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CIED - CRT

Redefining the Classifications of Response to Cardiac Resynchronization Therapy

Results From the REVERSE Study



Michael R. Gold, MD, PhD,^a John Rickard, MD, MPH,^b J. Claude Daubert, MD,^c Patrick Zimmerman, PhD,^d Cecilia Linde, MD, PhD^e

ABSTRACT

OBJECTIVES This study sought to assess the impact of a more detailed classification of response on survival.

BACKGROUND Cardiac resynchronization therapy (CRT) improves functional status and outcomes in selected populations with heart failure (HF). However, approximately 30% of patients do not improve with CRT by various metrics, and they are traditionally classified as nonresponders.

METHODS REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) was a randomized trial of CRT among patients with mild HF. Patients were classified as Improved, Stabilized, or Worsened using prespecified criteria based on the clinical composite score (CCS) and change in left ventricular end-systolic volume index (LVESVi). All-cause mortality across CRT ON subgroups at 5 years was compared.

RESULTS Of the 406 subjects surviving 1 year, 5-year survival differed between CCS subgroups ($p = 0.03$), with increased mortality in the Worsened response group. Of the 353 subjects with adequate echocardiograms, survival differed significantly between response groups ($p < 0.001$), also due to increased mortality in the Worsened group. When combining CCS and LVESVi results, the lowest survival was observed among subjects who worsened for both measures, whereas the highest survival occurred in subjects who did not worsen by either endpoint. Multivariate analysis showed that LVESVi worsening with CRT at 6 months, baseline LVESVi, and gender were independent predictors of survival.

CONCLUSIONS For both CCS and reverse remodeling, patients who worsen with CRT have a high mortality, although remodeling was the more important endpoint. Patients who stabilize early with CRT have a much better prognosis than previously recognized, suggesting that the current convention of nonresponder classification should be modified. (REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction]; [NCT00271154](https://doi.org/10.1016/j.jacep.2020.11.010)) (J Am Coll Cardiol EP 2021;7:871-80) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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ABBREVIATIONS AND ACRONYMS

CCS = clinical composite score

CRT = cardiac
resynchronization therapy

HF = heart failure

LV = left ventricle

LVESVI = left ventricular end-
systolic volume index

NYHA = New York Heart
Association

Cardiac resynchronization therapy (CRT) improves functional status and cardiac function, as well as decreases heart failure (HF) hospitalizations and mortality, among patients with HF with left ventricular (LV) systolic dysfunction and QRS prolongation (1-8). Many of these randomized controlled studies used symptomatic improvement to establish response to CRT, although this can be difficult to evaluate and is not always reproduc-

ible. New York Heart Association (NYHA) functional class alone or as part of a clinical composite endpoint is often combined with reverse remodeling to establish response to CRT; however, there is no consensus on the definition of nonresponders (9). Moreover, this designation fails to take into account the natural progression of HF. Accordingly, stabilization of disease severity may be an acceptable outcome (10). The present analysis was designed to evaluate a new classification of CRT response applied to 2 separate common endpoints on all-cause mortality in the preplanned 5-year follow-up of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) study.

METHODS

The design and primary results of the REVERSE trial were published previously (6,11,12). Briefly, eligible patients had American College of Cardiology/American Heart Association Stage C, NYHA functional class I (previously symptomatic, currently asymptomatic), or NYHA functional class II (mildly symptomatic). Patients were required to be in sinus rhythm with QRS duration ≥ 120 ms, a left ventricular (LV) ejection fraction $\leq 40\%$, and an LV end-diastolic dimension ≥ 55 mm. The ethics committee of each center approved the study protocol, the study complied with the Declaration of Helsinki, and all patients gave written informed consent to participate in REVERSE.

All patients underwent implantation of a CRT system (device and leads), with or without implantable cardioverter-defibrillator capabilities, based on standard clinical criteria (13,14). Patients who had undergone successful implantation ($n = 610$) were then randomly assigned in a 2:1 fashion to active CRT (CRT ON) or to a control group (CRT OFF). The period of randomization was 1 year in the United States and 2 years in Europe. The primary endpoint of REVERSE was the clinical composite score (CCS) measured at 12 months (12,15). The change in LV

end-systolic volume, indexed by body surface area (LV end-systolic volume index [LVESVi]), was the predefined and independently powered secondary endpoint of REVERSE. Following the randomization period (i.e., 1 to 2 years), CRT was programmed ON in all patients through 5 years postimplantation to assess the impact of this therapy on survival (16). However, only the patients randomized to CRT ON were included in the analyses of survival, as they had biventricular pacing throughout the study period.

