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Impact of Ejection Fraction on the Clinical Response to Cardiac Resynchronization Therapy in Mild Heart Failure

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Short title: CRT in mild left ventricular dysfunction

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ABSTRACT

Background: Current guidelines recommend cardiac resynchronisation therapy (CRT) in mild HF patients with QRS prolongation and ejection fraction (EF) $\leq$ 30%. To assess the effect of CRT in less severe systolic dysfunction, outcomes in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction(REVERSE) study were evaluated in which patients with LVEF > 30% were included.

Methods and Results: The results of patients with baseline EF > 30% (n=177) to those with EF $\leq$ 30% (n=431), as determined by a blinded core laboratory were compared. In the LVEF > 30% subgroup there was a trend for improvement in the clinical composite response with CRT ON vs CRT OFF (p=0.06) and significant reductions in LV end systolic volume index (-6.7 $\pm$ 21.1 ml/m^2 vs 2.1 ± 17.6 ml/m^2, p=0.01) and LV mass (-20.6±50.5 g vs 5.0±42.4 g; p=0.04) after 12 months. The time to death or first HF hospitalization was significantly prolonged with CRT (p =0.012, hazard ratio=0.26).

In the LVEF $\leq$ 30% subgroup, significant improvements in clinical composite response (p=0.02), reverse remodeling parameters and time to death or first HF hospitalization (p =0.047, hazard ratio=0.58) were observed. After adjusting for important covariates, the CRT ON assignment remained independently associated with improved time to death or first HF hospitalization (p=0.035, hazard ratio=0.54) whereas there was no significant interaction with LVEF.

Conclusion: Among subjects with mild HF, QRS prolongation and LVEF > 30%, CRT produced reverse remodeling and similar clinical benefit compared to subjects with more severe left ventricular systolic dysfunction.

Clinical Trial Registration: Clinicaltrials.gov identifier NCT00271154

Keywords: Cardiac resynchronization therapy, Heart failure, Electrical dyssynchrony, Mortality

Abbreviations:

CCS= clinical composite score

CRT= Cardiac resynchronization therapy

ECG= electrocardiogram

EF= ejection fraction

HF= heart failure

ICD= implantable cardioverter defibrillator

KCCQ= Kansas City Cardiomyopathy Questionnaire

LV= left ventricular

LBBB= left bundle branch block

LVESVi= left ventricular end-systolic volume index

LVEDVi= left ventricular end diastolic volume index

MLHFQ= Minnesota Living with Heart Failure Questionnaire

NYHA= New York Heart Association

INTRODUCTION

Cardiac Resynchronization Therapy (CRT) is well established for patients with severe left ventricular systolic dysfunction and ventricular conduction delay in advanced heart failure (HF) [1-7]. More recently, the benefit of CRT was expanded to patients with mild HF, with improved functional status and reductions in hospitalization and mortality observed[8-12]. The most consistent response was noted in subgroups with left bundle branch block (LBBB) and more prolonged baseline QRS duration[13,14]. However, the effect of left ventricular ejection fraction (LVEF) on CRT outcomes is less clear. Based on these results, current guidelines recommend CRT as a Class I indication for subjects with mild heart failure, LBBB and LVEF $\leq$ 35[15,16] or 30%[17] with LVEF criteria based on the inclusion criteria in the studies[15-17].

Of the three multicenter, randomized trials of CRT in mild HF, only REVERSE included subjects with EF > 30%. To determine whether CRT is effective in less severe left ventricular systolic dysfunction, the impact of EF on outcomes in REVERSE was studied. Specifically, we hypothesized that the benefit from CRT would be similar in patients with moderate LV dysfunction (LVEF > 30%) as in those with severe LV dysfunction (LVEF $\leq$ 30%).

METHODS

Study design and data collection:

REVERSE was a prospective, randomized, double-blind, parallel-controlled study designed to determine whether CRT limited the progression of heart failure compared to optimal medical

therapy alone. The study included ACC/AHA stage C, NYHA Class I or II heart failure patients with QRS ≥ 120ms, and LVEF ≤ 40% on optimal medical therapy**.** Patients were implanted with a CRT device with (CRT-D) or without (CRT-P) defibrillator and randomized 2:1 to CRT ON versus CRT OFF. Devices were then programmed as randomized through 12 months in North America and through 24 months in Europe. The rationale of the REVERSE study has been published previously[18]. For the present analysis, patients were grouped by LVEF > 30% or ≤ 30%, by core lab evaluation.

