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Effectiveness of cardiac resynchronization therapy by the frequency of revascularization procedures in ischemic cardiomyopathy patients

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Abstract

Background: *It is not known whether the number of revascularizations modifies clinical outcomes in patients with ischemic cardiomyopathy (ICM) implanted with cardiac resynchronization therapy defibrillator (CRT-D) vs. an implantable cardioverter-defibrillator (ICD)-only.*

Methods: *In Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), we evaluated the effect of CRT-D vs. ICD-only on heart failure (HF) or death, on ventricular tachycardia (VT), ventricular fibrillation (VF) or death, and on reverse remodeling in 592 ICM patients with left bundle branch block, by the number of pre-enrollment revascularizations (0, 1 or ≥ 2 revascularizations).*

Results: *There was a risk reduction of HF/death with CRT-D vs. ICD-only in all three sub-groups: ICM with no need for revascularization (HR 0.51 [0.26–1.02]; p = 0.055), ICM with 1 revascularization (HR 0.45 [0.30–0.70]; p < 0.001), and ICM with 2 or more revascularizations (HR 0.37 [0.20–0.66]; p < 0.001). Similarly, there was a risk reduction of VT/VF/death with CRT-D vs. ICD-only in patients with no need for revascularization (HR 0.55 [0.31–0.99]; p = 0.044); with 1 revascularization (HR 0.77 [0.51–1.18]; p = 0.23); or with ≥ 2 revascularizations (HR 0.63 [0.34–1.17]; p = 0.14). There was a similar degree of left ventricular reverse remodeling in all three sub-groups (p > 0.05 for LVESV, LVEDV, and LAV percent change at 1-year follow-up).*

Conclusions: *In ICM patients, CRT-D is associated with a reduction in HF or death and VT/VF or death — irrespective of the frequency of pre-enrollment revascularization procedures — and is accompanied by a similar degree of beneficial left ventricular reverse remodeling.*
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Key words: cardiac resynchronization therapy, implantable cardioverter-defibrillator, heart failure, ventricular tachyarrhythmias

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Introduction

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure (HF) hospitalization and mortality across the spectrum of patients with mild to severe drug-refractory HF, severely depressed left ventricular ejection fraction (LVEF), and a wide QRS [1–6].

In the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT), patients with ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) patients had similar reduction in HF events or death with an implanted cardiac resynchronization therapy with defibrillator (CRT-D) vs. an implantable cardioverter-defibrillator (ICD)--only [7]. However, response to CRT-D in ICM patients is not uniform and therefore, better stratification of CRT-D benefit is warranted in this cohort.

Prior studies suggested that the extent of scar among ICM patients predicts subsequent outcomes after CRT-D implantation [8–10]. However, scar burden is challenging to measure and quantify to this day. We hypothesized that a simple clinical parameter, the number of prior revascularization procedures might serve as a surrogate marker for the extent of myocardial scar. However, it is currently unknown whether CRT-D benefit might be stratified by the number of prior revascularization procedures among ICM patients.

Therefore, in this study, we aimed to assess clinical and echocardiographic response to CRT-D vs. an ICD-only in ischemic cardiomyopathy patients with left bundle branch block (LBBB) by the number of pre-enrollment revascularizations, enrolled in MADIT-CRT. We hypothesized that there will be a certain threshold of pre-enrollment revascularization procedure frequency, above which CRT-D vs. an ICD alone will no longer be clinically effective to improve outcomes.

Methods

Study population

The design, protocol and results of the MADIT-CRT study were published previously [11, 12]. Briefly, 1,820 patients with ICM (New York Heart Association [NYHA] functional class I or II) or NICM (NYHA functional class II only), LVEF of less than 30% and a prolonged QRS duration > 130 ms were randomized in a 3:2 ratio to receive CRT-D or ICD therapy. All eligible patients met the guideline criteria for ICD [13]. Patients were excluded with certain clinical characteristics, as described previously [11]. One hundred and ten hospital centers from North America and Europe participated in this international multicenter trial. The present study sample comprised 592 (of the 1,820) patients with ICM and LBBB enrolled in MADIT-CRT (33%) patients of whom 353 (60%) were randomized to CRT-D therapy. We also report outcomes on 434 patients with ICM and non-LBBB. The study was in compliance with the Declaration of Helsinki and all enrolling sites had the protocol being approved by the local Institutional Review Board. All patients provided informed consent before the enrollment.

