this respect, most of the evidence in favor of defibrillation in patients with NICM comes from studies evaluating patients with single- or dual-chamber implantable cardioverter-defibrillators (ICD) rather than CRT-D devices. Both CAT (Cardiomyopathy Trial) (6) and AMIOVIRT (Amiodarone Versus Implantable Cardioverter-Defibrillator Trial) (7) used single- and dual-chamber ICDs, but neither trial showed any survival benefit from ICDs in patients with NICM. Importantly, these studies involved small numbers of patients (each about 100). In the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) study (8), in which 458 patients with NICM were randomized to medical therapy or a single-chamber ICD, ICD therapy did not reduce total mortality, despite a significant reduction in SCD. A subgroup analysis of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), including patients with NICM, also failed to show a significant reduction in mortality from ICD therapy (9). In the recent DANISH (Defibrillator Implantation in Patients With Nonischemic Systolic Heart Failure) study, ICDs did not reduce total mortality in patients with NICM (10). These studies cast doubt on the relative benefit of CRT-D versus CRT-P in patients with NICM.

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All clinical outcome studies of ICDs in NICM (6–9,11), including DANISH (10), have defined NICM on the basis of findings from echocardiography, coronary angiography, and/or nuclear imaging. These imaging modalities, however, do not provide tissue characterization. In this regard, LV midwall fibrosis (MWF) is a specific form of myocardial scar found in approximately 30% of patients with NICM (**Figure 1**). It is now recognized that MWF, detected using cardiac magnetic resonance (CMR) imaging, portends a poor outcome in the general NICM population (12–15) and in CRT-P recipients (16). Increasing evidence supports a link between MWF and ventricular arrhythmias (12–14,17). On this basis, we hypothesized that the relative benefit of CRT-D over CRT-P is influenced by MWF.

METHODS

Patients were recruited from 2 centers (Good Hope Hospital and Queen Elizabeth Hospital, Birmingham, United Kingdom). All patients underwent successful CRT device implantation and pre-implantation CMR from July 2002 to January 2017. Some patients were included in a previous study (16). The present study extended to a larger group and a longer follow-up period.

The diagnosis of HF was made on the basis of clinical features plus echocardiographic evidence of LV systolic dysfunction. The diagnosis of NICM was made if LV dysfunction was associated with either no myocardial scar or with MWF (14). Exclusion criteria included a history of myocardial infarction, coronary revascularization, or diagnosis of ischemic cardiomyopathy on the basis of other investigations (e.g., nuclear imaging); ischemic pattern of scar on CMR; a diagnosis of hypertrophic or restrictive cardiomyopathy, primary valvular disease, sarcoidosis, amyloidosis, or myocarditis made on the basis of CMR or another investigation (e.g., echocardiography, cardiac biopsy, and/or positron emission tomography); and NICM and scar patterns other than MWF (patchy or subepicardial). The study was approved by the local ethics committee or the local clinical audit departments and conformed with the Declaration of Helsinki.

DEVICE THERAPY. In the United Kingdom, the National Institute of Clinical Excellence guidelines in 2007 recommended CRT-P rather than CRT-D for patients with NICM and indications for CRT. With a subsequent guideline change in 2014 recommending CRT-D for NICM (18), the proportion of CRT-D recipients increased thereafter.

Device implantation was undertaken using standard transvenous techniques under local anesthesia and intravenous sedation. After implantation, patients were followed at dedicated device therapy clinics. Before 2013, patients in sinus rhythm underwent transmitral Doppler-directed optimization of atrioventricular delay using an iterative technique prior to discharge and at every scheduled visit thereafter. After 2013, routine echocardiographic optimization was abandoned and undertaken only in the case of symptomatic nonresponders. Backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an interventricular delay of 0 to 4 ms, according to manufacturer instructions. In the case of patients in permanent atrial fibrillation, right ventricular and LV leads were implanted and a CRT generator was used, plugging the atrial port and programming to a ventricular triggered mode. Atrioventricular junction ablation was undertaken according to physicians' decision.

