

The Influence of Left Ventricular Ejection Fraction on the Effectiveness of Cardiac Resynchronization Therapy

MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

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- Objectives** The goal of this study was to evaluate the influence of left ventricular (LV) lead position on the risk of ventricular tachyarrhythmia in patients undergoing cardiac resynchronization therapy (CRT).
- Background** Left ventricular ejection fraction (LVEF) is a surrogate marker of heart failure (HF) status and associated risk. Data on the effectiveness of cardiac resynchronization therapy with defibrillator (CRT-D) in patients with mild HF and better LVEF are limited.
- Methods** In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study, the echocardiography core laboratory assessed baseline LVEF independent of the enrolling centers and identified a range of LVEFs, including those >30% (i.e., beyond the eligibility criteria). Echocardiographic response with CRT, defined as percent change in left ventricular end-diastolic volume (LVEDV), was analyzed in 3 prespecified LVEF groups: >30%, 26% to 30%, and ≤25%. The primary endpoint was HF or death. Secondary endpoint included all-cause mortality.
- Results** LVEF was evaluated in 1,809 study patients. There were 696 (38%) patients with LVEF >30% (in the range of 30.1% to 45.3%); 914 patients (50.5%) with LVEF 26% to 30%; and 199 patients with LVEF ≤25% (11%). The mean reduction in LVEDV with CRT-D therapy at the 1-year follow-up was directly related to increasing LVEF (LVEF >30%: 22.3%; LVEF 26% to 30%: 20.1%; and LVEF ≤25%: 18.7% reduction, respectively [$p = 0.001$]). CRT-D treatment similarly reduced the risk of HF/death in patients with LVEF >30% (hazard ratio [HR]: = 0.56 [95% confidence interval (CI): 0.39 to 0.82], $p = 0.003$), LVEF 26% to 30% (HR: 0.67; [95% CI: 0.50 to 0.90], $p = 0.007$), and LVEF ≤25% (HR: 0.57 [95% CI: 0.35 to 0.95], $p = 0.03$; all p values for LVEF-by-treatment interactions >0.1).
- Conclusions** In MADIT-CRT, the clinical benefit of CRT was evident regardless of baseline LVEF, including those with LVEF >30%, whereas the echocardiographic response was increased with increasing LVEF, indicating that CRT might benefit patients with better LVEF. (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2013;61:936–44) © 2013 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure (HF) symptoms, hospitalizations, and mortality in patients with moderate or severe drug-refractory HF, severely depressed left ventricular ejection fraction (LVEF), and prolonged QRS interval (1–3). CRT

provides electromechanical resynchronization, improves left ventricular systolic function, and induces left ventricular reverse remodeling (4).

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

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study, the RAFT (Resynchronization/Defibrillation in Ambulatory Heart Failure Trial) study, and the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial have further broadened CRT indication to patients with mild HF (5–7).

See page 945

Using the preselected cutoff point of left ventricular ejection fraction (LVEF) as inclusion criterion for CRT is considered an arbitrary method. Patients develop HF across the spectrum of LVEF. Depressed LVEF was shown to be a surrogate marker of HF status and is associated with increased risk of adverse events, all-cause mortality, and sudden cardiac death (8–10). However, the risk associated with LVEF is a continuum until the cutoff point of 45% (9). Therefore, there is a rationale for CRT in patients with less depressed LVEF.

In MADIT-CRT, inclusion criteria comprised patients with LVEF \leq 30% as evaluated by enrolling centers before enrollment. All patients additionally underwent central echocardiographic analysis of LVEF in the study core laboratory of Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, where a substantial proportion of patients were identified as having LVEF $>$ 30%, which is beyond the eligibility criteria. This provides a unique opportunity to evaluate the efficacy of cardiac resynchronization therapy with defibrillator (CRT-D) in patients with less decreased cardiac function.

The aims of the current study were to evaluate the relationship between LVEF and the following: 1) the clinical outcomes of patient with mild HF enrolled in MADIT-CRT; 2) the echocardiographic response to CRT-D in the trial; and 3) the clinical benefit of CRT-D, with a specific focus on the subset of patients with more preserved LVEF enrolled in the trial.

Methods

Study population. The design, protocol, and results of MADIT-CRT have been published previously (11,12). Briefly, 1,820 patients with ischemic cardiomyopathy (New York Heart Association [NYHA] functional class I or II) or nonischemic cardiomyopathy (NHYA functional class II only), LVEF $<$ 30%, and a prolonged QRS duration $>$ 130 ms were randomized to receive CRT-D or implantable cardioverter-defibrillator (ICD) therapy in a 3:2 ratio. All eligible patients met the guideline criteria for ICD (13). Patients were excluded if they were aged $<$ 21 years, if they had existing indication for CRT, implanted pacemaker, NYHA III or IV functional class in the past 90 days before enrollment, coronary artery bypass graft surgery, or percutaneous coronary intervention or myocardial infarction within the past 90 days before enrollment. A total of 110 hospital centers from North America and Europe participated in this international multicenter trial. The study was

in compliance with the Declaration of Helsinki, and all enrolling sites had the protocol approved by the local institutional review board. All patients provided written informed consent before enrollment.

Patients were excluded from the current study if their baseline LVEF measurement was not available due to missing images or poor quality of echocardiographic images. Accordingly, the study sample comprised 1,809 (99%) of the 1,820 patients enrolled in MADIT-CRT; 1,074 (60%) were randomized to CRT-D therapy. The baseline analysis was performed on an intention-to-treat basis.