Patients were evaluated at 1, 3, 6, and 12 months. Blinded personnel administered quality-of-life forms, patient global assessment, NYHA functional classification, 6-min walk test, and a physical examination. An unblinded independent Data Monitoring Committee consisting of 3 physician-scientists and a statistician reviewed accumulating hospitalization and mortality data. Patients were subsequently followed with in-office visits at least every 6 months through 5 years of follow-up, at which time patients were exited. Mortality was assessed during this period and classified by the Data Monitoring Committee.

PATIENT CLASSIFICATION BY CCS ENDPOINT. Using the CCS, patients were classified into 1 of 3 response groups: Improved, Stabilized (i.e., unchanged), or Worsened (15). Patients were judged to be Worsened if they died, were hospitalized due to or associated with worsening HF, crossed over to or permanently discontinued double-blind treatment due to worsening HF, or demonstrated worsening in NYHA functional class or moderate-marked worsening of patient global assessment. The classification of the patient global assessment has been detailed previously (12). Patients were judged to be Improved if they had not worsened and demonstrated improvement in NYHA class and/or moderate-marked improvement in patient global assessment. Patients who were not Worsened, or Improved were classified as Stabilized.

Of the 610 patients in REVERSE, 419 were randomized to CRT ON, 10 patients died in the first year, and 3 did not have adequate CCS endpoint data at 1 year. Accordingly, 406 subjects were included in the CCS analysis set.

PATIENT CLASSIFICATION BY REVERSE REMODELING ENDPOINT. Echocardiograms were obtained at baseline (before implantation) and after 6 months of randomization, with CRT turned off temporarily. Data were analyzed in 1 of 2 core laboratories (Philadelphia, Pennsylvania, and Pavia, Italy) blinded to clinical data. The methods to calculate LV dimensions have been previously described (17). For the remodeling endpoint, patients were again classified into 1 of 3 response groups: Patients were judged to be

Worsened if they had an increase in LVESVi at 6 months compared with baseline. Patients were judged to be Improved if they had a decrease of $\geq 15\%$ in LVESVi. Patients were classified as Stabilized if they had a decrease of 0% to $<15\%$ of LVESVi.

During the study, 66 of the 419 patients randomized to CRT ON did not have adequate echocardiograms available at both baseline and the 6-month follow-up, including 8 patients who died. Thus, 343 subjects were included in the LVESVi analysis set.

DATA ANALYSIS. Continuous variables are summarized with mean and standard deviation; categorical variables are presented as counts and percentages. The primary endpoint for this analysis is all-cause mortality. Time to event analyses used Kaplan-Meier estimates and the log-rank test. The Cox proportional hazards regression model was used to compute hazard ratios and assess the effect of 7 pre-defined covariates (age, gender, etiology of HF, baseline LVESVi, QRS duration, QRS morphology, and CRT-P vs. CRT-D) on risk of mortality. Chi-square tests for the proportionality assumption underlying the Cox models were examined, and C-statistics (also known as the concordance index) were calculated for each fitted model. The C-statistic provides a measurement of a model's predictive value and is equal to the proportion of pairs of patients where the observed and predicted outcomes are concordant out of all possible pairs where 1 patient experienced the event and 1 did not. In addition, to understand the sub-population that may be at risk of worsening when with CRT, a logistic regression model was used to compute odds ratios and assess the effect of 6 covariates (age, gender, etiology of HF, LVESVi, QRS duration, and QRS morphology) with respect to the CCS and the remodeling endpoints. The CRT OFF group was used in this study only for comparison of predictors of worsening, as these patients received CRT after 1 to 2 years, as noted previously. Patients with missing covariate values were excluded from multivariable analyses. A p value <0.05 was considered statistically significant and p values were not adjusted for multiple comparisons.