ABBREVIATIONS AND ACRONYMS

aHR = adjusted hazard ratio

CI = confidence interval

CMR = cardiac magnetic resonance

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy-defibrillation

CRT-P = cardiac resynchronization therapy-pacing

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

LV = left ventricular

MACE = major adverse cardiac event

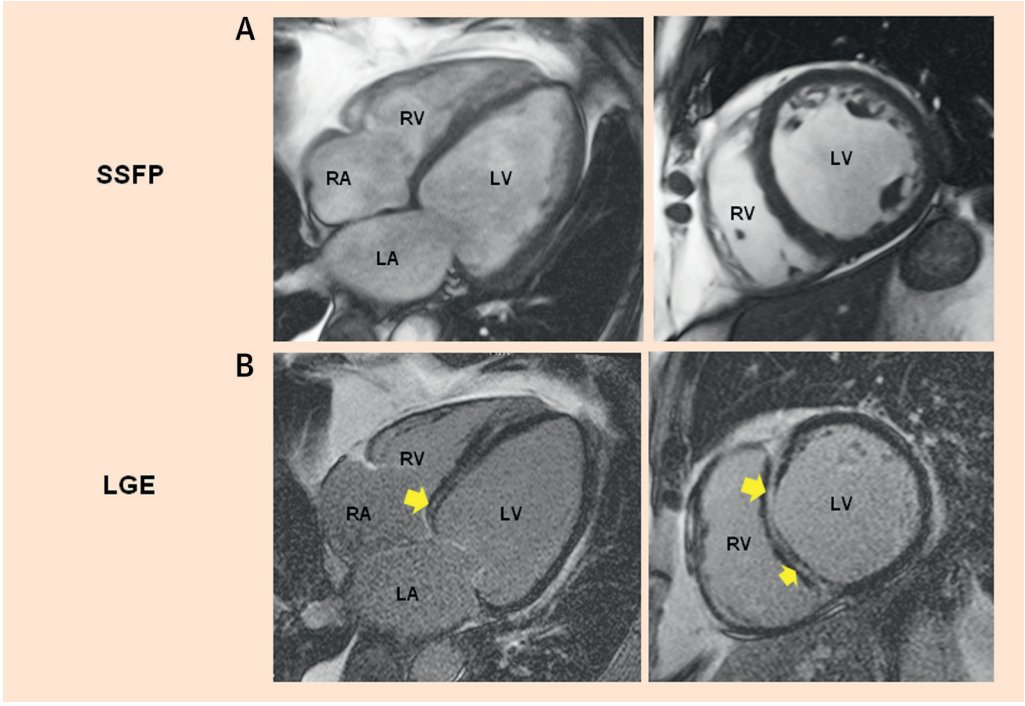
MWF = midwall fibrosis

NICM = nonischemic cardiomyopathy

NYHA = New York Heart Association

SCD = sudden cardiac death

FIGURE 1 Midwall Fibrosis in Nonischemic Cardiomyopathy



Cardiac magnetic resonance imaging of a patient with nonischemic cardiomyopathy depicts 4-chamber and short-axis **(A)** steady-state free precession (SSFP) images of a dilated left ventricle (LV) and **(B)** inversion recovery late gadolinium enhancement (LGE) images showing midwall enhancement **(yellow arrows)** in the interventricular septum, typical of midwall fibrosis. LA = left atrium; RA = right atrium; RV = right ventricle.

CMR IMAGING. CMR imaging was performed using 1.5-T scanners and a phased-array cardiac coil. A short-axis LV stack was acquired using a steady-state free precession sequence (repetition time 3.0 to 3.8 ms, excitation time 1.0 ms, image matrix 224 × 224, field of view 36 to 42 cm, flip angle 45°) in sequential 8-mm slices (2-mm interslice gap) from the atrioventricular ring to apex. Acquisition was performed during gated 8-s breath-holds (20 phases). Quantification of LV volumes was undertaken using semiautomatic manual planimetry of all short-axis, steady-state free precession sequence cine images with MASS (Medis, Leiden, the Netherlands) or Argus (Siemens, Erlangen, Germany) analysis software. Quantification of LV volumes and characterization of myocardial scar were undertaken by investigators certified by the British Society of Cardiovascular Magnetic Resonance using a common protocol. These investigators were blinded to echocardiographic and clinical outcome data. A previous cardiac device implantation (excluding loop recorders), end-stage renal failure, and renal replacement therapy were adopted as absolute contraindications to CMR.

Short-axis slices identical to the LV stack were acquired using a segmented inversion recovery technique, 10 min after the intravenous administration of gadolinium-diethylenetriaminepentaacetic acid (0.1 mmol/kg). Inversion times were adjusted to null normal myocardium (260 to 400 ms). Myocardial scars were classified as subendocardial, midwall, epicardial, transmural, or patchy (13). Scars in a subendocardial or transmural distribution following coronary artery territories were regarded as ischemic in etiology, whereas midwall scars and absence of scar were regarded as indicative of NICM. MWF was considered present if the area of late gadolinium enhancement was confined to intramural and/or subepicardial layers in 2 orthogonal views (19). As in other studies (12,14,16,17,20), we chose to use visual rather than quantitative assessment of MWF to make our findings clinically applicable without the need for scar quantification.

ENDPOINTS. The primary endpoint was total mortality, which included cardiac transplantation or implantation of a ventricular assist device. Secondary endpoints included the composite endpoint of total mortality or HF hospitalization and the composite endpoint of total mortality or unplanned hospitalization for major adverse cardiac events (MACEs). These included hospitalization for HF, myocardial infarction, acute coronary syndrome, and arrhythmia (ventricular tachycardia, ventricular fibrillation, or atrial fibrillation). Stroke and pulmonary embolism were not regarded as MACEs. In composite endpoints, the first event was included in the analysis. Mortality data were collected through medical records and, when appropriate, from interviews with patient caregivers. Clinical outcome data were collected every 6 months by investigators who were blinded to clinical and imaging data. Also, events were adjudicated by blinded investigators on a 6-month basis.

With respect to mode of death, a "natural, unexpected death due to cardiac causes, heralded by an abrupt loss of consciousness within 1 h of the onset of acute symptoms" (21) was regarded as an SCD. Death from pump failure was defined as "death after a period of clinical deterioration in signs and symptoms of HF despite medical treatment" (22).

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD. Normality was tested using the Shapiro-Wilk test. Comparisons between normally distributed continuous variables were made using analysis of variance. Categorical variables were analyzed using chi-square tests. Kaplan-Meier curves and the log-rank test were used to assess observed cumulative survival. Cox proportional hazard models were used to assess relative risks. Proportionality hypotheses were verified by visual examination of log (survival) graphs to ensure parallel slopes and by examining Schoenfeld residuals. Variables reaching $p < 0.10$ on univariate analyses were entered in multivariate models, and further backward elimination was applied for the final multivariate models. The predictive ability of MWF was assessed using Harrell's C statistic and Somers's D statistic (23). Interobserver and intraobserver agreement for the presence of MWF was assessed using Cohen's kappa statistic. Statistical analyses were undertaken using Stata version 14 (StataCorp, College Station, Texas). A 2-sided p value ≤0.05 was considered to indicate statistical significance.

RESULTS

In the total study population (n = 252), 68 patients (27%) had MWF. The +MWF and −MWF groups were well matched for age, sex, device type, comorbidities, atrial rhythm, QRS duration, QRS morphology, medication, and echocardiographic LV ejection fraction (Table 1). The +MWF group had more New York Heart Association (NYHA) functional class I, II, and IV patients but fewer NYHA functional class III patients than the −MWF group (p = 0.031).