Outcomes:

The primary endpoint of the REVERSE main study was the percentage of patients at 12 months with a worsened HF clinical composite score[19] (CCS), which scores patients as improved, unchanged, or worsened. The prospectively powered secondary endpoint was LV end-systolic volume index (LVESVi). Other secondary endpoints were hospitalization for worsening HF and mortality and additional measures of reverse remodeling. Quality of life was measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ)[20] and the Kansas City Cardiomyopathy questionnaire (KCCQ)[21]. During the blinded period patients were evaluated every 6 months, by blinded staff collecting NYHA class, 6-minute hall walk, quality of life, echocardiographic data, HF-related hospitalizations and mortality data. Heart failure hospitalizations were adjudicated for heart failure relatedness by the endpoint adjudication committee blinded to CRT assignment. This committee also adjudicated causes of death. Likewise, echocardiograms were assessed by two core labs blinded to CRT assignment, one in the US and one in Europe[18].

Statistical methods:

Statistical analyses followed the intent-to-treat principle. All p-values reported are two-sided and do not adjust for multiple comparisons. The primary endpoint was tested with a Fisher's exact test that compared the full distribution of clinical composite scores at 12 months by randomization group. The same testing procedure was used to assess NYHA class at 12 months. Kaplan-Meier curves were estimated for the combined endpoint of time to death or first HF hospitalization. Time 0 was the date of randomization. Since the length of the randomization period in the study differed by geography (12 months in North America and 24 months in Europe), patients without an observed event were censored at the end of their randomization period. Kaplan-Meier curves are truncated when fewer than 20 patients are at risk for a time point. A log-rank test compared survival curves between randomization groups. To assess CRT effects on time to death or HF hospitalization modified by LVEF subgroup, a Cox model was fit with main effects for CRT and LVEF subgroup and an interaction effect between them. The Cox model was then adjusted for other potentially confounding variables such as of age, intrinsic QRS duration, LVESVi, ischemic heart disease, and blood pressure at baseline. There were 43 patients with missing values for confounding factors that were discarded from the multivariable analysis. Within LVEF subgroup, changes between baseline and 12 months in LVEDVi, LVESVi, LVEF, LVEDD, LV mass, MLWHF, KCCQ and the 6-minute hall walk were compared between randomization groups with a two-sample t-test assuming unequal variances. Finally, regression towards the mean[22] is a real concern in subgroup analysis where patients are divided into high and low groups. To adjust for this effect, an ANCOVA model was fit for each

echo parameter where the outcome was the difference over time, the independent variable was CRT and the confounding variable was the baseline value of the echo parameter. Statistical analyses were conducted in R (http://www.r-project.org) and SAS 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics:

The baseline characteristics of the entire cohort and the main results were reported previously[9,10,22]. LVEF was available in 608 of the 610 randomized patients, in 565 subjects by core lab measurement and in 43 by implanting center measurement. Of this cohort 431 patients (76.3%) had LVEF ≤ 30% and the remaining 177 patients (23.7%) had LVEF > 30%, including 12.2% (n=74) with LVEF > 35%, reflecting the LVEF inclusion criterion of REVERSE. The mean center LVEF (26.7±7.0) did not differ from core lab LVEF (27.0±6.6). The distribution of LVEF measurements at baseline is shown in **Figure 1.** Consistent with clinical practice, the centers tended to report LVEF values in multiple of 5 (61.2%) or 10 (33.4%). Baseline characteristics grouped by LVEF are shown in **Tables 1-2**. Patients with LVEF > 30% were significantly older, more often had ischemic etiology, worse renal function and higher systolic blood pressure. Nonetheless, they were more often in NYHA I, and had smaller LV dimensions and volumes and lower LV mass than those with LVEF ≤ 30%. Moreover, quality of life both by the MLHFQ score and KCCQ and six minute walk distance tended to be better in the LVEF > 30% group. Although QRS duration was significantly shorter in the LVEF > 30% group than in

the LVEF < 30% group (147±20.4 ms vs 155.7 ± 22.2 ms; p<0.0001), the presence of LBBB was comparable between subgroups (58% vs 62%, respectively, p= 0.31). Both subgroups were well treated medically with most patients receiving both beta blockers and ACE inhibitors or angiotensin receptor blocker agents at baseline.

Echocardiographic Measurements:

The echocardiographic results are summarized in **Figure 2** and in **Table 3**. Overall the magnitude of improvement was smaller in the LVEF > 30% group than in the LVEF ≤ 30% group. A significant decrease of LVESVi after 12 months of CRT was observed in both LVEF subgroups compared to CRT OFF. A trend toward significant reduction in LVEDVi by CRT ON was observed in the LVEF > 30% group (-11.2 ± 27.0 ml/m^2 vs -4.3 ± 22.9 ml/m^2 in CRT OFF; p=0.12). A statistically significant decrease of LVEDVi and a significant increase in LVEF was only observed in the LVEF ≤ 30% group. Adjusting for the potential effect of regression to the mean did not affect the interpretation of the reverse remodeling results (**Table 4**).