Data acquisition and patient follow-up. The MADIT-CRT trial was conducted from December 22, 2004, through June 22, 2009. After device implantation, patients had an ambulatory follow-up at 1 month and every 3 months thereafter until the termination of the trial. The mean follow-up of the enrolled patients was 29.4 months. All patients had clinical evaluation at each follow-up visit or at any meaningful clinical event.

Echocardiographic methods. Echocardiograms were obtained according to a study-specific protocol at baseline, which was before device implantation ($n = 1,809$), and at 1 year. Paired echocardiograms from baseline and at 12 months with device turned on were available in 1,372 patients (623 patients in the ICD-only group and 749 in the CRT-D group).

Echocardiography investigators and sonographers were qualified to perform echocardiography according to the approved echocardiography protocol. Recordings were analyzed off-line at the Brigham and Women's Hospital as an independent echocardiography core laboratory. Echocardiography investigators analyzing the images were blinded to treatment assignment or clinical outcome.

Left ventricular volumes were measured by using Simpson's disk method in the apical 4- and 2-chamber views, and LVEF was calculated according to the established American Society of Echocardiography protocols (14). The coefficients of variation for end-diastolic volume, end-systolic volume, and LVEF were 5.2%, 6.2%, and 5.5%, respectively, as reported previously (4).

Left ventricular mechanical dyssynchrony was measured by using B-mode speckle tracking software (TomTec Imaging Systems, Unterschleissheim, Germany), as reported previously (15). Left ventricular mechanical dyssynchrony was determined as the SD of regional time-to-peak transverse strain, measured during systole in the 12 anatomic wall

Abbreviations and Acronyms

CI	= confidence interval
CRT	= cardiac resynchronization therapy
CRT-D	= cardiac resynchronization therapy with defibrillator
EF	= ejection fraction
HF	= heart failure
HR	= hazard ratio
ICD	= implantable cardioverter-defibrillator
LAV	= left atrial volume
LVEDV	= left ventricular end-diastolic volume
LVEF	= left ventricular ejection fraction
LVESV	= left ventricular end-systolic volume
NYHA	= New York Heart Association

segments (septum, lateral, anterior, and inferior walls basal, mid- and apical segments) of the left ventricle.

Definitions and endpoints. Patients with baseline LVEF measurements were divided into 3 prespecified groups based on the echocardiography core laboratory assessment: LVEF $\leq 25\%$, LVEF 26% to 30% (classic criterion), and LVEF $>30\%$ (beyond the eligibility criteria).

The primary endpoint of the current study was the first occurrence of an HF episode or death from any cause. Secondary endpoint included all-cause mortality.

The diagnosis of HF was made by physicians unblinded to treatment assignment, 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. Adjudication of the endpoints (both HF/death and death) was conducted by an independent mortality committee and by an HF committee unaware of treatment assignments, according to prespecified criteria, as described previously (11).

When analyzing the echocardiographic response to CRT, we evaluated the left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left atrial volume (LAV) percent changes at the 12-month follow-up in all 3 LVEF groups.

The left ventricular remodeling effect of CRT-D was defined as percent reduction in LVEDV between enrollment and 1-year echocardiogram (calculated as the difference between 1-year and baseline LVEDV, divided by baseline LVEDV). The left atrial remodeling effect of CRT-D was defined as percent reduction in LAV between enrollment and 1-year echocardiogram (calculated as the difference between 1-year volume and baseline volume, divided by baseline volume).

Statistical analysis. Continuous variables are expressed as mean \pm SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the prespecified subgroups stratified according to baseline LVEF by using the Kruskal-Wallis test for continuous variables and the chi-square test or Fisher exact test for dichotomous variables, as appropriate. The correlation of LVEF identified by the centers and measured by the echocardiography core laboratory was analyzed by using the Spearman's rank correlation method. The correlation of baseline LVEF, QRS duration, and left ventricular volumes were assessed by using the Pearson's correlation method. Regression models were conducted to evaluate the relation between baseline dyssynchrony and the degree of echocardiographic response to CRT (defined as percent change in LVESV at 1 year) within each ejection fraction (EF) category.

Cumulative probability of first HF or death events according to baseline LVEF and treatment arm within each LVEF group was displayed according to the Kaplan-Meier method, with comparisons of cumulative event rates according to the log-rank test. Multivariate Cox proportional

hazards regression analysis was used to identify and evaluate the impact of LVEF groups on the endpoint of HF/death or death. The Cox model was adjusted for relevant clinical covariates by using best subset regression modeling.

All statistical tests were 2-sided; a p value <0.05 was considered statistically significant. Analyses were conducted by using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

At baseline, 914 patients (50.5%) had LVEF 26% to 30% (median = 28.1%; quartile [Q] Q₁ = 27.1%; Q₃ = 29.0%), and 199 patients (11%) comprised the LVEF group of $\leq 25\%$ (median = 23.2%; Q₁ = 21.8%; Q₃ = 24.2%). The subgroup of LVEF $>30\%$ included 696 (38%) patients (in the range of 30.1% to 45.3%; median = 31.8%; Q₁ = 30.8%; Q₃ = 33.1%), as evaluated by the echocardiography core laboratory.

LVEFs identified by the enrolling centers were multiples of 5 in 72% of cases, possibly due to the fact that most centers used estimates for this measure. There was a weak but significant correlation between LVEFs identified by the centers and measured by the echocardiography core laboratory ($r^2 = 0.105$, $p < 0.001$). The distribution and correlation of LVEF identified by the enrolling centers and measured by the echocardiography core laboratory are shown in Figure 1.

