



The Association of Left Ventricular Remodeling with CRT Outcomes

Michael R. Gold, John Rickard, J. Claude Daubert, Jeffrey Cerkevnik, Cecilia Linde

► To cite this version:

Michael R. Gold, John Rickard, J. Claude Daubert, Jeffrey Cerkevnik, Cecilia Linde. The Association of Left Ventricular Remodeling with CRT Outcomes. Heart Rhythm, 2023, 20 (2), pp.173-180. 10.1016/j.hrthm.2022.11.016 . hal-03886558

HAL Id: hal-03886558

<https://hal.science/hal-03886558>

Submitted on 15 Dec 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

The Association of Left Ventricular Remodeling with CRT Outcomes

Michael R. Gold, MD, PhD^{1*}; John Rickard, MD, MPH²; J. Claude Daubert, MD³; Jeffrey
Cerkvenik, MS⁴; Cecilia Linde, MD, PhD⁵

¹Department of Medicine, Medical University of South Carolina, Charleston, South Carolina,
USA; ²Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic,
Cleveland Ohio, USA; ³Faculty of Medicine, University of Rennes 1, CIC IT, INSERM 642,
Rennes, France; ⁴Cardiac Rhythm Management, Medtronic Inc., Minneapolis, Minnesota, USA;
⁵Department of Medicine, Cardiology Unit, Karolinska Institute and Karolinska University
Hospital, Stockholm, Sweden

Short title: Left Ventricular Remodeling and CRT Outcomes

***Address for Correspondence:**

Michael R. Gold, MD, PhD
Division of Cardiology
Medical University of South Carolina
114 Doughty Street, MSC-592
Charleston, South Carolina 29425
E-mail: goldmr@musc.edu

Conflict of Interest: Drs. Gold, Linde, and Daubert have served as consultants to and received
research grants from Medtronic. Dr. Gold has served as a consultant and receives research grants
from Boston Scientific. Dr. Rickard has received a research grant from Abbott and has been a
consultant for Medtronic. Dr. Daubert has received research grants, speaker honoraria, and
consulting fees from Medtronic and St Jude Medical. Dr. Linde has received honoraria payments
from Medtronic, Abbott, and Impulse Dynamics; and has been supported by grants from the

24 Swedish Heart Lung Foundation and Stockholm City Council. Mr. Cerkenik is an employee
25 and shareholder of Medtronic.

26 **Word count:** 4,969

Journal Pre-proof

Abstract

Background: Cardiac resynchronization therapy (CRT) response stratified by left ventricular (LV) remodeling revealed differing mortality profiles for distinct patient cohorts. Measuring functional endpoints, as well as mortality, may better assess CRT efficacy and inform patient management. However, the association between LV remodeling and functional outcomes after CRT is not well understood.

Objective: To evaluate long-term CRT outcomes by extent of LV remodeling.

Methods: REsynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction (NCT002711154) was a prospective, double-blind, randomized CRT trial. Patients were classified based on LV end-systolic volume (LVESV) change from baseline to 6-months post-CRT: Worsened (increase); Stabilized (0 to $\leq 15\%$ reduction); Responder (>15 to $< 30\%$ reduction); and Super-responder ($\geq 30\%$ reduction). Subjects were evaluated annually for 5 years.

Results: The analyses included 353 patients randomized to CRT-ON arm. All-cause mortality was higher in the worsened group compared with the 3 other response groups (29.8% vs 8.0%, $p < 0.0001$), with no difference in survival among those groups ($p = 0.87$). A significant interaction between LVESV group and time was observed for health status and quality of life (both $p = 0.02$). The interaction was not significant for 6-minute hall walk ($p = 0.79$); however, super-responders had increased walk distance compared to the 3 other response groups ($p = 0.03$).

Conclusion: Preventing further increase in LVESV with CRT was associated with reduced mortality, whereas functional measure improvement was associated with LV remodeling magnitude. These results support consideration of functional and mortality endpoints to assess

50 CRT efficacy and provide further evidence the dichotomous ‘responder and non-responder’
51 classification should be modified.