Clinical Measurements:

The clinical results at 12 months are shown in **Table 3** and **Figure 3.** In the LVEF > 30% group the distribution of the CCS was better in CRT ON compared to OFF (p=0.06) but did not reach statistical significance. A statistically significant improvement was observed in the LVEF ≤ 30% group and in the full study group. In the overall group there was a significant improvement in NYHA class with CRT-ON (p=0.04). Although the numerical trends in the EF subgroups were in the same direction it did not reach statistical significance in either group.

Effect of CRT on time to first HF hospitalization or death in EF<=30 versus >30:

Time to first HF hospitalization or death was tracked through 12 months (North America) or 24 months (Europe) and is shown in **Figure 4.** Overall the composite morbidity and mortality rate was nearly twice as high in the LVEF ≤ 30% group; Death occurred in 3.7% of patients and 11.8% experienced the composite endpoint of HF hospitalization or death during the randomization period. Comparatively, in the LVEF > 30% group, 1.7% of patients died and 6.8% of patients experienced a HF hospitalization or death during the randomization period. There were significant prolonged time to first hospitalization for HF or death for CRT ON vs CRT OFF in both the LVEF ≤ 30% (p= 0.047, hazard ratio=0.58) and > 30% group (p=0.012, hazard ratio=0.26) with curves for CRT ON and OFF separating early within the first months **(Figure 4)**.

In the LVEF ≤ 30% group there were 16 deaths: 6 /141 patients in CRT OFF due to progressive HF, arrhythmia, stroke, electromechanical dissociation, renal cancer and by cause unknown and 10 /290 patients in CRT ON due to progressive HF (n=3), arrhythmia, bradyarrhythmia, pulmonary fibrosis, stroke, prostate cancer, and by cause unknown (n=2). In the LVEF > 30% group there were 3 deaths: 1/50 patients in CRT OFF (gastrointestinal bleeding) and 2/127 patients in CRT ON (gastrointestinal bleeding and pulmonary fibrosis). The effect of the interaction between CRT and LVEF subgroup on time to death or HF hospitalization was also assessed.

As there were some baseline differences between the two LVEF subgroups, a multivariable analysis was performed to adjust for potential confounding factors **(Table 5)**. After adjusting for

important covariates, the main effect for CRT assignment remained independently associated (p=0.035, hazard ratio=0.54) with improved outcomes among patients assigned to CRT ON. There was no statistically significant interaction between CRT and LVEF indicating that there was no evidence that the benefit of CRT varied with LVEF. Baseline LVESVi (p=0.0002) and QRS duration (p=0.003) were also independently associated with hospitalization for HF or death with better outcome in subjects with smaller left ventricular size and longer QRS duration. The etiology of heart disease (i.e. ischemic vs nonischemic) was not associated with outcome in this analysis.

DISCUSSION

The primary results of the present analysis show that the beneficial effect of CRT-ON on ventricular function and on time to death or first hospitalization occurs across the full spectrum of LVEF studied in REVERSE, with no sign that it is weaker in patients with LVEF>30 than those with LVEF<=30. These findings are strengthened by the randomized design of the study, with blinded comparison against CRT-OFF, and the rigorous exclusion of regression to the mean as a contributing factor.

Sub-studies of CRT results by different ejection fractions

In previous sub-studies of randomized controlled studies, no apparent difference in CRT benefit was observed in patients with LVEF > 20% or < 20% in moderate to severe[4,5] and mild[11,12] heart failure. Similar observations were made in a retrospective analysis of the PROSPECT study evaluating less severe LV dysfunction and an analysis of single center data[24,25]. PROSPECT[26]

was an open-label study which included patients with NYHA class III–IV, QRS ≥ 130 ms and LVEF ≤ 35%. CRT induced similar benefit among patients with LVEF ≤ 35% or LVEF > 35% with regard to reverse remodeling and the percentage improved by the CCS. Importantly, a recently published post hoc analysis of MADIT-CRT[27] of NYHA I-II patients also indicated a benefit of CRT in the subjects with LVEF > 30% in the study. As in our study and in PROSPECT[26], core lab evaluation resulted in some subects with higher LVEF than allowed by the study inclusion criteria. In agreement with our findings, the clinical benefit for time to HF hospitalizations or death was greater for the patients with LVEF > 30% compared to the other LVEF groups[27]. However, in contrast to our findings, the extent of reverse remodeling defined as decrease of LVESVi was higher for the LVEF > 30% patients[27] than for the other groups in spite of smaller baseline LV. The reason for this discrepancy is not clear, although subjects with less severe LV dysfunction were included in REVERSE.