Data acquisition and patient follow-up

The MADIT-CRT trial was carried out from December 22, 2004 through June 22, 2009. After publication of the primary results, post-trial follow--up was conducted for all 1,691 surviving study participants until September 10, 2010 (phase 1 of the extended follow-up).

Echocardiography methods

Echocardiography recordings were analyzed off-line at the Brigham and Women's Hospital, Boston, Massachusetts as an independent echocardiography core laboratory [11]. Echocardiography investigators analyzing the images were blinded to clinical characteristics, treatment assignment, or outcomes. Left ventricular (LV) volumes were measured by Simpson's disk method in the apical 4- and 2-chamber views and LVEF was calculated according to the American Society of Echocardiography protocols [14].

Definitions and endpoints

We restricted our analysis to patients with baseline LBBB morphology as previous studies illustrated that only LBBB patients demonstrated a significant reduction in the combined endpoint of HF or death with CRT-D vs. ICD-only, while patients with non-LBBB morphology demonstrated a trend towards higher mortality with CRT [15]. Revascularization was defined as any percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) performed prior to enrollment; patients without revascularization were deemed to have ICM if they have had any myocardial infarctions prior to enrollment or were classified ischemic by the enrolling physician.

The primary endpoint of the current study was the first occurrence of a HF episode or death from any cause (HF/death); the secondary endpoint was the first occurrence of ventricular tachycardia

(VT), ventricular fibrillation (VF), or death from any cause (VT/VF/death).

The diagnosis of HF was made if patients were exhibiting signs and symptoms consistent with congestive HF that resulted in intravenous decongestive treatment in an outpatient setting or augmented decongestive therapy with oral or parenteral medications during an in-hospital stay.

Arrhythmia episodes included VT or VF with appropriate therapy of anti-tachycardia pacing or shock. Definition of VT was set from a rate of 180 bpm (recommended programming) up to 250 bpm, ventricular (V) rate ≥ atrial (A) rate if 1:1 A:V, V-V changes drive A-A changes. VF was defined as ventricular rate > 250 bpm with disorganized ventricular electrocardiograms.

Adjudication of the endpoints was carried out by an independent mortality committee and a heart-failure committee unaware of treatment assignments and clinical parameters, according to pre-specified criteria, as described previously [11].

Statistical analysis

All analyses in the present study were carried out on an intention-to-treat basis (i.e., according to the original treatment assignment regardless of in-trial or post-trial crossovers). Variables were expressed as means ± standard deviation, and categorical data were summarized as frequencies and percentages. The clinical characteristics of the patients at baseline were compared between the subgroups, with the use of the Kruskal-Wallis test for continuous variables and the χ^2 test or Fisher's exact test for dichotomous variables.

The Kaplan-Meier method was used to determine cumulative probabilities of death from any cause, nonfatal heart-failure events, and ventricular tachyarrhythmias, according to treatment group, ischemic status, and the number of revascularizations. Between-group comparisons of cumulative event rates were calculated by means of the log-rank test.

Multivariate Cox proportional-hazards regression analyses were used to evaluate the effect of CRT-D on the following endpoints: 1) combined endpoint of death from any cause and a nonfatal heart-failure event; 2) combined endpoint of ventricular tachyarrhythmia or death from any cause. The Cox model was adjusted for relevant clinical covariates with the use of best-subset regression modeling. The benefit of CRT-D therapy as compared with ICD therapy alone among patients with LBBB and those without LBBB was assessed by including a term for interaction between treatment and presence or absence of LBBB.