The baseline clinical characteristics of patients with LVEF $\leq 25\%$, LVEF 26% to 30%, and LVEF $>30\%$ are shown in Table 1. Patients with increasing LVEF were older, more often female, had a lower heart rate, less often had left bundle branch block and more often right bundle branch block, and had an intraventricular conduction delay electrocardiography pattern. There was a trend toward more frequent ischemic cardiomyopathy and fewer previous episodes of severe HF (>3 months before enrollment) with less depressed LVEF. Baseline drug treatment was similar across LVEF ranges, with less use of diuretics and digitalis with increasing LVEF. Echocardiographic results showed gradually smaller LVEDV, LVESV, and LAVs across LVEF groups, demonstrating less advanced stage of the disease.

Baseline LVEF was inversely related to baseline QRS ($r = -0.22$, $p < 0.001$), and left ventricular volumes (LVEDV index $r = 0.35$, $p < 0.001$; LVESV index $r = 0.36$, $p < 0.001$), suggesting that these parameters were highly correlated in MADIT-CRT.

Effect of baseline LVEF on primary clinical outcome and all-cause mortality. The primary endpoint of HF or death was met in 375 patients (20.7%) with baseline LVEF measurements; 126 patients (7%) died, 78 (4.3%) of cardiac causes during the mean follow-up of 29.4 ± 11 months.

Patients with baseline LVEF $\leq 25\%$ showed significantly higher cumulative incidence of HF or death episodes

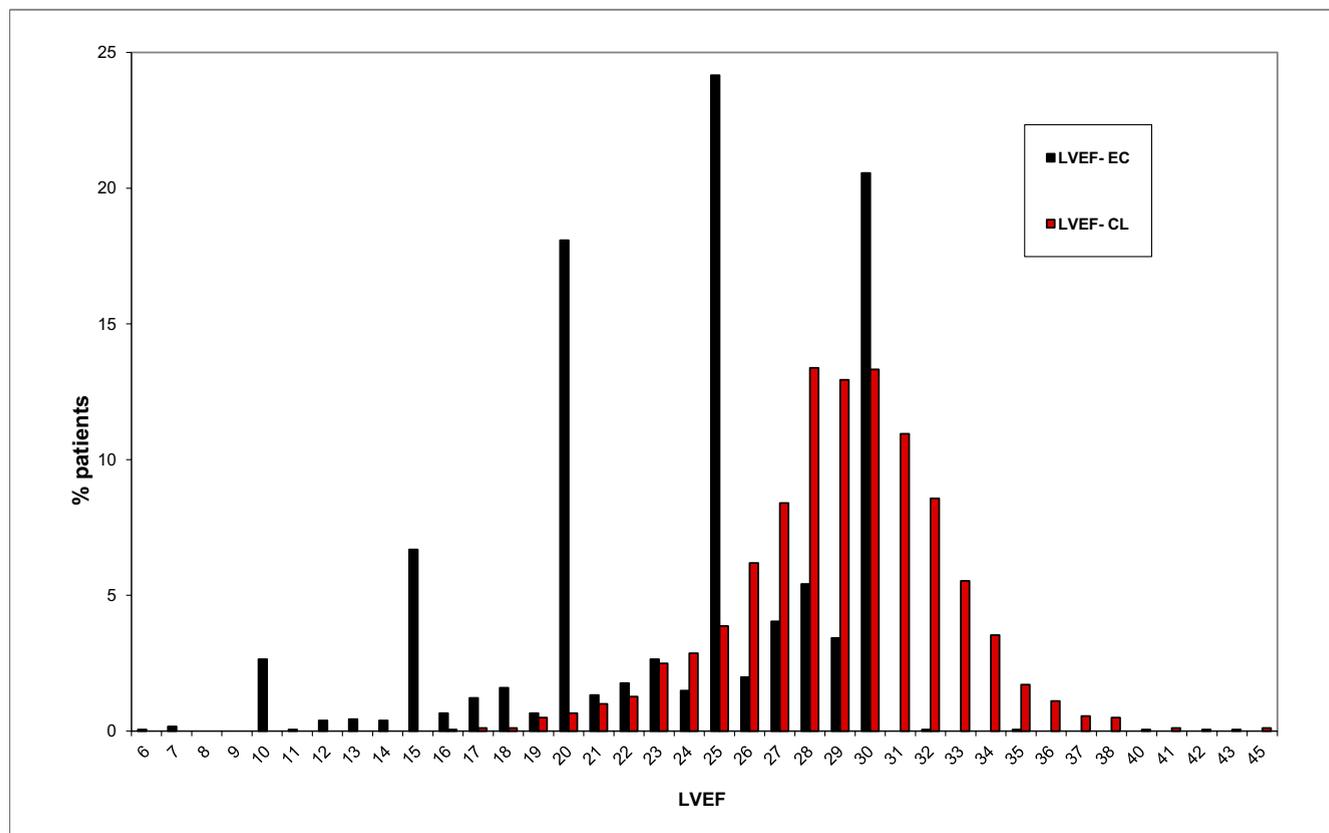


Figure 1 Distribution of Baseline LVEF Identified by the Centers and Measured by the Echocardiography Core Laboratory in All Patients

Left ventricular ejection fractions (LVEFs) identified by the enrolling centers were multiples of 5 in 72% of cases, suggesting that they used estimates for this measure, rather than a more quantitative approach. Accordingly, the LVEF values identified by the enrolling centers showed a skewed distribution in contrast to the echocardiography core laboratory–measured LVEFs that had a normal, Gaussian distribution pattern. LVEF-CL = LVEF measured by the echocardiography core laboratory; LVEF-EC = LVEF identified by the enrolling centers.

compared with patients with LVEF 26% to 30% or LVEF >30% (Fig. 2A).