Results in the present study with regard to LVEF

To our knowledge, only REVERSE included patients with LVEF ≤ 40%. In fact 12.2% (n=74) of our patients had LVEF > 35%, i.e. with LVEFs beyond the current guideline recommendations in the US[15,16]. In contrast, a smaller fraction of patients in the MADIT CRT sub-study had LVEF > 35%. Our results show some signs of significant reverse remodeling benefits by CRT at 12 months regardless of whether baseline LVEF was below or above 30%. In this study the patients with higher LVEF were more often older, had more ischemic heart disease and worse renal function implying negative prognostic impact. However, they were more often in NYHA I functional class and had smaller baseline LV volumes than patients with LVEF < 30%.

Moreover, multivariate analysis indicated that a smaller LVESVi at baseline was linked to greater magnitude of response to CRT which also suggests earlier intervention with CRT than indicated in present guidelines[15,16,17]. The magnitude of reverse remodeling in the higher LVEF group was less than observed in patients with severe heart failure and with worse LV function in the post hoc analysis of PROSPECT[24]. One contributing factor for this observation may be that patients in this group more often had underlying ischemic heart disease and shorter QRS duration which is known to be linked to less extensive reverse remodeling[6,14,28,29]. In the MIRACLE trial, the extent of reverse remodeling was half the magnitude in patients with ischemic etiology as in those with dilated cardiomyopathy[28]. Similar findings were made in the CARE-HF trial despite similar clinical benefit[29]. We have previously reported that ischemic heart failure patients in REVERSE had three times less reverse remodeling than patients with dilated cardiomyopathy[30] and that the magnitude of the QRS duration is an independent predictor of the extent of reverse remodeling[14]. The effect of QRS duration and etiology of heart failure on reverse remodeling has also been noted in studies of advanced HF[31]. Thus, the greater proportion of patients with ischemic etiology and shorter mean QRS duration in the LVEF > 30% group may partly explain the smaller reverse remodeling.

Nonetheless, CRT in LVEF > 30% was associated with significant clinical improvement as assessed by the time to mortality or hospitalizations for heart failure as in the LVEF $\leq$ 30% group over a follow up period of 12-24 months. In fact, the relative risk reduction was 74% in the LVEF > 30% group compared to 42% in the LVEF < 30% group suggesting a greater benefit. CRT was independently associated with outcome independent of LVEF. Age or baseline ischemic heart disease and diabetes were not independent predictors of clinical outcome.

Electrical dyssynchrony is critical for CRT induced improvements with the response increasing with longer intrinsic QRS duration and in particular left bundle branch morphology[13-14]. Our patients all had wide QRS (155.7 ± 22.2 ms in the LVEF < 30% and 147±20.4 ms in the LVEF > 30% group) and LBBB was present in about 60% of patients within each subgroup. These study results indicate that the benefits of CRT may be present for patients with QRS prolongation and mild HF with less severe left ventricular dysfunction than previously studied.

Presence of electrical dyssynchrony in HF patients with reduced and preserved LVEF

Approximately one third of HF patients have conduction disturbances evidenced by QRS duration > 120 ms[32,33,34]. Although electrical dyssynchrony is more common in HF patients with reduced LVEF it is prevalent over a wide range of ejection fractions[33] and linked to worse prognosis[33,34]. In a recent report from the Swedish heart failure registry[33] 39% of patients with LVEF< 40% , 25% with LVEF 40-49% and 18% of patients with LVEF > 50% had QRS duration > 120 ms that was associated with risk for mortality regardless of ejection fraction. Similar observations were made in the CHARM studies also including mild heart failure patients[35]. These observations indicate that electrical dyssynchrony is present in HF patients with mild to moderate reduction in ventricular function and potentially might be influenced by CRT. The findings in the present analysis of HF patients with LVEF 31-40% are encouraging.

Limitations:

The study should be interpreted in light of certain methodological limitations. This was a posthoc subgroup analysis that was not powered during study design and randomization was not

stratified based on EF. There were also some important clinical differences between subgroups, although multivariate analysis indicated that EF was not an independent predictor of response.

Conclusions:

In this analysis of REVERSE study patients with LVEF > 30%, CRT produced improvements in time to death or heart failure related hospitalizations and were associated with significant reduction in left ventricular end-systolic volume index and left ventricular mass consistent with reverse remodeling. These findings warrant further prospective validation.