RESULTS

PATIENT POPULATION. Analysis sets were described previously. Baseline characteristics according to response criteria of the patient population are presented in **Table 1**. This was a typical population of patients with mild HF receiving CRT. They were predominantly late middle-age men, with most having ischemic heart disease and an underlying left bundle branch block. Of note, the baseline

TABLE 1 Baseline Demographics

	CCS Analysis CRT ON (n = 406)	LVESVi Analysis CRT ON (n = 353)	All CRT ON (n = 419)
Age (yrs)	62.8 ± 10.6	63 ± 10.6	62.9 ± 10.6.0
Male	315 (77.6)	270 (76.5)	327 (78.0)
Ischemic etiology	227 (55.9)	200 (56.7)	236 (56.3)
CRT-D	335 (82.5)	290 (82.2)	345 (82.3)
NYHA functional class II	332 (81.8)	287 (81.3)	344 (82.1)
LBBB*	247 (61.3)	217 (62.0)	256 (61.5)
RBBB	37 (9.2)	30 (8.6)	37 (8.9)
IVCD	119 (29.5)	103 (29.4)	123 (29.6)
LVEF†	26.9 ± 7	26.8 ± 7	26.8 ± 7
LVESVi (ml/m ²)‡	98 ± 34	99 ± 35	99 ± 35
QRS (ms)	153 ± 21	153 ± 21	153 ± 21
Diabetes	90 (22.2)	77 (21.8)	91 (21.7)
ACE inhibitor or ARB	391 (96.3)	340 (96.3)	404 (96.4)
Beta-blocker	388 (95.6)	335 (94.9)	401 (95.7)
Diuretics	328 (80.8)	281 (79.6)	339 (80.9)

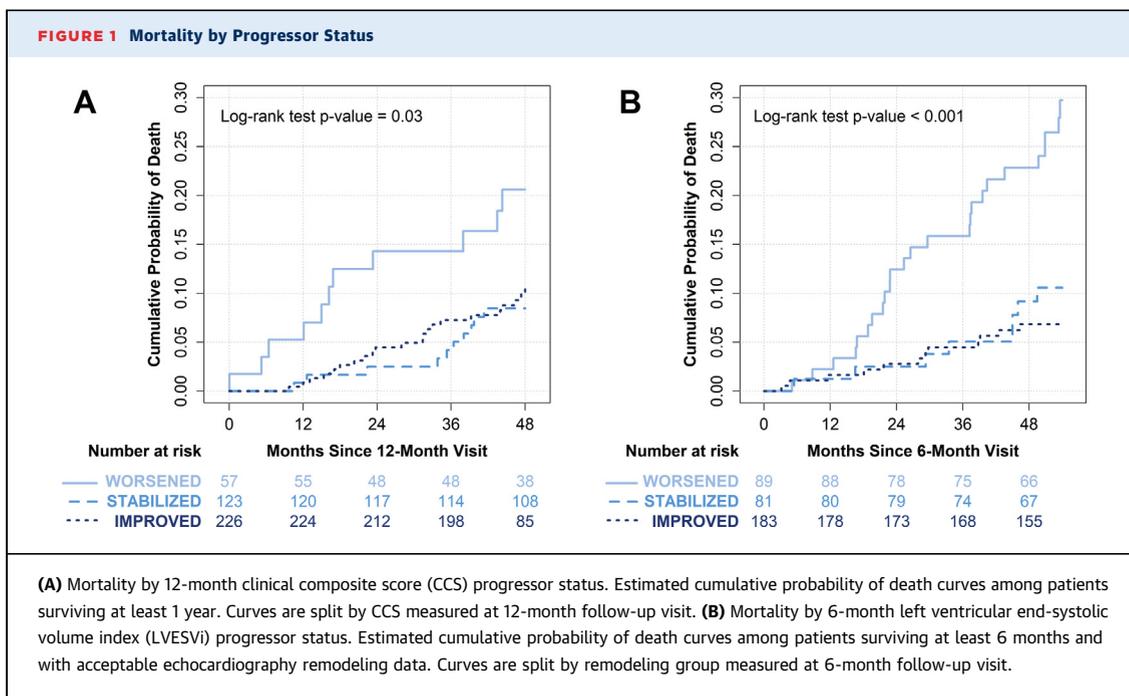
Values are mean ± SD or n (%). *QRS morphology missing for 3 subjects. †LVEF missing for 2 subjects. ‡LVESVi missing for 33 subjects.
 ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; CCS = clinical composite score; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy - defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; NYHA = New York Heart Association; RBBB = right bundle branch block.

characteristics of the included subjects and those excluded from the CCS endpoint differed only by a larger LVESVi in the excluded patients. In the LVESVi endpoint, the excluded patients were more likely to be receiving beta-blockers (100% vs. 95%).

MORTALITY. Among the 419 subjects in the CRT ON cohort, all-cause mortality estimated by Kaplan-Meier analysis was 13.5% at 5 years (95% confidence interval [CI]: 10.0% to 16.9%). Among the 406 subjects in the study population (which requires survival through the first year), all-cause mortality estimated by Kaplan-Meier analysis was 11.5% at 5 years (95% CI: 8.2% to 14.8%).