The multivariate Cox model after adjustment for relevant clinical covariates (treatment, ischemic etiology of cardiomyopathy, NYHA class III or IV greater than 3 months before enrollment, baseline heart rate, and age at enrollment) revealed similar findings. Patients with LVEF ≤25% had 55% higher risk of HF or death compared with patients with LVEF 26% to 30%, and 66% higher risk compared with patients with LVEF >30%. Patients with LVEF 26% to 30% and LVEF >30% demonstrated a similar risk of HF/death. LVEF as a continuous measure was a surrogate marker of the primary endpoint, demonstrating a significant 5% reduction in the risk of HF/death for each unit increment in LVEF (Table 2).

Patients had low and similar incidence of all-cause mortality irrespective of their LVEF group at baseline (3-year Kaplan-Meier cumulative event rates in LVEF ≤25%: 9%; LVEF 26% to 30%: 8%; LVEF >30%: 8% [p log-rank test = 0.709]) (Fig. 2B). This finding was confirmed in the multivariate model after adjustment for relevant clinical covariates (data not shown).

Effect of CRT therapy on the primary clinical outcome and all-cause mortality by LVEF. Evaluating the treatment effects of CRT-D versus ICD-only therapy, 1,809 patients (1,074 CRT-D patients and 735 ICD patients) with baseline LVEF data available were analyzed on an intention-to-treat basis.

Univariate Kaplan-Meier survival analysis showed that compared with ICD-only therapy, treatment with CRT-D showed borderline significance in decreasing the cumulative incidence of HF/death in patients with LVEF ≤25% (p = 0.062). This effect was statistically significant among patients with LVEF 26% to 30% (p = 0.003) and with LVEF 30% (p = 0.009) (Fig. 3).

Consistent with these findings, the multivariate Cox model after adjustment for relevant clinical covariates found that CRT-D treatment was associated with a significant 43% reduction in the risk of HF or death in patients with LVEF ≤25% (p = 0.03), a 33% risk reduction in patients with LVEF 26% to 30% (p = 0.007), and a significant 44% risk reduction among those with LVEF >30% (p = 0.003). The interaction p value was not significant for all LVEF groups (all p values for treatment-by-LVEF interactions

Table 1 Clinical Characteristics of All Patients in Terms of Baseline LVEF Ranges

Clinical Characteristic	LVEF ≤25% (n = 199)	LVEF 26% to 30% (n = 914)	LVEF >30% (n = 696)	p Value
Age (yrs)	61.4 ± 11.0	64.3 ± 10.8	65.3 ± 10.4	<0.001
Females	36 (18)	220 (24)	195 (28)	0.012
CRT-D treatment	115 (58)	554 (61)	416 (60)	0.755
Ischemic NYHA class I	25 (13)	121 (13)	118 (17)	0.077
Ischemic NYHA class II	74 (37)	388 (42)	267 (38)	0.162
Nonischemic NYHA class II	100 (50)	405 (44)	311 (45)	0.300
Worst NYHA class >2 (>3 months before enrollment)	24 (13)	102 (12)	56 (8)	0.063
QRS complex (ms)	166.6 ± 22.5	159.1 ± 20.0	154.4 ± 17.6	<0.001
LBBB	168 (84)	656 (72)	450 (65)	<0.001
RBBB	9 (5)	111 (12)	106 (15)	<0.001
IVCD	22 (11)	146 (16)	139 (20)	0.006
Heart rate	69.8 ± 12.0	67.8 ± 10.6	67.0 ± 10.7	0.007
Systolic blood pressure	119.2 ± 17.5	121.9 ± 16.7	124.4 ± 18.1	<0.001
ACE inhibitors/ARB	163 (82)	685 (75)	546 (78)	0.168
Beta-blocker	180 (90)	854 (93)	653 (94)	0.236
Diuretics	142 (71)	653 (69)	446 (64)	0.035
Digitalis	68 (34)	241 (26)	156 (22)	0.003
LVEDV indexed by BSA	150.7 ± 40.7	125.5 ± 26.7	112.9 ± 19.1	<0.001
LVESV indexed by BSA	116.6 ± 32.4	90.5 ± 19.8	76.6 ± 13.7	<0.001
LAV indexed by BSA	57.0 ± 10.7	48.4 ± 8.8	41.2 ± 7.9	<0.001

Values are mean ± SD or n (%) of patients.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BSA = body surface area; CRT-D = cardiac resynchronization therapy with defibrillator; IVCD = intraventricular conduction delay; LAV = left atrial volume; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; RBBB = right bundle branch block.

>0.10), indicating that the clinical benefit of CRT-D was maintained regardless of baseline LVEF (Table 3).

The treatment effect on the endpoint of all-cause mortality was neutral in patients with LVEF <25% (hazard ratio [HR]: 1.49 [95% confidence interval (CI): 0.60 to 3.70], $p = 0.387$), LVEF 26% to 30% (HR: 0.89 [95% CI: 0.54 to 1.46], $p = 0.647$), and LVEF >30% (HR: 0.85 [95% CI: 0.46 to 1.58], $p = 0.614$), possibly due to the relatively low rate of mortality events in each LVEF group during the trial (Fig. 2B).