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DISCLOSURES

Dr. Linde reports research grants, speaker honoraria, and consulting fees from Medtronic, and speaker honoraria and consulting fees from St. Jude Medical. Dr. Daubert reports speaker honoraria and consulting fees from Medtronic and St. Jude Medical. Dr. Abraham reports research grants, speaker honoraria, and consulting fees from Medtronic, St. Jude Medical, and Biotronik. Dr. St. John Sutton reports research grant support, speaker honoraria, and consulting fees from Medtronic as well as research support from Paracore. Dr. Ghio reports consulting fees from Medtronic. Dr Herre reports consulting fees from Medtronic and research grants from St Jude Medical, Boston Scientific and Medtronic. Dr. Bergemann is employed at Medtronic as a principal statistician. Dr. Gold reports consulting fees from Medtronic and Boston Scientific and lecture fees and research grants from Medtronic, Boston Scientific, and St. Jude Medical.

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Legends

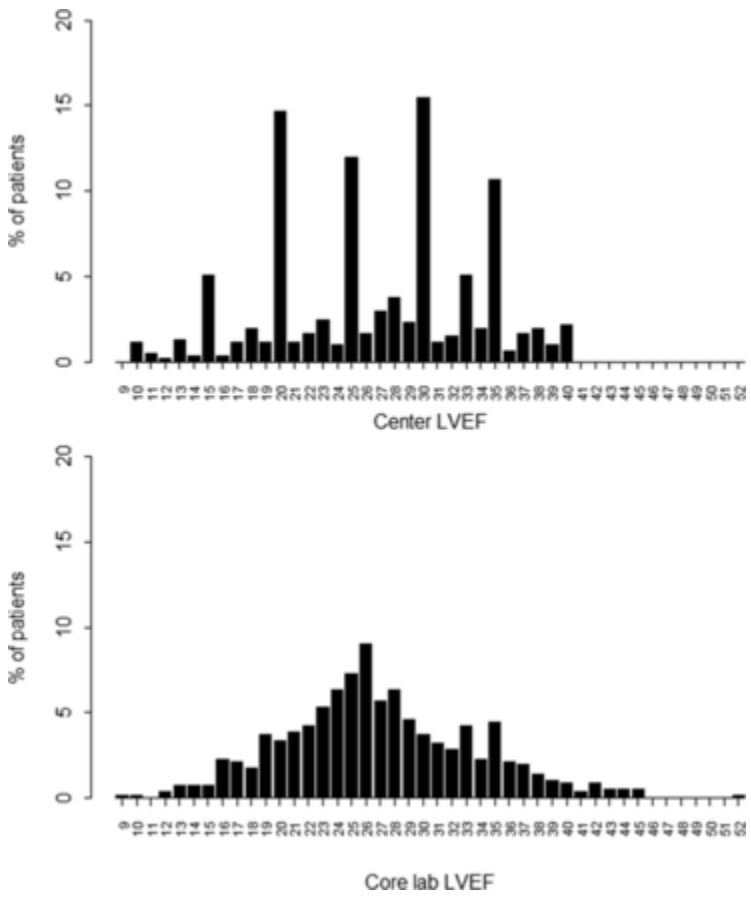


Figure 1. Distribution of center lab (top) and core lab (bottom) baseline left ventricular ejection fraction results in all patients.