CLINICAL COMPOSITE SCORE. Of the 406 subjects, 56% were Improved, 30% were Stabilized, and 14% Worsened by CCS. Clinical characteristics for individuals assessed by CCS according to response definitions are presented in **Supplemental Table 1**. Worsened patients tended to more frequently have ischemic etiology and non-left bundle branch block (non-LBBB) morphology, less frequently had baseline NYHA II functional status, and had smaller QRS durations compared with Stabilized and Improved patients.

The estimated 5-year all-cause mortality rates differed between CCS response categories, as shown in **Figure 1A** and the **Central Illustration** (p = 0.03). The mortality rate in the combined Improved or Stabilized



subgroups was significantly lower compared with the Worsened subgroup (10% vs. 21%; $p = 0.01$), representing a 51% reduction in mortality. There were no statistical differences in mortality between the Stabilized and Improved subgroups. The CCS multivariable model had a C-statistic of 77%, indicating a model with good predictive value. In the multivariable model, gender and baseline LVESVi were independent predictors of outcome (Supplemental Table 2).

REVERSE REMODELING. Of 353 subjects with acceptable echocardiography remodeling data to define LVESVi response, 52% were Improved, 23% were Stabilized, and 25% were Worsened. Clinical characteristics for each response category are presented in Supplemental Table 3. The Worsened patients were more likely to be male, have ischemic etiology, a non-LBBB morphology, diabetes, and a shorter QRS duration. Survival at 5 years after implantation again differed significantly between subgroups ($p < 0.001$), due to increased mortality in the Worsened subgroup and with no statistical difference between the Improved and Stabilized subgroups (Figure 1B, Central Illustration). Overall the 5-year mortality in patients classified by LVESVi change was significantly lower among the Improved and Stabilized patients than in those who Worsened (8% vs 30%; $p < 0.01$), representing a 73% reduction in mortality. The remodeling multivariable model had a C-statistic of 81%, indicating a model with very good predictive value. In the multivariable model, LVESVi Worsened

significantly increased mortality risk relative to LVESVi Improved (hazard ratio: 2.63; $p < 0.01$), but LVESVi Stabilized was similar to LVESVi Improved (hazard ratio: 1.06; $p = 0.90$) (Supplemental Table 4).

ADJUDICATED CAUSES OF DEATH. The mortality rates for the adjudicated causes of death are presented in Table 2. This shows that for the CCS endpoint, subjects classified as Worsened were more likely to die of HF deaths, whereas for the remodeling endpoint, both sudden and HF deaths were more common in the subgroup that Worsened.

INTERACTION OF RESPONSE MEASURES. Although there are similarities between the mortality curves of the 3 response measures for the CCS and remodeling endpoints, it cannot be discerned from these pooled group results how often individual patients have the same response. To investigate this further, histograms are shown with the distributions of CCS response based on the remodeling response (Figure 2). Concordant results were more common than discordant, as indicated by proportion of patients who Stabilized or Improved by these endpoints. Although CCS Worsened was the most common outcome among patients who had LVESVi worsened, there is clearly overlap with the other outcomes. To evaluate this further, we compared mortality of patients who Worsened by both outcomes with those who Worsened by only 1 outcome and with those who did not worsen by either outcome. These results are shown in Figure 3 and