All statistical tests were 2-sided and a p-value of < 0.05 was considered statistically significant. The p values for interaction are reported. Analyses were carried out with the use of SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

Study population

The median follow-up of the enrolled patients during the trial was 2.4 years (interquartile range, 1.8–3.2). Clinical characteristics of the 592 patients included in this study were similar in the ICD-only and CRT-D groups. However, as the amount of revascularizations increased among the studied sub-groups, there was an increasing amount of patients of white race and ischemic NYHA I, while patients were less likely to be female (Table 1).

Among the 299 ischemic patients that had undergone 1 revascularization, 163 had a prior CABG and 136 had prior PCI. For the 152 ischemic patients with multiple revascularizations, 117 had a history of a prior CABG, while 135 had a history for a prior PCI. These patients had a range of revascularization procedures from 2 to a maximum of 9 revascularizations.

CRT-D effect in ICM patients with LBBBs based on the number of revascularizations

In ICM patients with no revascularizations, univariate cumulative probabilities for HF or death illustrate a statistically significant benefit for CRT-D therapy ($p = 0.030$; Fig. 1A), and a trend for benefit for VT/VF/death ($p = 0.051$; Fig. 2A) at 4 years. In the multivariate analysis adjusted for current smoking, female sex, left ventricular end-systolic volume (LVESV), and history of prior ventricular arrhythmias, there was a trend toward CRT-D benefit for the primary outcome of HF or death (HR 0.51, 0.26–1.02, $p = 0.055$; Table 2), and a statistically significant benefit of CRT-D vs. an ICD alone for VT/VF/death (HR 0.55, 0.31–0.99, $p = 0.044$; Table 3) in LBBB patients with no pre-enrollment revascularizations.

In ICM patients with 1 revascularization, univariate estimates for HF or death showed a statistically significant benefit for CRT-D therapy vs. ICD-only ($p < 0.001$; Fig. 1B) and a trend towards CRT-D vs. ICD for VT/VF/death at 4 years ($p = = 0.153$; Fig. 2B). In the multivariate analysis, there was a significant benefit of CRT-D for HF/

Table 1. Baseline characteristics of the study population by the number of pre-enrollment revascularization procedures.

	No revascularization (n = 141)	One prior revascularization (n = 299)	Two or more prior revascularization (n = 152)	P
Prior CABG	0 (0%)	163 (55%)	117 (77%)	**< 0.001***
Prior non-CABG (PCI)	0 (0%)	136 (45%)	135 (89%)	**< 0.001***
Age at enrollment [years]	67.1 ± 9.0	68.1 ± 9.1	69.3 ± 8.1	0.16
Female	30 (21%)	51 (17%)	15 (10%)	**0.026***
White race	125 (89%)	282 (94%)	146 (97%)	**0.018***
CRT-D treatment	86 (61%)	170 (57%)	97 (64%)	0.34
Diabetes	43 (30%)	112 (37%)	66 (44%)	0.07
Smoking	19 (14%)	30 (10%)	13 (9%)	0.32
Heart rate	67.5 ± 9.6	67.9 ± 11.5	66.1 ± 9.7	0.36
Systolic blood pressure	124.0 ± 17.8	122.7 ± 17.7	124.6 ± 17.3	0.50
Creatinine [mg/dL]	1.20 ± 0.35	1.20 ± 0.32	1.22 ± 0.35	0.88
Prior atrial arrhythmia	14 (10%)	51 (17%)	25 (17%)	0.13
Prior ventricular arrhythmia	14 (10%)	22 (7%)	15 (10%)	0.54
ACEI or ARB	137 (97%)	285 (95%)	141 (93%)	0.21
Aldosterone antagonists	41 (29%)	93 (31%)	37 (24%)	0.33
Amiodarone	6 (4%)	35 (12%)	15 (10%)	**0.044***
Beta-blockers	132 (94%)	272 (91%)	145 (95%)	0.21
Diuretics	100 (71%)	212 (71%)	106 (70%)	0.96
QRS [ms]	160.3 ± 17.9	160.9 ± 19.5	159.0 ± 17.0	0.84
LVEF [%]	29.0 ± 3.0	28.6 ± 3.2	28.5 ± 3.7	0.35
LVEDV indexed by BSA	123.7 ± 27.5	123.5 ± 26.3	122.1 ± 27.6	0.55
LVESV indexed by BSA	88.2 ± 22.3	88.5 ± 21.0	87.9 ± 23.2	0.61
LAV indexed by BSA	45.8 ± 9.6	47.2 ± 10.1	48.3 ± 11.0	0.10