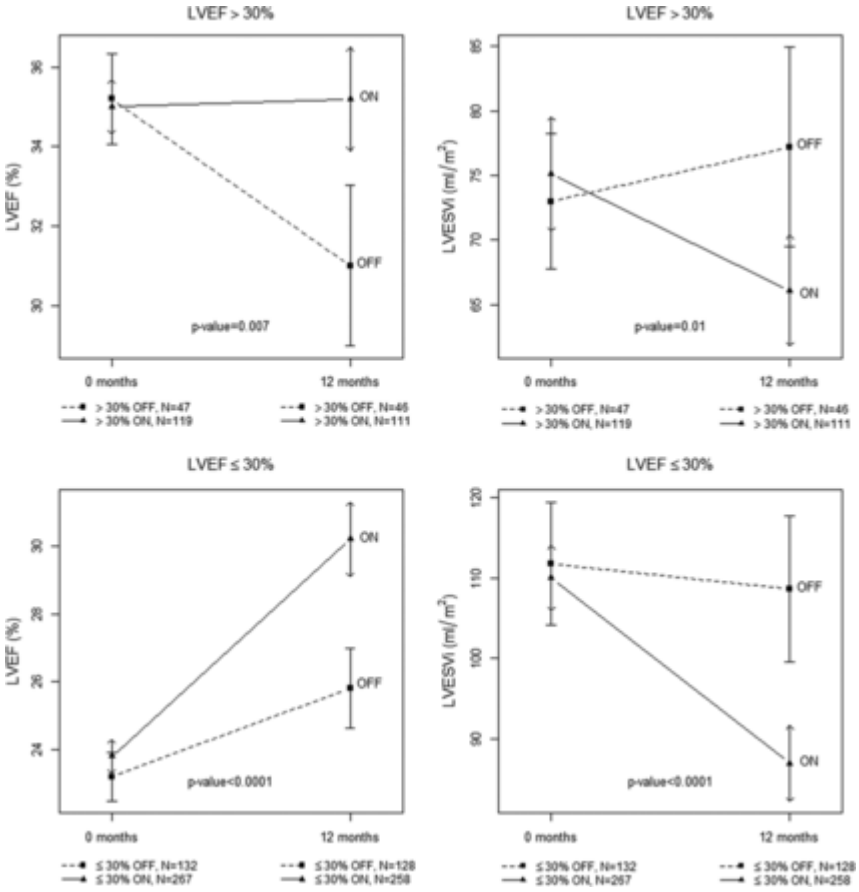


Figure 2. Left ventricular reverse remodeling of LVESVi and LVEF with baseline LVEF > 30% (upper panel) or ≤ 30% (lower panel) in relation to CRT ON and OFF assignment. Error bars reflect 95% confidence intervals about the mean values.

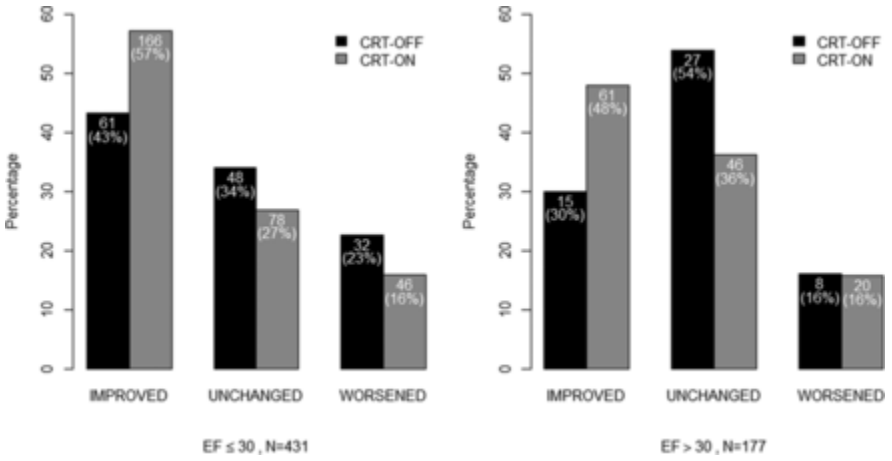


Figure 3. Clinical composite response distribution in patients with baseline LVEF ≤ 30% or > 30% in relation to CRT ON and OFF assignment.

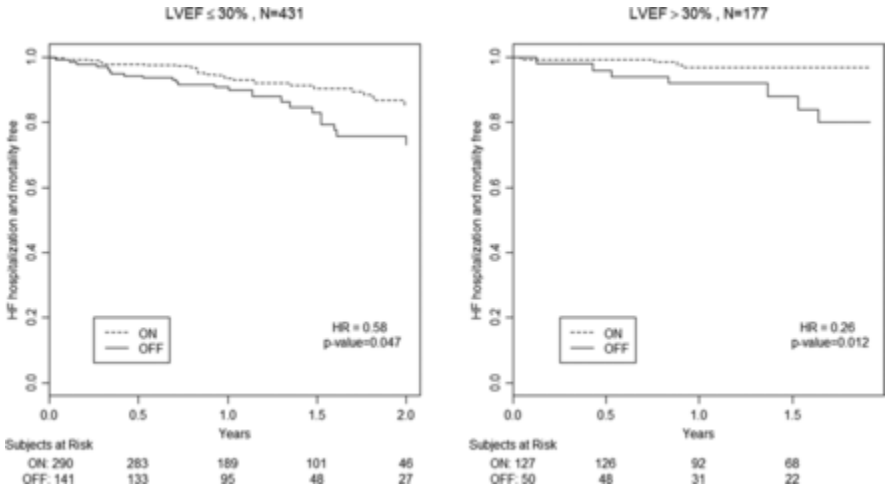


Figure 4. Time to death or hospitalization for heart failure in patients with baseline LVEF ≤ 30% or > 30% in relation to CRT ON and OFF assignment.

Table 1. Baseline clinical characteristics divided by LVEF ≤ 30% and > 30%.