TABLE 1 Patient Characteristics

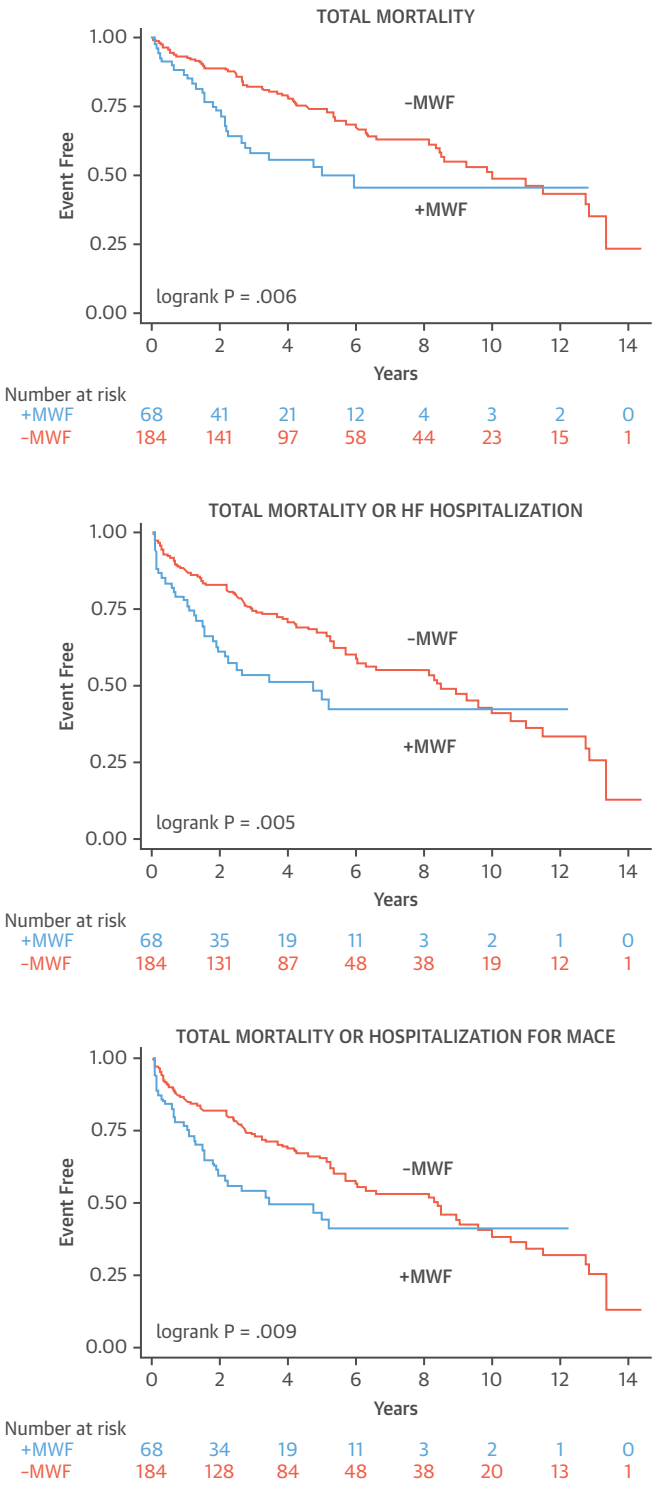
	+MWF (n = 68)	−MWF (n = 184)	p Value*
Male	46 (67.65)	108 (58.70)	0.196
Age, yrs	66.6 ± 10.0	66.4 ± 15.0	0.905
NYHA functional class			
I	7 (10.29)	11 (5.98)	0.031
II	9 (13.24)	16 (8.70)	
III	39 (57.35)	140 (76.09)	
IV	13 (19.12)	17 (9.24)	
Device type			
CRT-D	22 (32.35)	40 (21.74)	0.082
CRT-P	46 (67.65)	144 (78.26)	
Comorbidities			
Diabetes mellitus	12 (17.65)	30 (16.30)	0.800
Hypertension	21 (30.88)	44 (23.91)	0.262
ECG variables			
Sinus rhythm	50 (73.53)	131 (71.20)	0.715
Atrial fibrillation†	18 (26.47)	53 (28.80)	
QRS morphology (LBBB)	44 (64.71)	106 (57.61)	0.308
QRS duration, ms	151.5 ± 27.0	149.7 ± 24.0	0.628
LV lead type			
Quadripolar	17 (25)	35 (19)	0.298
Nonquadripolar	51 (75)	149 (80)	
Medications			
Loop diuretic agents	66 (97.06)	166 (90.22)	0.075
ACE inhibitors/ARBs	61 (89.71)	171 (92.93)	0.400
Beta-blockers	48 (70.59)	117 (63.59)	0.299
MRAs	31 (45.59)	87 (47.28)	0.811
Echocardiographic LVEF, %	21.3 (14.9–31.5)	25 (17.8–31.2)	0.325
CMR variables			
LV end-diastolic volume, ml	273.3 (106.8)	228.0 (82.7)	<0.001
LV end-systolic volume, ml	214.4 (105.1)	168.2 (77.4)	<0.001
LVEF, %	24.8 (12.4)	28.2 (11.4)	0.043

Values are n (%), mean ± SD, or median (interquartile range). *Differences between the groups from analysis of variance for continuous variables and from chi-square tests for categorical variables. †Includes permanent, persistent, and paroxysmal atrial fibrillation.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CMR = cardiac magnetic resonance; CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; ECG = electrocardiographic; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; MWF = midwall fibrosis; NYHA = New York Heart Association.

MWF AND OUTCOMES. Total mortality was 29 of 68 (42.6%) in the +MWF cohort and 63 of 184 (34.2%) in the −MWF arm, amounting to annualized rates of 12.8% for +MWF and 6.86% for −MWF. Cardiac mortality was 27 of 68 (39.7%) and 43 of 184 (23.4%) for the +MWF and −MWF groups, respectively. Over a maximum follow-up period of 14 years (median

FIGURE 2 Clinical Outcomes



The presence of midwall fibrosis (MWF) was associated with higher total mortality as well as hospitalization for heart failure (HF) and major adverse cardiac events (MACEs).

3.8 years [interquartile range (IQR): 2.0 to 6.1 years] for +MWF and 4.6 years [IQR: 2.4 to 8.3 years] for −MWF; p = 0.525), +MWF was associated with higher total mortality in Kaplan-Meier survival analyses (log-rank p = 0.006) (**Figure 2**). Univariate Cox proportional hazards analyses are shown in **Table 2**. In multivariate analyses (**Table 3**), +MWF was associated with higher total mortality (adjusted hazard ratio [aHR]: 2.31; 95% confidence interval [CI]: 1.45 to 3.68), independent of age, NYHA class, CRT type, hypertension, and atrial rhythm. Other potential confounders did not reach significance in multivariate models. The C statistic for the multivariate model to predict total mortality was 0.68 without inclusion of MWF status and 0.70 with inclusion of MWF status; Somers's D was 0.36 and 0.40, respectively. Although follow-up times were different between the implanting centers (Good Hope Hospital, 10.7 years [IQR: 8.7 to 12.8 years]; Queen Elizabeth Hospital, 3.2 years [IQR: 2.0 to 5.3 years]; p < 0.001), implanting center did not emerge as a predictor of any endpoint in univariate analyses (data not shown).