The magnitude of echocardiographic response to CRT-D by LVEF groups. Echocardiographic response was assessed at 12-month follow-up in patients with implanted CRT-D; crossovers were excluded from this analysis ($n = 119$).

Echocardiographic response to CRT-D was directly correlated to LVEF. Patients with LVEF ≤25% exhibited less decrease of LVEDV percent change from baseline to 1 year ($-18.7 ± 11.6%$) compared with patients with LVEF 26% to 30% ($-20.1 ± 10.7%$) or patients with LVEF >30% ($-22.3 ± 12.3%$) ($p = 0.001$). Furthermore, patients with LVEF >30% showed a significantly greater reduction in LVEDV than patients with LVEF 26% to 30% ($p = 0.001$).

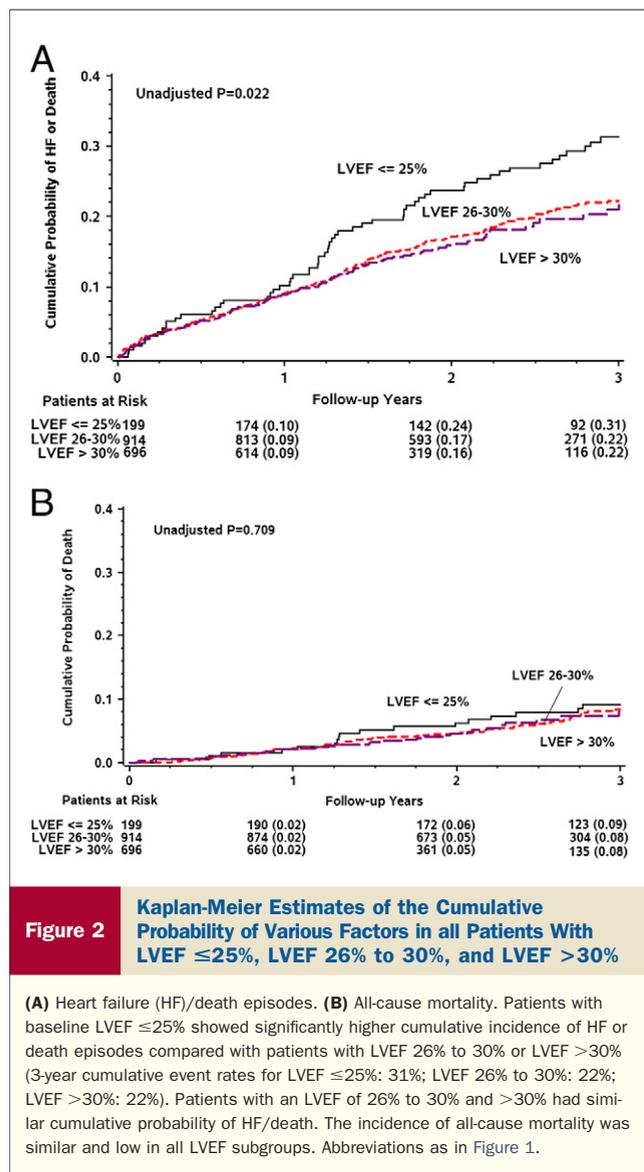
Similarly, the degree of LVESV percent reduction with CRT-D therapy was also directly correlated to increasing LVEF groups ($-31.4 ± 13.5%$ change vs. $-32.0 ± 13.8%$ vs. $-33.6 ± 17.1%$ change; $p < 0.001$ for the overall difference). Patients with LVEF >30% exhibited a greater reduction in LVESV than patients with LVEF 26% to 30% ($p = 0.029$).

Consistent findings were seen in LAV reduction ($-22.67 ± 10.9%$ vs. $-27.6 ± 11.6%$ vs. $-30.4 ± 12.5%$; $p < 0.001$). Again, patients with LVEF >30% gained more pronounced left atrial remodeling than those with LVEF 26% to 30% ($p = 0.001$) (Fig. 4).

We also analyzed LV dyssynchrony data available in 587 (61.5%) of 955 patients undergoing CRT-D. Patients with LVEF ≤25% exhibited greater baseline left ventricular dyssynchrony ($207.1 ± 63.1$ ms) compared with patients with LVEF 26% to 30% ($194 ± 64.4$ ms) or LVEF >30% ($175.5 ± 65.3$ ms) ($p < 0.001$). However, the reduction in left ventricular dyssynchrony at 12 months of follow-up was similar across LVEF groups ($-13.4 ± 49.1%$ vs. $-19.0 ± 43.0%$ vs. $-14.0 ± 55.8%$ change; $p = 0.93$). We further correlated the relation between baseline dyssynchrony and the degree of echocardiographic response to CRT (defined as percent change in LVESV at 1 year) within each EF category prespecified by using a regression model. This analysis showed that among patients with LVEF >30% and LVEF 26% to 30%, the degree of baseline dyssynchrony was directly correlated with the percent reduction in LVESV ($p < 0.001$ for both categories). Among those with a lower LVEF, there was no correlation between dyssynchrony and echocardiographic response to CRT ($p = 0.99$).