CENTRAL ILLUSTRATION Responder Classification and Mortality by Progressor Status

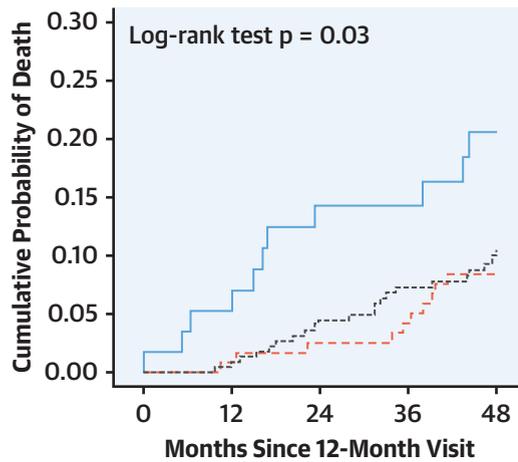
12-Month CCS Responder Classification

56% Improved
 30% Stabilized
 14% Worsened

6-Month LVESVi Responder Classification

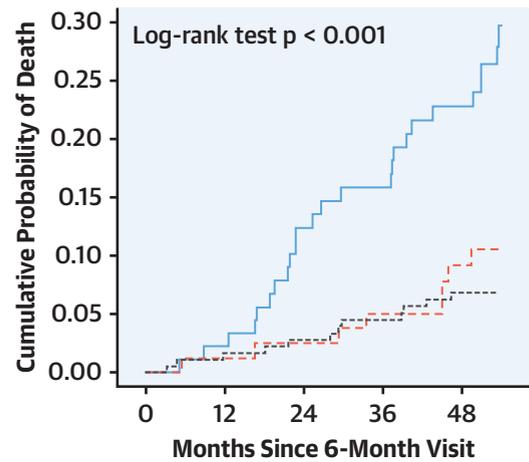
52% Improved
 23% Stabilized
 25% Worsened

Mortality by 12-Month CCS Progressor Status



No. at risk:		0	12	24	36	48
—	Worsened	57	55	48	48	38
- - -	Stabilized	123	120	117	114	108
· · ·	Improved	226	224	212	198	85

Mortality by 6-Month LVESVi Progressor Status



No. at risk:		0	12	24	36	48
—	Worsened	89	88	78	75	66
- - -	Stabilized	81	80	79	74	67
· · ·	Improved	183	178	173	168	155

Gold, M.R. et al. J Am Coll Cardiol EP. 2021;7(7):871-80.

(Left) Mortality by 12-month clinical composite score (CCS) progressor status. Estimated cumulative probability of death curves among patients surviving at least 1 year. Curves are split by clinical composite score measured at 12-month follow-up visit. **(Right)** Mortality by 6-month left ventricular end-systolic volume index (LVESVi) progressor status. Estimated cumulative probability of death curves among patients surviving at least 6 months and with acceptable echocardiography remodeling data. Curves are split by remodeling group measured at 6-month follow-up visit.

reveal that the poorest outcome is for patients who worsen for both CCS and LVESVi endpoints and the best outcome is for patients who do not worsen by either endpoint. There is an intermediate mortality rate for subjects who are classified as Worsened by only 1 measure. The differences between distributions were highly significant ($p < 0.001$). For subjects who Worsened by both endpoint measures, the 5-year mortality was 32%, whereas it was 6% for those who did not worsen by either measure.

A multivariate analysis was performed to predict mortality, which included clinical factors known to be associated with CRT response and the 2 endpoint measures in this study (CCS and LVESVi). This analysis demonstrated that LVESVi Worsening at 6 months and baseline LVESVi (large as opposed to small) were

predictors of increased mortality, whereas female sex was predictive of reduced mortality (Table 3). In contrast, a Worsened CCS was not predictive of mortality after accounting for other variables.

PREDICTORS OF WORSENING OF CCS AND REVERSE REMODELING.

To understand better the subpatient population that Worsened with CRT, and to rule out that worsening by CRT implied a detrimental effect of CRT itself rather than the natural history of the disease, we performed additional analyses. Specifically, we compared Worsened patients in the CRT ON group noted previously with those in the CRT OFF arm of REVERSE ($n = 191$, with 167 having complete echocardiography data). In the CRT OFF group, 21% (40 of 191) of patients Worsened by CCS at 1 year compared

TABLE 2 Mortality Rates

Cause of Death	Remodeling Endpoint			CCS Endpoint		
	Improved (n = 183)	Stabilized (n = 81)	Worsened (n = 89)	Improved (n = 226)	Stabilized (n = 123)	Worsened (n = 57)
Cardiac						
Sudden	1 (0.5)	1 (1.2)	5 (5.6)	7 (3.1)	0 (0)	1 (1.8)
Nonsudden heart failure	5 (2.7)	2 (2.5)	7 (7.9)	6 (2.7)	2 (1.6)	5 (8.8)
Nonsudden non-heart failure	1 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
Noncardiac	5 (2.7)	5 (6.2)	11 (12.4)	9 (4.0)	6 (4.9)	4 (7.0)
Unknown	0 (0)	0 (0)	2 (2.2)	0 (0)	2 (1.6)	0 (0)
Total	12 (6.6)	8 (9.9)	25 (28.1)	22 (9.7)	10 (8.1)	11 (19.3)

Values are n (%).
Abbreviation as in Table 1.