Total mortality or HF hospitalization was 34 of 68 (50%) in +MWF and 76 of 184 (41.3%) in −MWF, amounting to annualized rates of 16.9% for +MWF and 9.2% for −MWF. In Kaplan-Meier survival analyses, +MWF was associated with higher total mortality or HF hospitalization (log-rank p = 0.005) (**Figure 2**). In multivariate analyses, +MWF was associated with higher total mortality or HF hospitalization (aHR: 2.02; 95% CI: 1.32 to 3.09), independent of age, NYHA functional class, hypertension, and left bundle branch block. Other potential confounders did not reach significance in multivariate models.

Total mortality or hospitalization for MACE was 35 of 68 (51%) in +MWF and 81 of 184 (44%) in −MWF, amounting to annualized rates of 17.6% for +MWF and 9.9% for −MWF. In Kaplan-Meier survival analyses, +MWF was associated with lower survival (log-rank p = 0.009) (**Figure 2**). In multivariate analyses, +MWF was associated with higher total mortality or hospitalization for MACE (aHR: 2.02; 95% CI: 1.32 to 3.07), independent of age, NYHA class, CRT type, and diabetes. Other potential confounders did not reach significance in multivariate models.

With respect to mode of death, this was unknown in 1 patient who underwent CRT-P (−MWF). Excluding this patient, +MWF was associated with a higher mortality from pump failure (aHR: 1.95; 95% CI: 1.11 to 3.41) (**Figure 3,** Online Table 1). As shown in **Figure 4**, SCD (aHR: 3.75; 95% CI: 1.26 to 11.2) and the combined endpoint of SCD or hospitalization for

TABLE 2 Univariate Analyses

	Total Mortality			Total Mortality or HF Hospitalization			Total Mortality or Hospitalization for MACEs		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
MWF	1.86	1.19–2.90	0.007	1.79	1.18–2.70	0.006	1.70	1.14–2.55	0.010
Male	1.25	0.81–1.92	0.317	1.10	0.75–1.63	0.623	0.98	0.68–1.43	0.929
Age	1.03	1.01–1.05	0.001	1.04	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001
NYHA functional class									
III	1.71	0.68–4.30	0.252	1.30	0.62–2.73	0.484	1.45	0.70–3.03	0.321
IV	3.57	1.33–9.58	0.011	3.00	1.34–6.73	0.008	3.04	1.35–6.81	0.007
Device type (CRT-D)	0.35	0.15–0.80	0.013	0.60	0.33–1.10	0.099	0.55	0.30–1.00	0.052
Comorbidities									
Diabetes mellitus	1.50	0.88–2.56	0.134	1.54	0.95–2.48	0.081	1.68	1.06–2.67	0.027
Hypertension	2.03	1.32–3.13	0.001	1.75	1.18–2.61	0.006	1.60	1.08–2.37	0.020
ECG variables									
Atrial fibrillation*	1.59	1.04–2.43	0.032	1.23	0.82–1.84	0.310	1.30	0.88–1.92	0.190
QRS morphology (LBBB)	0.70	0.46–1.07	0.102	0.63	0.43–0.92	0.018	0.65	0.45–0.94	0.023
QRS duration	1.00	1.00–1.01	0.331	1.00	1.00–1.01	0.501	1.00	1.00–1.01	0.448
Medications									
Loop diuretic agents	1.15	0.55–2.39	0.713	1.55	0.75–3.21	0.240	1.34	0.67–2.67	0.401
ACE inhibitors/ARBs	0.98	0.45–2.11	0.949	0.76	0.40–1.45	0.404	0.59	0.32–1.07	0.081
Beta-blockers	0.87	0.57–1.32	0.501	0.82	0.56–1.20	0.296	0.76	0.52–1.09	0.137
MRAs	1.25	0.83–1.88	0.294	1.15	0.79–1.67	0.481	1.23	0.85–1.78	0.268
LVEF†	0.99	0.97–1.01	0.342	0.99	0.97–1.01	0.331	0.99	0.96–1.01	0.157

*Includes permanent, persistent, and paroxysmal atrial fibrillation. †Obtained from echocardiography.
CI = confidence interval; HF = heart failure; HR = hazard ratio; MACE = major adverse cardiac event; other abbreviations as in Table 1.

ventricular arrhythmias (aHR: 2.60; 95% CI: 1.02 to 6.63) were also higher in +MWF (Online Table 1).

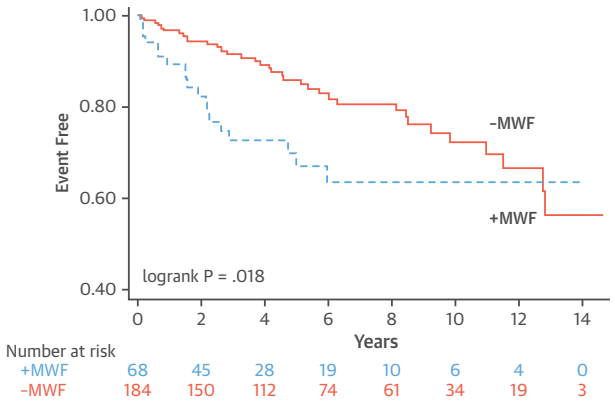
MWF AND DEVICE TYPE. In univariate (Table 2) and multivariate (Table 3) analyses of the total population, CRT-D was superior to CRT-P with respect to total mortality (aHR: 0.33; 95% CI: 0.14 to 0.77) and total mortality and hospitalization for MACEs (aHR: 0.51; 95% CI: 0.27 to 0.97) but not total mortality or HF hospitalization. A significant interaction between MWF and device type was found (likelihood-ratio test comparing models with and without MWF status and device type yielded a p value of 0.007). In separate analyses of the +MWF and −MWF groups (Figure 5, Online Table 2), CRT-D was associated with lower total mortality (hazard ratio [HR]: 0.23; 95% CI: 0.07 to 0.75), total mortality or HF hospitalization (HR: 0.32; 95% CI: 0.12 to 0.82), and total mortality or hospitalization for MACEs (HR: 0.30; 95% CI: 0.12 to 0.78) than CRT-P in +MWF, but not in −MWF. Event rates are shown in Table 4.