*Statistical significance; Continuous variables are shown as mean ± standard deviation. Categorical variables are shown as numbers (%); CABG — coronary artery bypass graft; PCI — percutaneous coronary intervention; CRT-D — cardiac resynchronization therapy with defibrillator; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LAV — left atrial volume; BSA — body surface area

/death (HR 0.45, 0.30–0.70, p < 0.001; Table 2) with a trend towards benefit of CRT-D vs. ICD alone for VT/VF/death (HR 0.77, 0.51–1.18, p = 0.23; Table 3).

Among ICM patients with 2 or more revascularizations, Kaplan-Meier analyses for HF or death suggested a statistically significant benefit for CRT-D vs. ICD-only (p = 0.003; Fig. 1C). Furthermore, there was a lower albeit non-significant cumulative probability of VT/VF/death with CRT-D vs. ICD alone during the follow-up (p = 0.236; Fig. 2C). In the multivariate analysis, the significant benefit of CRT-D vs. an ICD to reduce HF or death was confirmed (HR 0.45, 0.30–0.66, p < 0.001; Table 2) and there was a trend towards a significant reduction in VT/VF/death with CRT-D vs. an ICD-only (HR 0.63, 0.34–1.17, p = 0.14; Table 3).

Echocardiographic reverse remodeling to CRT-D by the number of revascularization procedures

In patients randomized to CRT-D therapy, echocardiographic data at 1 year of follow-up illustrated a similar degree of reverse remodeling with respect to LV end-diastolic volume percent change (p = 0.66), LVESV percent change (p = 0.61), and left atrial volume percent change (p = 0.30) between the various groups of revascularization (Fig. 3).