	LVEF ≤ 30% (n=431)	LVEF > 30% (n=177)	p-value[1]
Clinical Characteristics			
Age, yrs	61.8 ± 11.3	64.2 ± 10.0	0.01
Gender, male n (%)	336 (78)	142 (80)	0.59
Ischemic, n (%)	222 (52)	110 (62)	0.02
Hypertension, n(%)	216 (50)	98 (55)	0.25
Diabetic, n (%)	93 (22)	43 (24)	0.46
ACE inhibitors or ARBs, n (%)	416 (97)	172 (97)	0.81
Beta-blockers, n (%)	405 (94)	173 (98)	0.06
Intrinsic QRS width (ms)	155.7 ± 22.2	147.3 ± 20.4	< 0.0001
QRS morphology			
LBBB[2], n (%)	266 (62)	102 (58)	0.31
IVCD[2], n (%)	127 (30)	54 (31)	
RBBB[2], n (%)	35 (8)	21 (12)	
Glomerular filtration rate(ml/min)	87.6 ± 34.1	82.0 ± 30.3	0.048
Supine systolic BP, mm Hg	122.9 ± 18.1	129.1 ± 19.8	0.0003
Supine diastolic BP, mm Hg	71.7 ± 10.9	73.2 ± 11.8	0.16
CRT-ICD implanted, n (%)	361 (84)	145 (82)	0.63

[1] p-values were calculated using a t-test (assuming unequal variances) for continuous variables and Fisher's exact test for categorical variables

[2] Sample sizes for QRS morphology are n=428 (LVEF ≤ 30%) and n=177 (LVEF > 30%)

Table 2. Baseline functional characteristics and echocardiographic data divided by LVEF ≤ 30% and > 30%.

	LVEF ≤ 30% (n=431)	LVEF > 30% (n=177)	p-value[1]
Functional Characteristics			
NYHA class II, n (%)	369 (86)	133 (75)	0.003
LVEF(center), %	25.0 ± 6.8	30.7 ± 5.9	< 0.0001
LVEF (core)[2], %	23.6 ± 4.1	35.1 ± 3.9	< 0.0001
LVEDD[3], cm	7.1 ± 0.9	6.5 ± 0.9	< 0.0001
LVESD[3], cm	6.0 ± 1.0	5.2 ± 1.0	< 0.0001
LV mass[4], g	276.7 ± 75.9	253.6 ± 75.9	0.01
LVESVi[2], ml/m^2	110.6 ± 37.6	74.5 ± 23.0	< 0.0001
LVEDVi[2], ml/m^2	143.8 ± 43.7	114.3 ± 33.0	< 0.0001
MLHFQ[5], (0-105)	28.6 ± 20.8	25.0 ± 20.0	0.06
KCCQ[6], (0-100)	71.8 ± 20.2	75.3 ± 19.3	0.06
6-min hall walk[7], m	390.8 ± 128.2	409.5 ± 124.3	0.10

[1] p-values were calculated using a t-test (assuming unequal variances) for continuous variables and Fisher's exact test for categorical variables

[2] Sample sizes for core lab LVEF, LVEDVi and LVESVi are n=399 (LVEF ≤ 30%) and n=166 (LVEF > 30%)

[3] Sample sizes for LVEDD and LVESD are n=298 (LVEF ≤ 30%) and n=114 (LVEF > 30%)

[4] Sample sizes for LV mass are n=281 (LVEF ≤ 30%) and n=94 (LVEF > 30%)

[5] Sample sizes for MLWHF are n=420 (LVEF ≤ 30%) and n=164 (LVEF > 30%)

[6] Sample sizes for KCCQ are n=374 (LVEF ≤ 30%) and n=146 (LVEF > 30%)

[7] Sample sizes for 6-min hall walk are n=425 (LVEF ≤ 30%) and n=176 (LVEF > 30%)

Table 3. Changes in functional and echocardiographic variables from the baseline visit to the 12 month follow-up divided by LVEF ≤ 30% and > 30% at baseline.