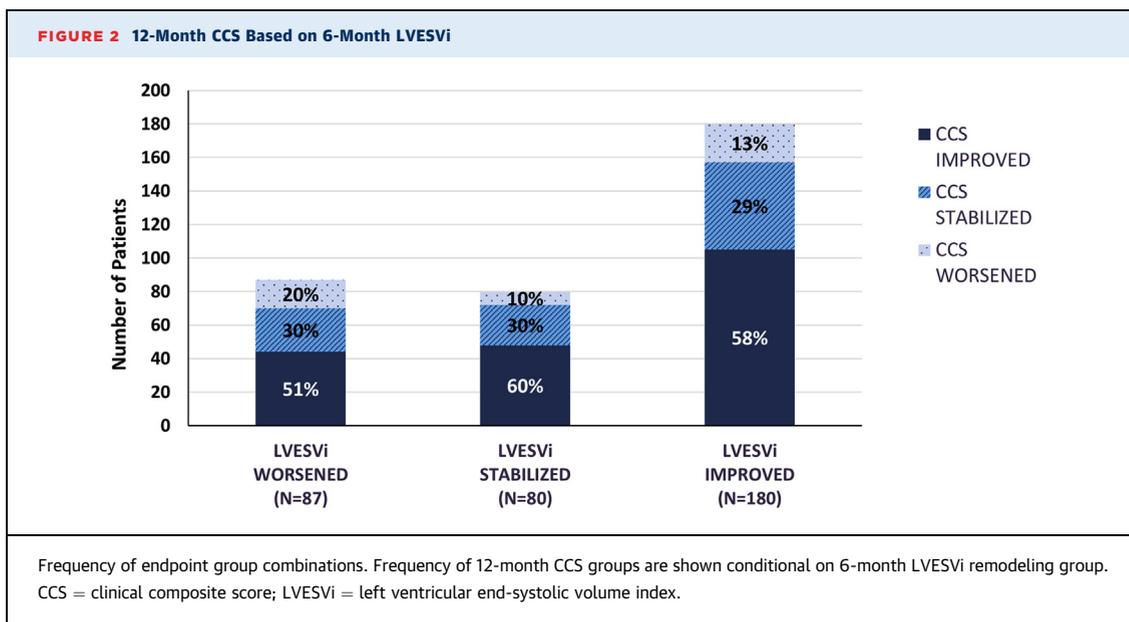
with 16% (67 of 419) of patients in the CRT ON group ($p = 0.17$). For the purpose of this analysis of CCS endpoints, we included the additional patients who died during the first year of treatment. There were 13 such patients in the CRT ON group, so that a total of 419 patients were part of the CCS response analysis for the CRT ON group. For the remodeling endpoint, 38% (64 of 167) of patients Worsened for CRT OFF versus 25% (89 of 353 patients) for CRT ON ($p < 0.01$).

Multivariate analysis of clinical factors associated with worsening were performed for each of the 2 endpoints (Supplemental Figures 1 and 2). For the CCS, non-LBBB morphology and QRS duration were both significant predictors of worsening among CRT ON patients; however, QRS morphology was not a significant predictor in CRT OFF patients. Overall multivariate modeling did not find significant interactions between any variables and treatment

(CRT ON vs. OFF), suggesting that CRT was not adversely affecting outcomes in any subgroup, but rather was likely less effective to reduce mortality in certain subgroups. For the remodeling endpoint, male gender and non-LBBB morphology were significant predictors of worsening among CRT ON patients, but not CRT OFF patients. Ischemic etiology was a significant predictor of worsening in CRT OFF patients only. Overall multivariate modeling found a significant interaction with age such that older patients were less likely to benefit from CRT when other covariates were held constant.

DISCUSSION

This is the first multicenter study, to our knowledge, that indicates that patients classified as Stabilized have a comparable survival benefit as those classified