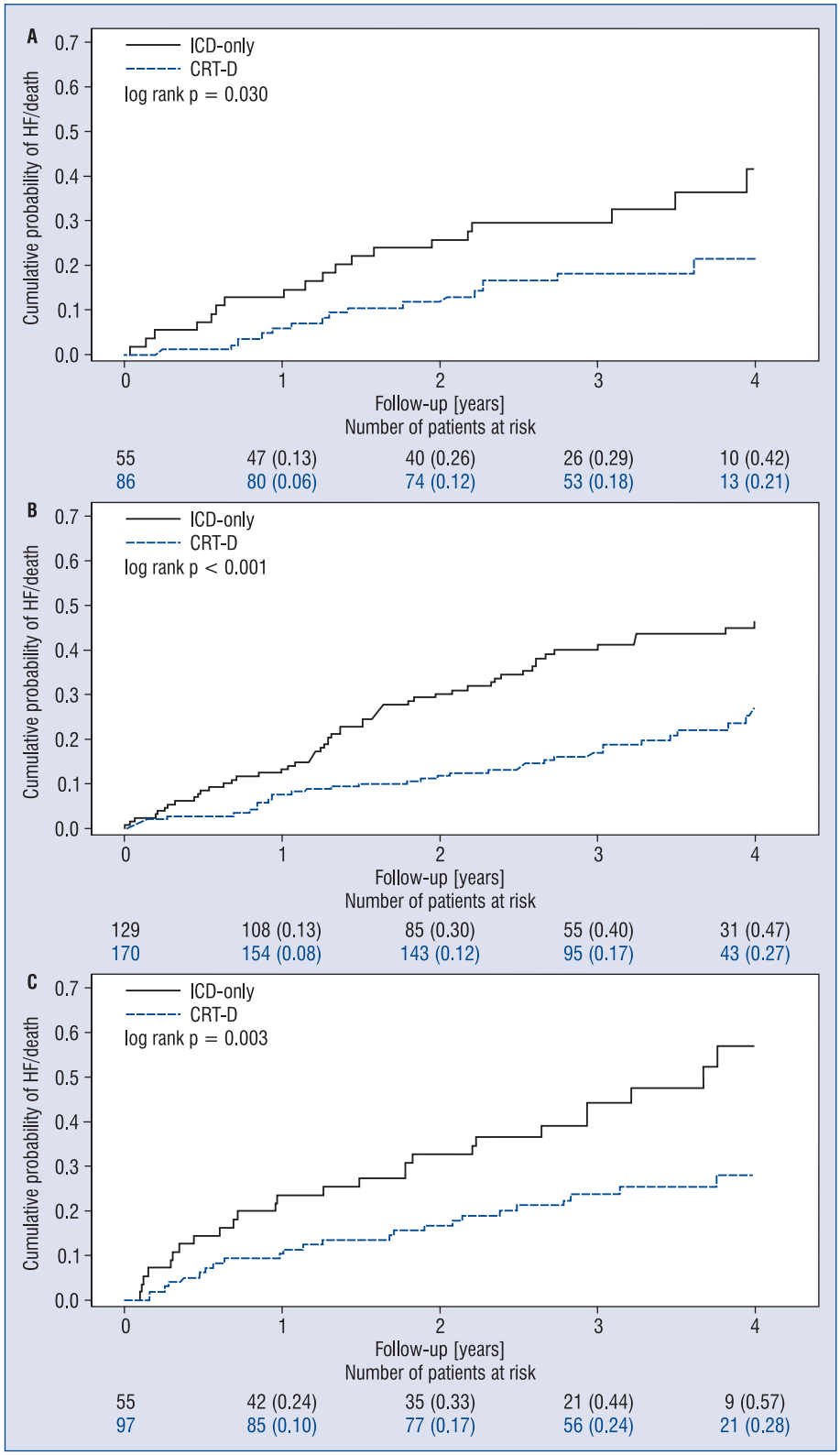

Figure 1. Kaplan-Meier curves of the cumulative probability of heart failure (HF) or death in patients with left bundle branch block. Kaplan-Meier curves illustrate a statistically significant benefit of cardiac resynchronization therapy with defibrillator (CRT-D) vs. implantable cardioverter-defibrillator (ICD)-only for patients with no revascularization (**A**), one revascularization (**B**), and two or more revascularizations (**C**).