TABLE 3 Multivariable Analyses*

	Total Mortality			Total Mortality or HF Hospitalization			Total Mortality or Hospitalization for MACEs		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
+MWF	2.31	1.45–3.68	<0.001	2.02	1.32–3.09	0.001	2.02	1.32–3.07	0.001
Age	1.03	1.01–1.05	0.013	1.03	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001
NYHA functional class IV	1.86	1.13–3.05	0.014	2.06	1.30–3.24	0.002	1.79	1.13–2.84	0.013
Device type (CRT-D)	0.33	0.14–0.77	0.010		–		0.51	0.27–0.97	0.039
Diabetes mellitus		–			–		1.86	1.16–2.98	0.010
Hypertension	1.85	1.18–2.89	0.007	1.66	1.10–2.51	0.016		–	
Atrial fibrillation†	1.78	1.16–2.75	0.009		–			–	
QRS morphology (LBBB)		–		0.64	0.43–0.94	0.023		–	

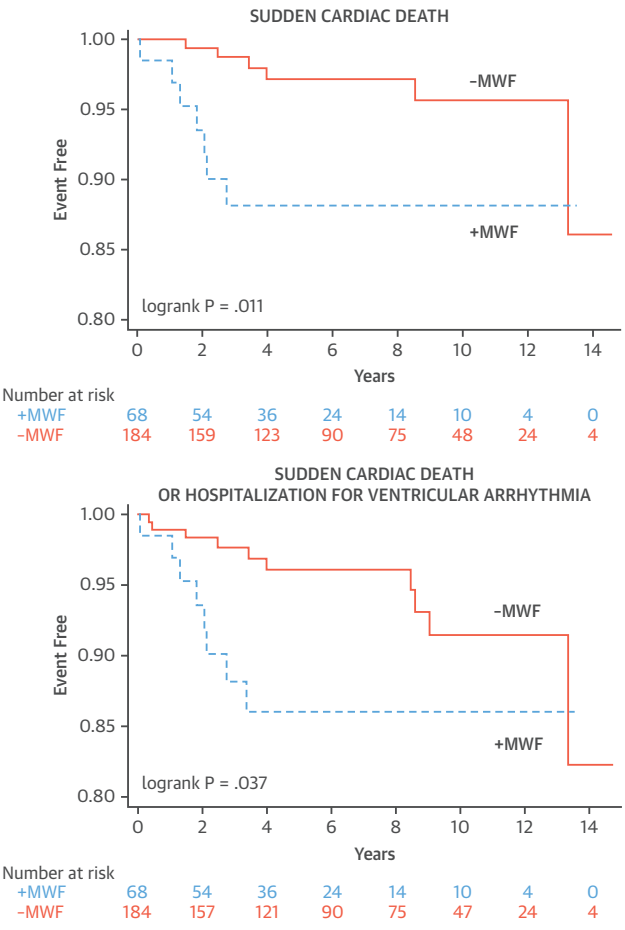
*Only variables with p values <0.10 on univariate analyses were included in multivariate models. †Includes permanent, persistent, and paroxysmal atrial fibrillation.
Abbreviations as in Tables 1 and 2.

FIGURE 3 Death From Pump Failure



Presence of midwall fibrosis (MWF) resulted in increased death from pump failure.

FIGURE 4 Sudden Cardiac Death and Ventricular Arrhythmias



Presence of midwall fibrosis (MWF) significantly increased the risk for sudden cardiac death and the composite endpoint of sudden cardiac death or hospitalization ventricular arrhythmias.

In order to exclude a possible time-related bias, we first explored whether date of implantation emerged as a predictor of total mortality in univariate Cox proportional hazards analysis, but no significant effect was found (data not shown). We also split our sample in 3 time periods, corresponding to changes in U.K. national guidelines for CRT. In this analysis, no difference in total mortality between CRT-D and CRT-P emerged between the time periods (HR: 0.70 [95% CI: 0.44 to 1.10] for 2007 to 2013; HR: 0.46 [95% CI: 0.20 to 1.06] for 2014 to 2017) compared with 2002 to 2006.