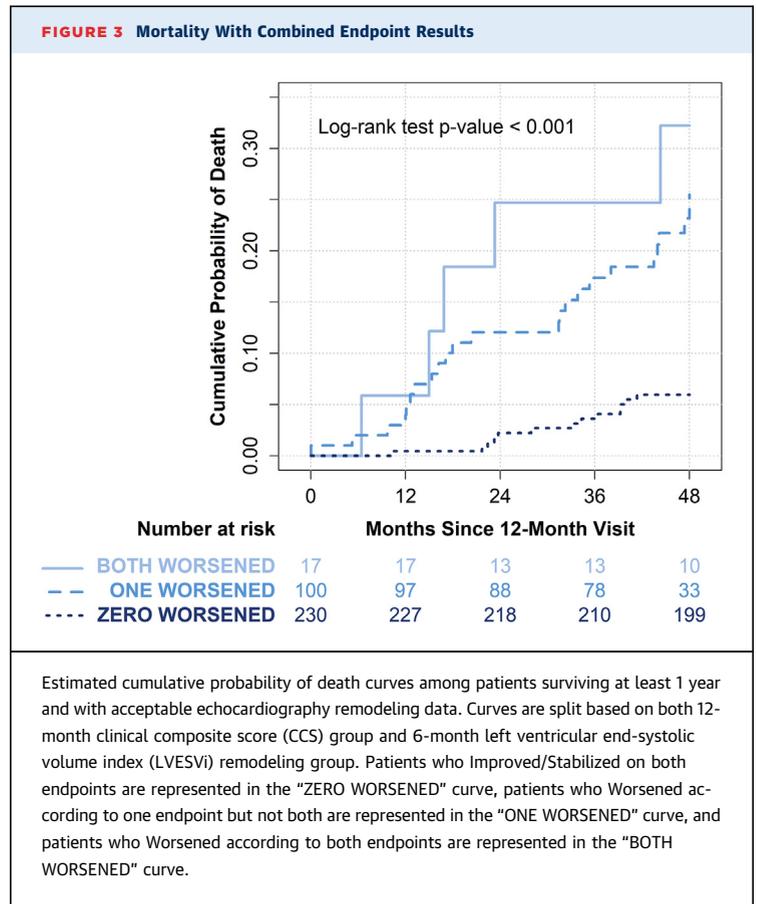


as Improved to CRT. Such Stabilized patients with CRT thus have a much better prognosis than previously appreciated, suggesting that the current responder classification should be modified.

This outcome was observed for both a clinical measure of response, the CCS, and a remodeling endpoint. Conversely, patients who Worsened despite CRT have a much worse prognosis than those who Stabilized or Improved. Whereas the 2 endpoints evaluated are very different with regard to what they measure, the results were quite similar. Moreover, both endpoints have been validated in previous studies and are commonly used in HF trials (1-5,7,8,18,19). This supports the concept that worsening despite CRT is a unique “phenotype” of response. Thus, pooling patients who Stabilized with those who Worsened as nonresponders is misleading, as has often been done in the past, particularly for measures of reverse remodeling (17,20).

The etiology of HF affects the reverse remodeling response to CRT. Patients with ischemic etiology have smaller LV volumes at baseline, more scar tissue, and thus less propensity for reverse remodeling with CRT (21). However, the reductions in mortality and hospitalizations are at least as large as in patients with nonischemic etiology (22,23). Thus, basing CRT eligibility by traditional response measures of early reverse remodeling and symptomatic improvement in patients may be inappropriate, particularly among patients with ischemic heart disease. Indeed, despite being recommended in international guidelines (3,24), CRT remains underused (25). Our results indicate that a Stabilized response, particularly with regard to LV remodeling, may well portend a good prognosis that hopefully would result in better adoption of guidelines. Although Stabilized response for CCS was also associated with a good prognosis, it will be important to assess if this is observed in other cohorts with more advanced HF at baseline.

The worsening of clinical and remodeling function in a subset of patients may represent the ineffectiveness of CRT to offset the natural history of HF or alternatively it may reflect an adverse effect of the pacing therapy. The Echo CRT study showed that CRT increases mortality among patients with a QRS duration <130 ms despite baseline mechanical dyssynchrony (26). Such narrow QRS patients were excluded from REVERSE. In an effort to help differentiate ineffectiveness from harm, we compared clinical characteristics of CRT ON and OFF patients who Worsened by either endpoint. Overall, the groups were similar in characteristics, although fewer patients Worsened with CRT ON. This suggests that ineffectiveness rather than harm was the primary



cause of Worsened outcomes for patients who satisfied CRT indications. However, further studies will be needed to determine if there is a subset of such Worsened patients who would improve with deactivation of therapy.

When combining the 2 endpoints of this study, the highest mortality was observed among patients who had a Worsened CCS and also had further remodeling.

TABLE 3 Multivariate Modeling for Long-Term Mortality

	Hazard Ratio	95% Confidence Interval	p Value
6-month LVESVi worsened	2.58	1.35-4.93	0.004
12-month CCS worsened	1.72	0.82-3.60	0.151
Female vs. male	0.11	0.01-0.81	0.030
LBBB	0.65	0.31-1.37	0.257
Baseline QRS duration (increase 10 ms)	0.87	0.73-1.03	0.099
Ischemic	0.65	0.27-1.61	0.356
Device type (CRT-P to CRT-D)	0.51	0.23-1.11	0.090
Age (increase 10 yrs)	1.32	0.93-1.87	0.126
Baseline LVESVi (increase 10 ml/ms ²)	1.14	1.04-1.24	0.004

CRT-P = cardiac resynchronization therapy pacemaker; LBBB = left bundle branch block; other abbreviations as in Table 1.