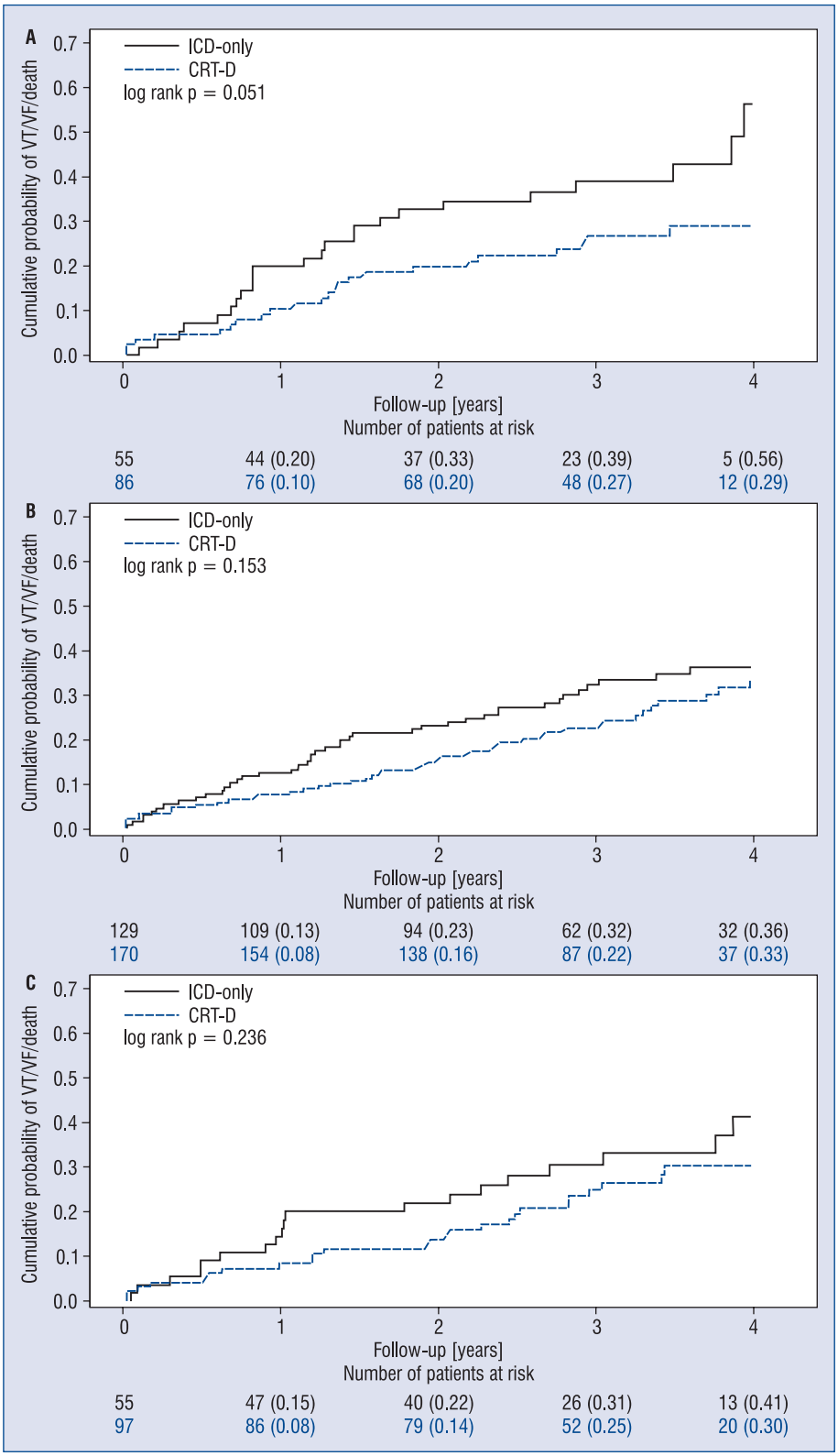

Figure 2. Kaplan-Meier curves of the cumulative probability of ventricular tachycardia/ventricular fibrillation (VT/VF) or death in patients with left bundle branch block. Kaplan-Meier curves illustrate a trend towards risk reduction with cardiac resynchronization therapy with defibrillator (CRT-D) vs. implantable cardioverter-defibrillator (ICD)-only in patients with no revascularization (**A**), one revascularization (**B**), and two or more revascularizations (**C**).

Table 2. Multivariate analysis for CRT-D vs. ICD benefit for the primary outcome (heart failure/ /death) by the number of pre-enrollment revascularization procedures.

Endpoint	HR*	CI	P†
CRT-D vs. ICD in patients with no revascularization	0.51	0.26–1.02	0.055
CRT-D vs. ICD in patients with 1 revascularization	0.45	0.30–0.70	**< 0.001**
CRT-D vs. ICD in patients with ≥ 2 revascularizations	0.37	0.20–0.66	**< 0.001**

†All p values for interaction for revascularization subgroups and treatment > 0.05; *Hazard ratio (HR) comparing CRT-D to ICD with models adjusted for current smoking, female sex, left ventricular end-systolic volume, and history of ventricular arrhythmias; CRT-D — cardiac resynchronization therapy with defibrillator; ICD — implantable cardioverter-defibrillator; CI — confidence interval

Table 3. Multivariate analysis for CRT-D vs. ICD benefit for ventricular tachycardia/ventricular fibrillation/death by the number of pre-enrollment revascularization procedures.