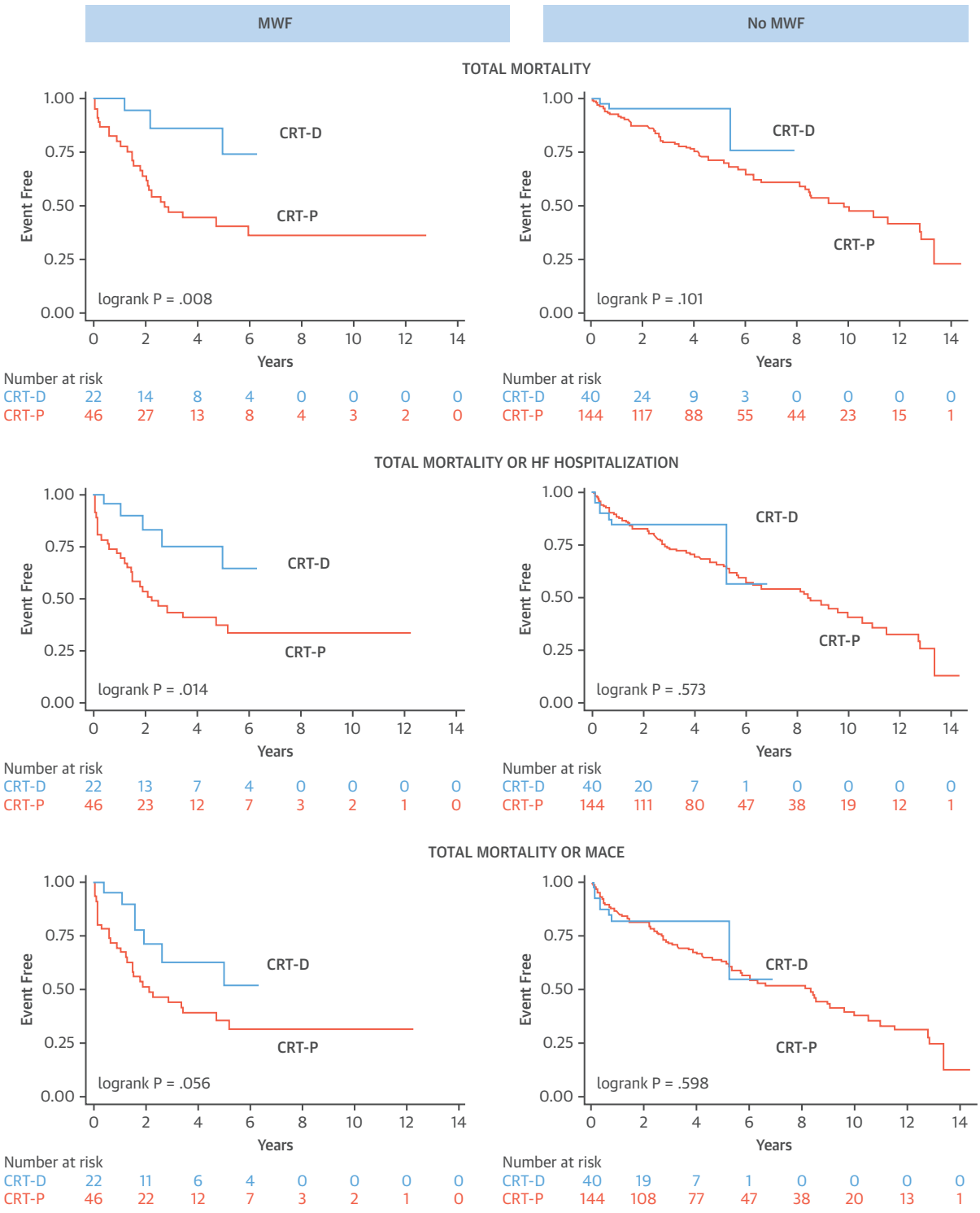
Interobserver and intraobserver agreement for the presence of MWF on 30 randomized scans for 2 observers, in terms of Cohen's kappa, was 0.84 (95% CI: 0.51 to 0.96) and 0.92 (95% CI: 0.60 to 0.99), respectively.

DISCUSSION

This is the first study to compare clinical outcomes after CRT-D and CRT-P in patients with NICM, categorized according to the presence or absence of MWF, identified by CMR. Several findings have emerged. First, in the total study population, CRT-D was superior to CRT-P with respect to total mortality and total mortality or MACE. Second, CRT-D was markedly superior to CRT-P in terms of total mortality, cardiovascular mortality, and all composite endpoints in +MWF, but no benefit from CRT-D over CRT-P was observed in −MWF with respect to any of the endpoints. Third, MWF independently predicted total mortality as well as total mortality or HF hospitalization, cardiovascular mortality, and total mortality or MACEs. Fourth, the association between MWF and total mortality was linked to pump failure as well as SCD and hospitalization for ventricular arrhythmias. These findings suggested that MWF is pivotal with respect to the benefit of CRT-D over CRT-P in patients with NICM (Central Illustration).

CRT-D VERSUS CRT-P IN NICM. Our findings have emerged following the elegant DANISH study, in which 1,116 patients were randomized to ICDs or usual clinical care (control group) (10). After a median follow-up period of 5.63 years, ICDs did not reduce total mortality (HR: 0.87; 95% CI: 0.68 to 1.12; p = 0.28), despite a significant reduction in SCD (HR: 0.50; 95% CI: 0.31 to 0.82; p = 0.005). We should consider, however, that a meta-analysis undertaken prior to DANISH showed that larger numbers of patients (at least 1,457) are needed to show a significant effect of ICDs on total mortality in NICM (3). This was also the case in recent meta-analyses that included

FIGURE 5 Clinical Outcomes According to Device Type and Midwall Fibrosis Status



Although use of cardiac resynchronization therapy-defibrillation (CRT-D) was superior to cardiac resynchronization therapy-pacing (CRT-P) in the presence of midwall fibrosis (MWF) for the primary and secondary endpoints, there was no significant difference between the devices in patients without MWF.

TABLE 4 Event Rates According to Device Type and Midwall Fibrosis Status*

	N	Total Mortality	Total Mortality or HF Hospitalization	Total Mortality or Hospitalization for MACEs
+MWF				
CRT-D	22	4.3	7.6	7.6
CRT-P	46	16.5	21.5	22.6
Total	68	12.8	16.9	17.6
−MWF				
CRT-D	40	2.8	7.9	7.9
CRT-P	144	7.4	9.3	10.2
Total	184	6.9	9.2	9.9

Values are %. *Data are expressed in terms of annualized event rates.
Abbreviations as in Tables 1 and 2.

DANISH (24–26). It is possible, therefore, that DANISH was underpowered to show an effect of ICD therapy on total mortality. In contrast, we found that CRT-D was superior to CRT-P, even in a relatively small sample of patients (n = 252).

The contrasting findings of our comparison between CRT-D and CRT-P in the present study and that of DANISH (10) may be due to differences in study design and statistical power. In the present study, all patients in the comparator group underwent CRT, compared with only 58% in the control group of DANISH. In addition, more patients in the present study were in NYHA functional class III or IV (57%) than in DANISH (46%). It is therefore not surprising to see that total mortality in the present study was higher (between 6.9 and 12.8 per 100 person-years in −MWF and +MWF groups, respectively) than in DANISH (between 4.4 and 5.0 per 100 person-years in the ICD and control groups, respectively). Similarly, cardiac mortality in the present study (39.7% in +MWF and 23.4% in −MWF) was also higher than in DANISH ("cardiovascular mortality" of 13.8% in the ICD group and 17% in the control group). It would appear, therefore, that compared with patients in DANISH, patients in the present study were "sicker," and a greater proportion died from cardiac causes.

In separate analyses of +MWF and −MWF, CRT-D was superior to CRT-P in NICM +MWF. Even though patient numbers were approximately 3 times higher in the −MWF subgroup, no differences in outcomes emerged between CRT-D and CRT-P. Admittedly, total mortality was lower in −MWF than in +MWF (annualized rate of 6.9 vs. 12.8), raising the possibility that larger numbers might be needed to show a benefit from CRT-D over CRT-P in NICM −MWF. Notwithstanding, our findings suggested that MWF identifies a subpopulation of patients with NICM who are more likely to benefit from CRT-D.