Discussion

Our study demonstrates that patients with mild HF with LVEF ≤25% at baseline had an increased risk for subse-



quent HF or death compared with patients with LVEF 26% to 30% or LVEF >30%. However, the clinical benefit of CRT-D was maintained across all LVEF groups; the echocardiographic response to CRT-D was even more pronounced among patients with higher LVEFs, including those with LVEF >30% (beyond the eligibility criteria of this study). These findings suggest that mildly symptomatic HF patients with LVEF >30% might be potential candidates for CRT-D. Furthermore, this subset of patients may derive a more favorable echocardiographic response to CRT-D than patients currently indicated for treatment with the device, which could translate into improved clinical outcome during long-term follow-up.

Previous smaller studies have suggested that patients with severe HF (NYHA III and IV) and higher baseline LVEF could be eligible for CRT; they have shown improvement in clinical status and echocardiographic parameters (16,17). Recently, Chung et al. (18) reported that 86 (24%) of 361

patients enrolled in the PROSPECT (Predictors of Response to Cardiac Re-Synchronization Therapy) trial had LVEF >35% measured by the echocardiography core laboratory. They found that CRT improved the clinical composite score and was associated with similar decrease of LVESV in patients with LVEF ≤35% or >35%. The REVERSE trial included patients with mild HF and LVEF <40% (6); however, the mean LVEF in the study was low (26.8 ± 7.0% in the group with the CRT device turned ON [CRT ON] CRT-ON arm), indicating that the proportion of patients with better LVEF might have been small. In contrast to the PROSPECT substudy, our analysis showed that patients with LVEF >30% exhibited even more pronounced echocardiographic response to CRT-D than patients with lower LVEF.

The findings of this analysis seem to be in contrast to previous data that the sickest patients may benefit most from device therapy due to increased long-term risk (19). However, we suspect that as with most therapies, there is a “sweet spot” for CRT, whereby there may be benefit as ventricular function worsens to some extent, but that when ventricular function worsens beyond a certain level, there is no further benefit because the ventricle becomes too “sick” to respond.

The importance of a preventive strategy in HF has been demonstrated by a study by Gasparini et al. (20); in a population of >500 patients, 26% achieved left ventricular remission (defined as return to NYHA I and EF >50%). Notably, in multivariate analysis, an LVEF 30% to 35% and LVEDV <180 ml were strongly associated with the HF remission phase. We have shown similar effect in the current analysis in patients with mild HF and CRT implantation.

Notably, patients with LVEF >30% showed a clinical response to CRT-D similar to that of patients with lower LVEF, despite the fact that they had a higher frequency of right bundle branch block and intraventricular conduction delay and less wide QRS durations, characteristics which were proven to be associated with unfavorable response in MADIT-CRT (21). There was a significant correlation between baseline QRS duration and LVEF and baseline QRS duration and LVEDV/LVESV index. Furthermore, patients with LVEF >30% had significantly smaller end-diastolic and end-systolic volumes, indicating less advanced

Table 2 Baseline LVEF Groups and the Risk of HF/Death

Parameter	HF/Death		
	Hazard Ratio	95% CI	p Value
LVEF ≤25% : LVEF 26% to 30%	1.55	1.16-2.08	0.003
LVEF ≤25% : LVEF >30%	1.66	1.21-2.28	0.002
LVEF 26% to 30% : LVEF >30%	1.07	0.84-1.36	0.588
LVEF (continuous)	0.95	0.92-0.98	0.001

Model was adjusted for treatment, ischemic etiology of cardiomyopathy, NYHA class >2 greater than 3 months before enrollment, baseline heart rate, and age at enrollment.
 HF = heart failure; CI = confidence interval; other abbreviations as in Table 1.