Endpoint	HR*	CI	P†
CRT-D vs. ICD in patients with no revascularization	0.55	0.31–0.99	**0.044**
CRT-D vs. ICD in patients with 1 revascularization	0.77	0.51–1.18	0.23
CRT-D vs. ICD in patients with ≥ 2 revascularizations	0.63	0.34–1.17	0.14

†All p values for interaction for revascularization subgroups and treatment > 0.05; *Hazard ratio (HR) comparing CRT-D to ICD with models adjusted for current smoking, female sex, left ventricular end-systolic volume, and history of ventricular arrhythmias; CRT-D — cardiac resynchronization therapy with defibrillator; ICD — implantable cardioverter-defibrillator; CI — confidence interval

Table 4. Multivariate analysis for heart failure (HF)/death and ventricular tachycardia/ventricular fibrillation or death (VT/VF/death) by the number of pre-enrollment revascularization procedures in non-left bundle branch block patients.

Endpoint	HR*	CI	P†
HF/death			
No revascularization	0.77	0.29–2.08	0.602
1 revascularization	1.04	0.60–1.81	0.894
≥ 2 revascularizations	0.96	0.51–1.77	0.885
VT/VF/death			
No revascularization	0.90	0.42–1.93	0.79
1 revascularization	1.43	0.91–2.25	0.12
≥ 2 revascularizations	0.75	0.43–1.32	0.32

†All p values for interaction for revascularization subgroups and treatment > 0.05; *Models adjusted for current smoking, female sex, left ventricular end-diastolic volume, and history of ventricular arrhythmias; HR — hazard ratio; CI — confidence interval

Outcomes in non-LBBB patients by the number of revascularization procedures

In patients with non-LBBB electrocardiography morphology at baseline, there were no statistically significant reductions in HF or death, or VT/VF or death by the number of pre-enrollment revascularization procedures (Table 4).

Discussion

The major finding of the present study is that among ICM patients with LBBB morphology, CRT-D was associated with a significant risk reduction of HF events or death compared to an ICD-only, irrespective of the frequency of pre-enrollment revascularization procedures. However, there was a less pronounced benefit of CRT-D to reduce ventricular tachyarrhythmias or death that was seen among all three sub-groups compared to an ICD-only, possibly due to a higher potential for arrhythmogenesis in patients with any prior revascularization.

In the original MADIT-CRT study, subgroup analyses suggested that both patients with ICM and NICM derive similar benefit from implantation of a CRT-D with reduction of HF or death compared to an ICD alone [12]. However, after the publication of the primary report [12], additional analyses illustrated more pronounced LV reverse remodeling to CRT-D in patients with NICM patients compared to the ICM patients [7].

Differences in outcomes to CRT between patients with ICM or NICM are well established. While prior studies focused on differential response to CRT by the presence of ICM, in this analysis, we aimed to further subdivide ICM patients by the number of prior revascularization procedures as a proxy for the burden of nonviable myocardium to stratify the benefit to CRT-D.

Why did we choose prior revascularization procedures as the focus of our study? It is conceivable that a significant modifier of clinical outcomes in patients with ICM is the burden of nonviable myocardium related to prior coronary events. However, measuring scar burden is currently a challenging task. There have been prior studies assessing outcomes to CRT-D by scar burden measured by strain echocardiography imaging, positron emis-