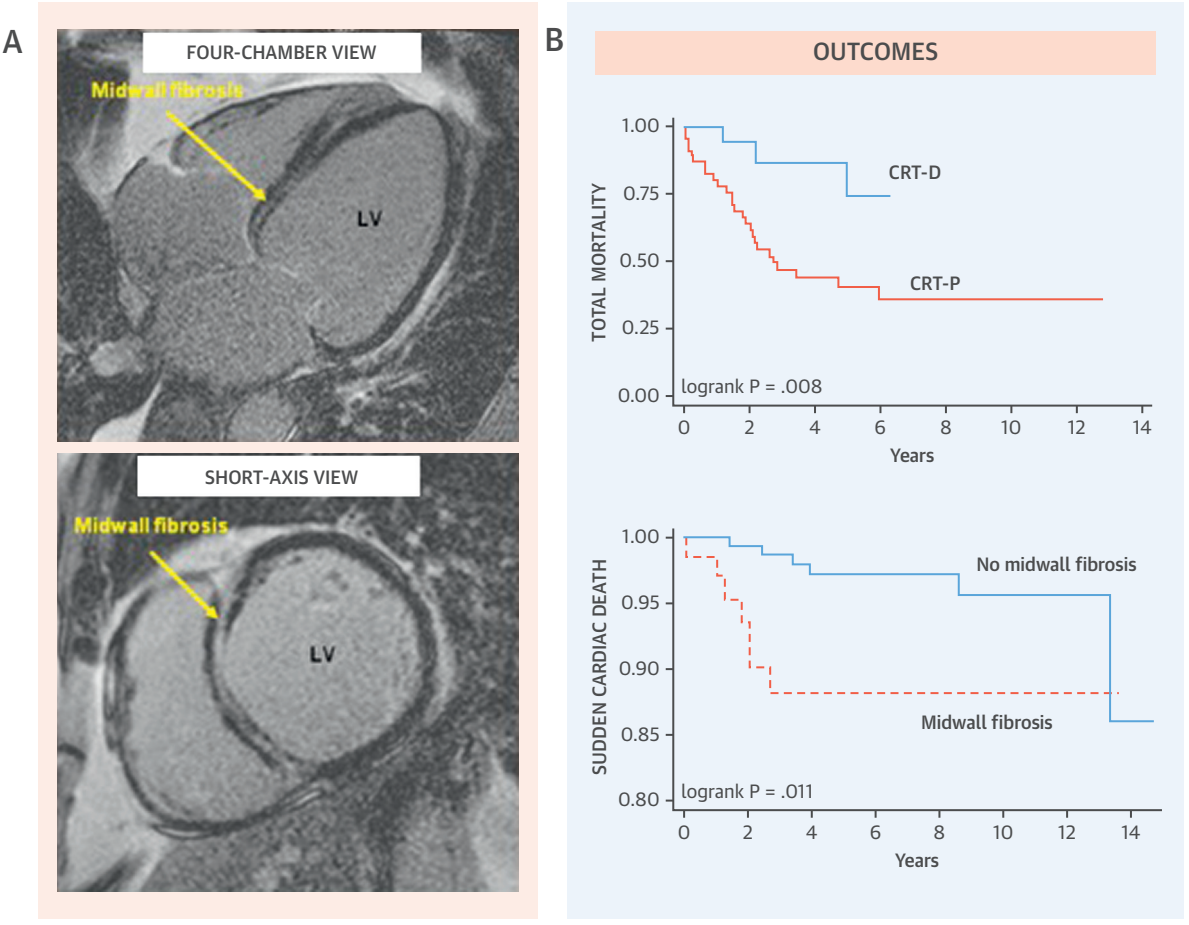
Our finding of a higher risk for pump failure deaths and HF hospitalizations in +MWF was not unexpected. We have previously shown that MWF is associated with a selective impairment of circumferential LV myocardial strain, apical rotation, and diastolic function (27). The result is a "stiff" left ventricle, which is less able to twist to an applied torque (rotation) and more likely to move as a solid body. These mechanical disturbances may be responsible for the known associations of MWF with HF and the suboptimal response to medical and device therapy (12–14,16,17).

In the present study, we found that compared with −MWF, +MWF was associated with a 3.75-fold higher risk for SCD and a 2.6-fold higher risk for the combined endpoint of SCD or hospitalization for ventricular arrhythmias. These findings were consistent with those of Wu et al. (28), using Langendorff hearts, in which myocardial fibrosis was shown to provide continuous re-entry. Clinical studies have also shown that MWF is associated with an increased risk for ventricular arrhythmias (12–14,17). Other studies supported the use of T1 mapping in predicting ventricular arrhythmias in ICD recipients (29).

Physicians may refer to the DANISH study as a basis for making decisions on the choice of device therapy in patients with NICM. We should consider, however, that DANISH did not use CMR for tissue characterization of the underlying cardiomyopathy. In the present study, we showed that NICM with MWF behaves differently than NICM without MWF. On this basis, MWF should be regarded as a "high-risk feature" in patients with NICM and raises the possibility that patients with MWF may derive a clinical benefit from CRT-D over CRT-P.

STUDY LIMITATIONS. This study has the typical limitations of an observational study. Rather than by study design, the choice of device therapy in patients with NICM was governed by U.K. guidelines, which, prior to 2014, did not recommend CRT-D for patients with NICM (18). Because we did not use telemonitoring, we cannot clarify whether patients who were coded as having died from pump failure could have died from arrhythmic events. Importantly, this was an observational study, and any parallels or discrepancies with randomized, controlled trials should be interpreted with caution. We did not use quantification of myocardial scar, but we cannot discount the possibility that semiautomatic methods (30) may further improve

CENTRAL ILLUSTRATION **Cardiac Resynchronization Therapy in Nonischemic Cardiomyopathy With or Without Left Ventricular Midwall Fibrosis**



Leyva, F. et al. J Am Coll Cardiol. 2017;70(10):1216–27.