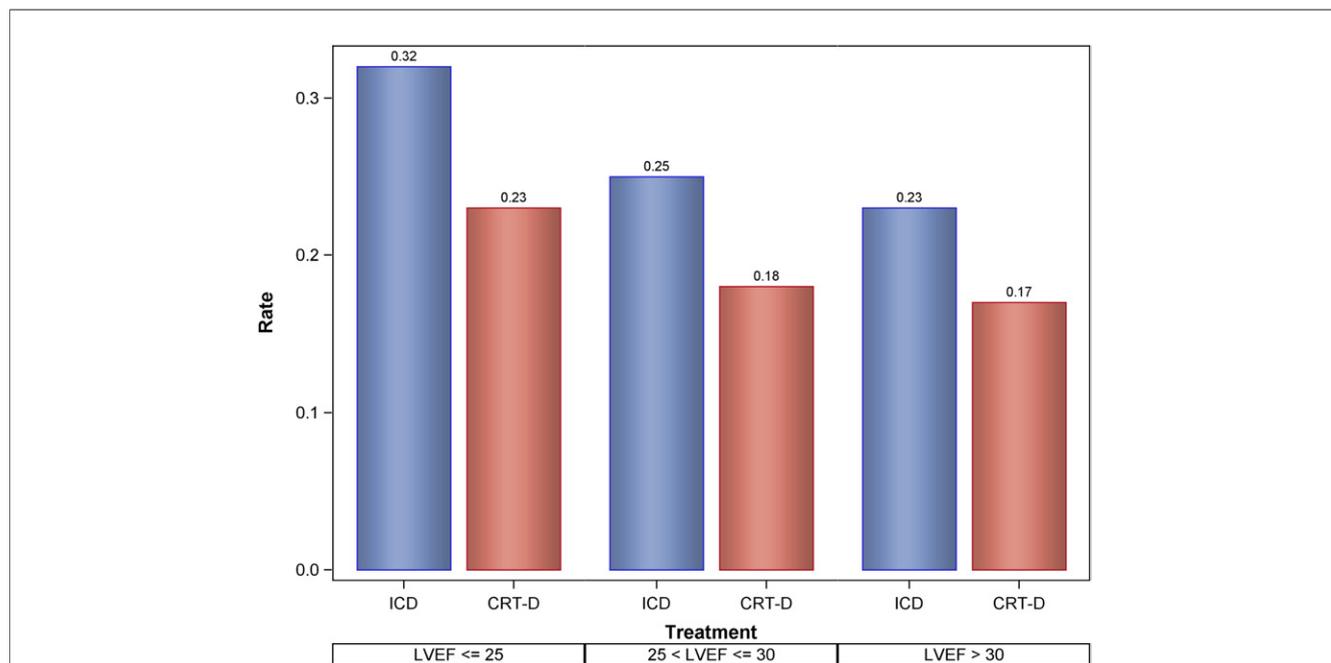


Figure 3 **Kaplan-Meier 2.5-Year Event Rates of the Cumulative Probability of HF/Death Episodes by Treatment Arm in Patients With LVEF ≤25%, LVEF 26% to 30%, and LVEF >30%**

Cardiac resynchronization therapy with defibrillator (CRT-D) treatment was associated with a borderline significant decrease in the cumulative incidence of HF or death in patients with LVEF ≤25% (p = 0.062), and a statistically significant decrease in patients with LVEF 26% to 30% (p = 0.003), compared with the implantable cardioverter-defibrillator (ICD)-treated patient population. Importantly, patients with baseline LVEF >30% (p = 0.009) gained significant benefit of CRT-D in HF and death reduction compared with ICD-only. p < 0.05 for comparison between ICD and CRT-D treatment arms. Abbreviations as in Figures 1 and 2.

stage of the disease. This finding highlights the importance of HF progression prevention in this patient population.

The risk of HF or death was significantly higher in the patient group with LVEF <25%; however, the curves diverged only after 1 year. This phenomenon might be explained by the fact that those patients implanted with a CRT-D device develop left ventricular reverse remodeling within 1 year, which is associated with a subsequent reduction in the risk of HF or death events. This mechanism is consistent with a previous publication from MADIT-CRT, which showed that changes in left ventricular volumes with CRT therapy are highly correlated with subsequent clinical outcomes (4).

Similar to the primary MADIT-CRT report, in which treatment with CRT-D was not associated with a statistically significant effect on the risk of all-cause mortality (12), the current study also found no significant mortality reduction with CRT-D in any of the LVEF subgroups. This can be explained by the fact that patients with asymptomatic or mild HF enrolled in MADIT-CRT experienced a relatively low rate of death during the trial, possibly requiring a longer follow-up period to show a significant mortality benefit from the device.

We found a significant reduction in LAV in all 3 LVEF groups, which might be explained by significant reduction in mitral regurgitation as reported in the total CRT-D population compared with ICD patients (published elsewhere

[4,22]). Another publication from our group evaluated the reduction in LAV and subsequent decrease in atrial arrhythmias, suggesting that reduction in LAV was associated with significantly lower risk of atrial arrhythmias (22). Therefore, we hypothesize that patients with LVEF >30% have more significant reduction in LAV, probably due to a more pronounced decrease in mitral regurgitation that might be associated with lower risk of atrial arrhythmias during follow-up. Furthermore, LAV often reflects the cumulative effects of left ventricular filling pressures over time and thus may provide a more sensitive morphophysiologic expression of the remodeling effects of CRT than the left ventricle.

The relationship of baseline dyssynchrony and clinical outcome in MADIT-CRT has been reported earlier (4). Briefly, those patients with mild to moderate baseline

Table 3 **Treatment Effect of CRT-D Stratified According to Baseline LVEF Groups for the Primary Endpoint of HF/Death**

Parameter	Endpoint: HF/Death		
	Hazard Ratio	95% CI	p Value
LVEF ≤25%	0.57	0.35–0.95	0.031
LVEF 26% to 30%	0.67	0.50–0.90	0.007
LVEF >30%	0.56	0.39–0.82	0.003

Model was adjusted for female sex, ischemic etiology, and QRS duration. Interaction p values with treatment are >0.1 in all patient groups and LVEF subgroups. Abbreviations as in Tables 1 and 2.

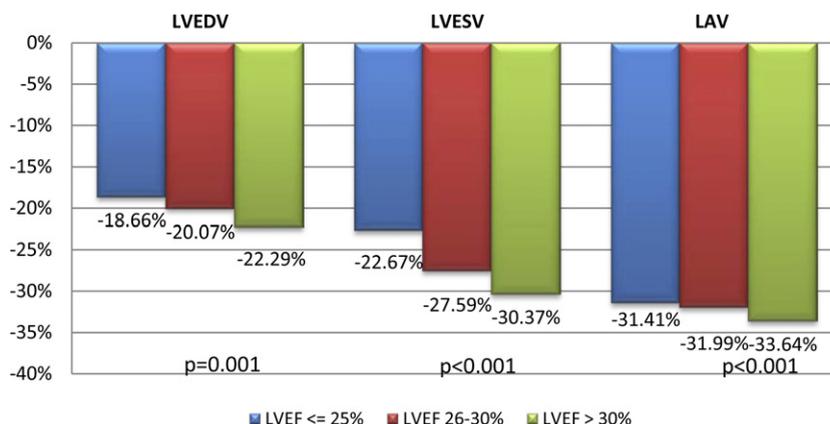


Figure 4 Effects of CRT-D on Echocardiographic Parameters After 1 Year in Patients With LVEF ≤25%, LVEF 26% to 30%, and LVEF >30%