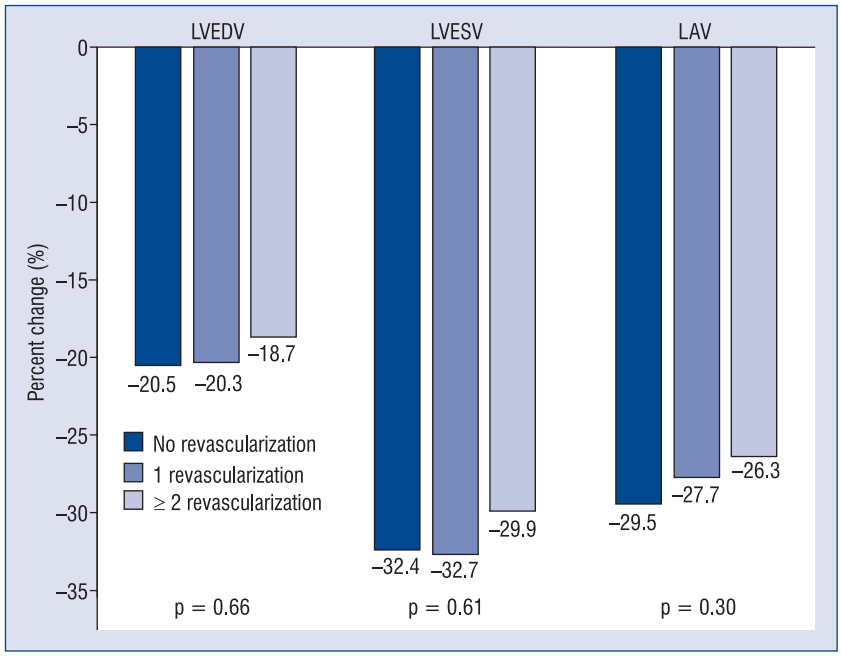

Figure 3. Echocardiographic reverse remodeling to cardiac resynchronization therapy with defibrillator (CRT-D) by prior revascularization procedures. The effect of pre-enrollment revascularizations on CRT-D is independent from echocardiographic reverse remodeling as studied from baseline to 1-year of follow-up. All three groups demonstrated echocardiographic reverse remodeling with 25% reduction in left ventricular end-systolic volume (LVESV), 15% reduction in left ventricular end-diastolic volume (LVEDV), and 20% reduction in left atrial volume (LAV).

sion tomography studies or magnetic resonance imaging, however, most of these methods have not been validated, require special equipment with extra time and costs for recording the images, and take a long time to analyze [16, 17]. Our study is unique in regarding the use of a simple clinical parameter, the number of prior revascularization procedures, as a surrogate marker for the burden of nonviable myocardium. Interestingly, the response to CRT-D for reduction in HF/death and VT/VF/death was not compromised with an increasing number of revascularization procedures in ICM patients.

The potential explanation to our findings is that with increasing number of revascularization procedures, patients are closer to "complete revascularization" and have less nonviable myocardium; thus, these patients derive a similar benefit with CRT-D for both VT/VF, HF, and death. An alternative explanation is that patients that did not undergo revascularization had an established myocardial infarction with a subsequent larger scar burden; therefore, these patients are at higher risk for ventricular tachyarrhythmias and the CRT-D effect is more pronounced. This was illustrated in a study by Barsheshet et al. [18] in which patients without prior revascularization had a significantly higher risk of VT/VF/death compared to those with prior revascularizations.

In a prior MADIT-CRT sub-study by Barsheshet et al. [19], high echocardiographic reverse remodeling — defined as greater than 25% reduction in LVESV — was associated with a significant reduction in the risk of ventricular tachyarrhythmias compared to an ICD-only. Similarly, in our study, each subgroup demonstrated both echocardiographic reverse remodeling and a benefit of CRT-D to reduce ventricular tachyarrhythmias compared to ICD-only.

Our findings have important clinical implications. Clinicians can find evidence that patients with ICM and any number of pre-enrollment revascularizations can benefit from CRT-D with respect to HF events, tachyarrhythmias, and death.

Limitations of the study

There are several limitations of the present study. First, this is a post-hoc analysis, the study groups were not equal in size and we had a relatively small number of events leading to a limited statistical power. All interaction p-values for revascularization subgroups and treatment were > 0.05. Our findings can only be hypothesis generating and further testing is required. Second, we used a number of revascularizations as a proxy for nonviable myocardium, as reported by the enrolling

physicians. However, the source data for this information was verified at the enrolling sites to ensure that this information is reliable. Finally, without complete catheterization data there is an unknown extent and vascular distribution of prior ischemic events in this cohort however, such data are not available from prior CRT studies either. A larger, prospective study to assess CRT-D benefit with detailed information on prior myocardial events, and myocardial scar burden might be warranted.

Conclusions

Our sub-study from MADIT-CRT shows that in ICM patients with LBBB, CRT-D is associated with a significant reduction HF events or death and VT/VF/death, irrespective of the number of pre-enrollment revascularization. Furthermore, the benefit of CRT-D to reduce HF, ventricular tachyarrhythmias or death is accompanied with LV reverse remodeling.

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Clinical Trial Registration: http://clinicaltrials.gov/ct2/show/NCT00180271

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