We sought to determine whether cardiac resynchronization therapy–defibrillation (CRT-D) was superior to cardiac resynchronization therapy–pacing (CRT-P) in patients with nonischemic cardiomyopathy (NICM) with or without midwall fibrosis. **(A)** Four-chamber and short-axis inversion recovery late gadolinium enhancement cardiac magnetic resonance images show midwall enhancement **(yellow arrows)** in the interventricular septum, typical of midwall fibrosis. **(B)** Survival curves for patients with NICM demonstrated that CRT-D was superior to CRT-P for total mortality and the presence of midwall fibrosis affected the likelihood of sudden cardiac death.

risk stratification. Unfortunately, only 52 patients underwent CRT implantation using a quadripolar lead. Although we found no interaction between lead type and outcomes, this might be due to statistical underpowering. The lack of systematic, prospective collection of device interrogation data might also have led to an underestimation of the overall benefit from CRT-D. Novel CMR techniques, such as mapping of border zone of scar and scar morphology, which were not addressed in the present study, might add to the risk stratification.

CONCLUSIONS

In our total population of patients with CMR-confirmed NICM, CRT-D was superior to CRT-P. This benefit, however, was evident in +MWF but not −MWF patients. In the total study population, MWF emerged as an independent predictor of mortality and morbidity in patients with NICM undergoing CRT, a relationship that was mediated by pump failure, SCD, and ventricular arrhythmias. These findings reinforce a tailored approach in the choice of

device in patients with NICM and support the use of CMR in risk stratification. Randomized controlled trials of CRT-D versus CRT-P in patients with NICM with or without myocardial scar should be considered.

ACKNOWLEDGMENT The authors are grateful to Boston Scientific for an unrestricted educational grant.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with NICM who have MWF detected by CMR face worse clinical outcomes than those without MWF. Hence, patients with MWF may benefit from devices with defibrillation capability (CRT-D).

TRANSLATIONAL OUTLOOK: Prospective trials are needed to confirm the utility of CMR for detection of MWF as a guide to selection of patients with NICM for device-based therapies.

REFERENCES

1. Cleland JGF, Daubert J-C, Erdmann E, et al., for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.

2. Bristow MR, Saxon LA, Boehmer J, et al., for the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced heart failure. N Engl J Med 2004;350:2140–50.

3. Colquitt J, Mendes D, Clegg A, et al. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. Health Technol Assess 2014;18:1–560.

4. Linde C, Abraham WT, Gold MR, Daubert C. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study. J Am Coll Cardiol 2010;56:1826–31.

5. Wikstrom G, Blomstrom-Lundqvist C, Andren B, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur Heart J 2009;30:782–8.

6. Bansch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). Circulation 2002;105:1453–8.

7. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. J Am Coll Cardiol 2003;41:1707–12.

8. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.

9. Packer DL, Prutkin JM, Hellkamp AS, et al. Impact of implantable cardioverter-defibrillator, amiodarone, and placebo on the mode of death in stable patients with heart failure: analysis from the sudden cardiac death in heart failure trial. Circulation 2009;120:2170–6.

10. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–30.

11. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.

12. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA 2013;309:896–908.

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

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

15. Di Marco A, Anguera I, Schmitt M, et al. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. J Am Coll Cardiol HF 2017;5:28–38.

16. Leyva F, Taylor RJ, Foley PW, et al. Left ventricular midwall fibrosis as a predictor of mortality and morbidity after cardiac resynchronization therapy in patients with nonischemic cardiomyopathy. J Am Coll Cardiol 2012;60:1659–67.

17. Wu KC, Weiss RG, Thiemann DR, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:2414–21.

18. National Institute of Health and Care Excellence. NICE technology appraisal [TA 314]: implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure 2014 June 24:1–68. Available at: https://www.nice.org.uk/guidance/ta314/chapter/1-guidance. Accessed May 12, 2017.

19. Hundley WG, Bluemke DA, Finn JP, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol 2010;55:2614–62.

20. Almehmadi F, Joncas SX, Nevis I, Zahrani M, Bokhari M, Stirrat J. Prevalence of myocardial fibrosis patterns in patients with systolic dysfunction: prognostic significance for the prediction of sudden cardiac arrest or appropriate implantable cardiac defibrillator therapy. Circ Cardiovasc Imaging 2014;7:593–600.

21. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Braunwald E, editor. Heart Disease: A Textbook of Cardiovascular Medicine. New York, NY: W.B. Saunders, 1997:742–79.

22. Rockman HA, Juneau C, Chatterjee K, Rouleau JL. Long-term predictors of sudden and low output death in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1989;64:1344–8.

23. Harrell FJ. Regression Modelling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, NY: Springer, 2001:53–85.

24. Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. Eur Heart J 2017;38:1738–46.

25. Golwala H, Bajaj NS, Arora G, Arora P. Implantable cardioverter-defibrillator for non ischemic cardiomyopathy: an updated meta-analysis. Circulation 2017;135:201–3.

26. Al-Khatib SM, Fonarow GC, Joglar JA, et al. Primary prevention implantable cardioverter defibrillators in patients with nonischemic cardiomyopathy: a meta-analysis. JAMA Cardiol 2017;2:685–8.

27. Taylor R, Umar F, Lin E, et al. Mechanical effects of left ventricular midwall fibrosis in non-ischemic cardiomyopathy. J Cardiovasc Magn Reson 2016;18:1.

28. Wu TJ, Ong JJ, Hwang C, et al. Characteristics of wave fronts during ventricular fibrillation in human hearts with dilated cardiomyopathy: role of increased fibrosis in the generation of reentry. J Am Coll Cardiol 1998;32:187–96.

29. Chen Z, Sohal M, Voigt T, et al. Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non-ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. Heart Rhythm 2015;12:792–801.

30. Mikami Y, Kolman L, Joncas SX, et al. Accuracy and reproducibility of semi-automated late gadolinium enhancement quantification techniques in patients with hypertrophic cardiomyopathy. J Cardiovasc Magn Reson 2014;16:85.

KEY WORDS cardiac magnetic resonance imaging, heart failure, implantable cardioverter-defibrillator, major adverse cardiac events, pacing

APPENDIX For supplemental tables, please see the online version of this article.