In contrast, the best outcome was observed in those patients classified as Improved or Stabilized by both endpoints. Specifically, in the patients who survived the first year of CRT ON therapy and had acceptable remodeling data, those who Improved or Stabilized by both end points had a remarkably low (6%) all-cause mortality in the subsequent 4 years. Importantly, patients who stabilize do better than those who worsen, as shown in **Figure 1**. Therefore, we believe grouping them together as nonresponders is inappropriate.

The primary endpoint of this study was all-cause mortality. This is the standard measure of mortality in CRT trials with prolonged follow-up (4,5,7,8), including REVERSE. Approximately half of the deaths in REVERSE during the 5-year follow-up were classified as noncardiac; however, the primary results of the present analysis were not affected if only cardiac deaths were considered an endpoint. Specifically, similar rates of cardiac deaths were noted for the Stabilized and Improved subgroups, with much higher mortality in the Worsened groups for both CCS ($p < 0.01$) and reverse remodeling ($p < 0.01$) measures (**Supplemental Figure 3**).

CLINICAL IMPLICATIONS. The results of this study indicate that patients who worsen with CRT, either assessed by remodeling measures or clinical status, represent a very high-risk cohort. A reasonable clinical approach is to obtain an echocardiogram at 6 months after initiation of therapy. For those patients who show continued remodeling, as evidenced by an increase in LVESVi, possible reversible causes for poor response should be aggressively evaluated, such as poor lead position, suboptimal medical therapy, or inadequate LV pacing due to competing arrhythmias such as atrial fibrillation or frequent ventricular ectopy. We previously showed in REVERSE that apical LV lead position was associated with a significantly smaller decrease in LVESVi (27). If unfavorable baseline electrocardiogram characteristics, lead position, or measures of electrical delay are noted, then consideration should be given to inactivating CRT. If clinical condition, as assessed by the CCS or other measures, also deteriorates, then consideration for advanced therapies or alternatives to CRT should be considered. Another important implication of these findings is that the commonly stated 30% nonresponder rate with CRT is an overestimation of the proportion of patients who do not benefit from this therapy. In fact, the percentage of patients who worsened by both endpoint measures was only 4.9%.

STUDY LIMITATIONS. This study should be interpreted in the face of several methodological

limitations. First, only the CRT ON arm was used for the principal analyses performed, so there was no control group for comparison, as the CRT OFF group was crossed over to CRT ON by protocol after 1 to 2 years. Second, this was a study of mild HF, so it is unknown if these findings can be extrapolated to advanced HF. Third, there is intraobserver variability in echo measures that may affect the interpretation of results for individual subjects. However, the concordance correlation coefficient is very high (0.90) for LVESVi in the REVERSE cohort (28). Fourth, although the analyses presented here found minimal interactions between CRT treatment group and patient baseline characteristics predicting CCS or LVESVi worsening, this analysis was ad hoc in nature and was not appropriately powered for detecting such interaction effects. Finally, since completion of enrollment in REVERSE, advances have been made in identifying optimal LV lead position and programming algorithms, which likely improve outcomes (29-31).

CONCLUSIONS

In the prespecified 5-year follow-up of REVERSE, patients with Worsened functional or remodeling endpoints despite CRT have markedly higher mortality compared with those with Stabilized or Improved statuses. These results indicate that the term CRT nonresponder is obsolete, so we propose to classify CRT outcomes into 3 categories: Improved, Stabilized, or Worsened.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Stabilization of mild heart failure with CRT, either measured by clinical symptoms or echocardiographic measures of remodeling, is associated with low 5-year mortality. Patients who clinically worsen despite CRT have a poor prognosis and should be evaluated for reversible causes of ineffective CRT or for advanced therapies.

TRANSLATIONAL OUTLOOK: Comparing survival in CRT patients with advanced heart failure (NYHA functional class III/IV) who stabilize versus improve is important to determine, as this is a cohort with higher mortality. It is important to explore if there are subgroups of "improved" patients with better outcomes, such as those with larger responses (i.e., super responders) or those who improve by multiple metrics.

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KEY WORDS cardiac resynchronization therapy, heart failure, mortality, remodeling, response

APPENDIX For supplemental tables and figures, please see the online version of this paper.



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