	LVEF ≤ 30%			LVEF > 30%			Full study		
	CRT OFF (n=141)	CRT ON (n=290)	p-value	CRT OFF (n=50)	CRT ON (n=127)	p-value	CRT OFF (n=191)	CRT ON (n=419)	p-value[1]
CCR									
% improved	43	57		30	48		40	54	
% unchanged	34	27	0.02	54	36	0.06	39	30	0.003
% worsened	23	16		16	16		21	16	
NYHA class[2]									
% improved	22	33.5		20	28		22	32	
% unchanged	64	56.5	0.055	72	59	0.31	66	57	0.04
% worsened	14	10		8	13		12	11	
LVEF (core)[3], %	2.5 ± 5.4	6.6 ± 9.2	< 0.0001	-3.8 ± 7.4	-0.1 ± 7.5	0.007	0.8 ± 6.6	4.6 ± 9.3	< 0.0001
LVEDD[4], cm	0.0 ± 0.6	-0.3 ± 0.8	0.002	-0.1 ± 0.7	-0.2 ± 0.7	0.63	-0.1 ± 0.6	-0.3 ± 0.8	0.005
LVEDVi[3], (ml/m^2)	-0.5 ± 29.6	-22.9 ± 33.8	< 0.0001	-4.3 ± 22.9	-11.2 ± 27.0	0.12	-1.5 ± 27.9	-19.3 ± 32.2	< 0.0001
LVESVi[3], (ml/m^2)	-2.9 ± 25.2	-23.5 ± 30.4	< 0.0001	2.1 ± 17.6	-6.7 ± 21.1	0.01	-1.6 ± 23.4	-18.3 ± 28.9	< 0.0001
LV mass[5], g	-10.9 ± 49.9	-14.3 ± 53.4	0.65	5.0 ± 42.4	-20.6 ± 50.5	0.04	-7.6 ± 48.6	-16.0 ± 52.6	0.19
MLHFQ[6], (0-105)	-7.4 ± 16.7	-9.0 ± 17.6	0.35	-4.7 ± 13.3	-6.7 ± 15.8	0.43	-6.7 ± 15.9	-8.4 ± 17.1	0.25

KCCQ[7], (0-100)	9.6 ± 17.1	9.2 ± 18.4	0.84	5.6 ± 12.6	7.0 ± 15.7	0.56	8.5 ± 16.1	8.7 ± 17.8	0.92
6-min hall walk[8], (m)	27.7 ± 95.8	25.5 ± 93.6	0.83	13.5 ± 100.1	3.4 ± 109.0	0.56	23.8 ± 96.9	18.6 ± 98.8	0.55

[1] p-values were calculated using a t-test (unequal variance) for continuous variables and Fisher's exact test for categorical variables

[2] Sample sizes for NYHA at 12 month follow-up are n=416 (LVEF ≤ 30%) and n=175 (LVEF > 30%)

[3] Sample sizes for core lab LVEF, LVEDVi and LVESVi are n=360 (LVEF ≤ 30%) and n=149 (LVEF > 30%)

[4] Sample size for LVEDD is n=212 (LVEF ≤ 30%) and n=79 (LVEF > 30%)

[5] Sample size for LV mass is n=202 (LVEF ≤ 30%) and n=65 (LVEF > 30%)

[6] Sample size for MLWHF is n=404 (LVEF ≤ 30%) and n=161 (LVEF > 30%)

[7] Sample size for KCCQ is n=362 (LVEF ≤ 30%) and n=143 (LVEF > 30%)

[8] Sample size for 6-min hall walk is n=401 (LVEF ≤ 30%) and n=171 (LVEF > 30%)

Table 4. ANCOVA models for echocardiographic parameters to adjust for regression to the mean

	LVEF $\leq$ 30%		LVEF > 30%	
	CRT ON -CRT OFF	p-value	CRT ON - CRT OFF	p-value
LVEF (core)[3], %	4.4 ± 0.9	< 0.0001	3.7 ± 1.3	0.003
LVEDD[4], cm	-0.3 ± 0.1	0.003	-0.1 ± 0.2	0.63
LVEDVi[3], (ml/m^2)	-22.7 ± 3.5	< 0.0001	-7.3 ± 4.3	0.09
LVESVi[3], (ml/m^2)	-20.9 ± 3.2	< 0.0001	-9.0 ± 3.5	0.01
LV stroke volume index, (ml/m^2)	-1.4 ± 0.9	0.16	1.6 ± 1.7	0.33
LV mass[5], g	-7.1 ± 7.1	0.32	-26.6 ± 12.0	0.03

Table 5. Multivariable Analysis of the Hazard Rate for Time to Death or HF Hospitalization using the Cox Proportional Hazards Model

Baseline Parameter	Units / Level	Hazard Ratio	p-value
Unadjusted (n=608)			
CRT	Yes	0.57	0.048
LVEF > 30%	Yes	0.77	0.55
Interaction of CRT and LVEF > 30%	Yes/Yes	0.44	0.21
Adjusted (n=565)			
CRT	Yes	0.54	0.035
LVEF > 30%	Yes	0.76	0.57
Interaction of CRT and LVEF > 30%	Yes/Yes	0.46	0.27
Age	Per 10 years	1.21	0.18
QRS duration	Per 10 ms	0.82	0.003
LVESVi	Per 10 ml/m^2	1.14	0.0002
Ischemic	Yes	1.55	0.16
Supine systolic BP	Per 1 mm Hg	0.99	0.35
Supine diastolic BP	Per 1 mm Hg	1.02	0.38