Echocardiographic response to CRT-D was directly correlated to LVEF. Patients with LVEF ≤25% at baseline showed less pronounced decrease of left ventricular end-diastolic volume (LVEDV) percent change, left ventricular end-systolic volume (LVESV) percent change, and left atrial volume (LAV) change from baseline to 1 year compared with patients with LVEF 26% to 30% or with patients with LVEF >30%. Furthermore, patients with LVEF >30% exhibited significantly greater reductions in LVEDV, LVESV, and LAV than patients with LVEF 26% to 30%.

dyssynchrony demonstrated the greatest benefit from CRT-D, whereas those with lower or higher degrees of dyssynchrony derived a lower benefit, displaying a J-shaped pattern within quartiles. In the current analysis, it also seems that patients with a lower EF, who had a greater degree of baseline dyssynchrony, had a lower echocardiographic response to CRT compared with patients in the higher EF categories. This finding is further supported by the correlation of dyssynchrony and echocardiographic response in the LVEF 26% to 30% group and the LVEF >30% group, whereas patients with LVEF ≤25% did not show association between dyssynchrony and echocardiographic response. These results differ from previous reports among patients with more advanced HF symptoms, in which there was a direct correlation between the degree of dyssynchrony and response to CRT. Thus, our findings regarding the interaction among baseline LVEF, dyssynchrony, and response to CRT may be unique to the patients with mild HF who are treated with the device.

The current study found a pronounced difference between the echocardiographic assessment of LVEF at the sites and the central core laboratory assessment. Thus, 38% of the patients who were identified by the centers as having LVEF ≤30%, and therefore deemed eligible for the study, were subsequently determined by the core laboratory as having LVEF >30%. These differences are similar to those shown in the PROSPECT study (18) and may be possibly explained by the fact that a nonblinded reading of cardiac function can be biased by the patient's condition, and by inclusion bias, and may therefore underestimate LVEF. LVEF identified by the centers were in multiples of 5 in 72% of cases, suggesting that sites used visual estimation rather than a more quantitative approach (as was used in the core laboratory).

This is the first report of data presented from a large patient cohort analyzing the impact of baseline LVEF, including those with LVEF >30% on the primary endpoint of HF or death in patients with NYHA class I or II undergoing CRT implantation.

Study limitations. This is a post hoc analysis by echocardiographic groups that were not part of the original design of MADIT-CRT, and the incomplete datasets or images with poor quality were excluded from the analysis. Another possible limitation is that some study patients with images at baseline might be deactivated from the study or die before the 1-year reassessment. Our results did not show a statistically significant difference in the benefit of CRT-D for the primary endpoint among the EF subgroups according to interaction term analyses. However, the lack of statistical significance of the interaction tests may be related to sample size and the number of primary endpoint events in MADIT-CRT.

Conclusions

We demonstrated that the clinical benefit of CRT is present regardless of LVEF groups in patients enrolled in MADIT-CRT, including those with LVEF >30% (beyond the eligibility criteria). The echocardiographic response was directly correlated with increasing LVEF, indicating that patients with better baseline LVEF may derive benefit from CRT.

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REFERENCES

1. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–50.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–53.
3. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–49.
4. Solomon SD, Foster E, Bourgoun M, et al. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. *Circulation* 2010;122:985–92.
5. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;363:2385–95.
6. Linde C, Abraham WT, Gold MR, St. John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52:1834–43.
7. Daubert C, Gold MR, Abraham WT, et al. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol* 2009;54:1837–46.
8. Moss AJ. Prognosis after myocardial infarction. *Am J Cardiol* 1983;52:667–9.
9. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* 2005;112:3738–44.
10. Gorgels AP, Gijssbers C, de Vreede-Swagemakers J, Lousberg A, Wellens HJ. Out-of-hospital cardiac arrest—the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J* 2003;24:1204–9.
11. Moss AJ, Brown MW, Cannom DS, et al. Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol* 2005;10:34–43.
12. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329–38.
13. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1–62.
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.
15. Poulleur AC, Knappe D, Shah AM, et al. Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial. *Eur Heart J* 2011;32:1720–9.
16. Fung JW, Zhang Q, Yip GW, Chan JY, Chan HC, Yu CM. Effect of cardiac resynchronization therapy in patients with moderate left ventricular systolic dysfunction and wide QRS complex: a prospective study. *J Cardiovasc Electrophysiol* 2006;17:1288–92.
17. Foley PW, Stegemann B, Smith RE, Sanderson JE, Leyva F. Cardiac resynchronization therapy in patients with mildly impaired left ventricular function. *Pacing Clin Electrophysiol* 2009;32 Suppl 1:S186–9.
18. Chung ES, Katra RP, Ghio S, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail* 2010;12:581–7.
19. Moss AJ. Implantable cardioverter defibrillator therapy: the sickest patients benefit the most. *Circulation* 2000;101:1638–40.
20. Gasparini M, Regoli F, Ceriotti C, et al. Remission of left ventricular systolic dysfunction and of heart failure symptoms after cardiac resynchronization therapy: temporal pattern and clinical predictors. *Am Heart J* 2008;155:507–14.
21. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;123:1061–72.
22. Brenyo A, Link MS, Barsheshet A, et al. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;58:1682–9.

Key Words: cardiac resynchronization therapy ■ heart failure ■ implantable cardioverter-defibrillator ■ left ventricular ejection fraction.