52 **Keywords:** Cardiac Resynchronization Therapy; response; heart failure; remodeling; mortality;
53 quality of life; exercise capacity

Introduction

Heart failure with a reduced ejection fraction (HFrEF) is a progressive process that can be effectively treated in selected cohorts with cardiac resynchronization therapy (CRT).¹⁻⁷ CRT improves survival, exercise capacity, and quality of life, while reducing heart failure (HF) hospitalization among patients with both mild, moderate, and advanced HFrEF in the presence of QRS prolongation. Large multicenter, randomized trials have consistently shown the benefit of CRT in these cohorts. The current method of assessing CRT benefit classifies patients as ‘responder or non-responder’ based on arbitrary cut-offs for clinical and/or echocardiographic measures of response, such as left ventricular end-systolic volume (LVESV), to measure the extent of reverse remodeling. Approximately 30% of CRT patients are classified as ‘non-responders’ using the traditional dichotomous CRT response classification; however, this approach may underestimate the true clinical benefit of CRT, so alternative classification methods have been proposed.⁸⁻¹⁰

The traditional ‘non-responder’ group includes patients that worsen as well as those that stabilize after CRT. Recent evidence demonstrated a favorable CRT response among patients with early stabilization of disease progression (neither improved nor worsened LV function at 6-months post CRT) as they have better survival than those who worsen over time.^{9, 10} Stabilized patients are a unique cohort, and therefore should not be considered ‘non-responders’. Some patients have an early “super-response” to CRT (normalization or near-normalization of LV function at 6-months post CRT) and may experience maximal benefit; however, super-responders are not extensively studied.^{11, 12} These collective findings support revision of the current dichotomous classification of response, as multiple unique CRT response cohorts exist. In addition to mortality, patient quality of life and functionality measures are important factors

for assessing CRT therapy benefit and important for patients. However, little is known about the relationship between the magnitude of early response, such as LVESV change, and these outcomes. A better understanding of this relationship, as well as baseline characteristics or “phenotypes” of distinct CRT response cohorts, may enhance knowledge of patient selection and allocation of patient management resources.

The current study was a post-hoc analysis of patients enrolled in the large randomized controlled trial (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction or REVERSE). The aims of this analysis were to evaluate baseline ‘phenotypes’ and long-term outcomes of four early CRT response cohorts determined by the magnitude of LV remodeling (measured by LVESV change) at 6-months post-CRT. Moreover, we evaluated multiple different outcome measures to determine whether the relationship between the magnitude of LV remodeling and individual outcomes differ.

Methods

Study design

REVERSE (NCT00271154) was a prospective, multicenter, international, double-blind, randomized trial of CRT in patients with mild HF. Details regarding the study design were previously published.¹³⁻¹⁵ The study protocol complied with the Declaration of Helsinki and was approved by the institutional review board or ethics committee of each center. All study patients gave written informed consent to participate in the trial.

Patients and procedures

Patients included in the trial exhibited mild HF (New York Heart Association (NYHA) Class I/II), sinus rhythm with QRS duration ≥ 120 ms, left ventricular end-diastolic diameter (LVEDD)

≥ 55mm, and left ventricular ejection fraction (LVEF) ≤ 40%. Additional details on the inclusion and exclusion criteria were reported elsewhere.¹³ Baseline data were collected prior to implant including medical history, NYHA Class, patient-reported health status (measured by Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score), Quality of Life (measured by Minnesota living with heart failure® Questionnaire or MLHFQ), 6-minute walk test (6MWT), and a full echocardiogram. KCCQ and MLHFQ scores provide complimentary information since KCCQ overall score reflects integrated information on physical limitations, symptoms, self-efficacy, social interference and quality of life is a measure of health status,¹⁶ whereas the Minnesota score provides how the HF condition restricted the quality of life of the patient. Eligible patients were implanted with a Medtronic CRT system with or without defibrillation capability in accordance with country or region-specific guidelines.¹⁷⁻¹⁹ Patients with a successful CRT system implant (n=610) were then randomized in a 2:1 fashion to either a CRT-ON (n= 419) or a CRT-OFF (n=191) group. During the 12-month randomization period in North America and 24 months in Europe, patients were evaluated at 1, 3, 6, 12, 18 and 24 months in a blinded fashion for MLHFQ, KCCQ overall summary score, and 6MWT. A full echocardiography assessment was completed at 6-month post-implant. Following the randomization period, all patients were converted to CRT-ON and further evaluated annually for up to 5 years in an unblinded fashion (including annual assessment for MLHFQ, KCCQ overall summary score, and 6MWT). The current analyses of outcomes only included the patients initially randomized to the CRT-ON group with adequate, paired echocardiograms at baseline and 6-month post-implant. The CRT-OFF group was used only to compare patient characteristics associated with response classification.

CRT Response Classification

Echocardiograms were obtained at baseline (before CRT implantation) and 6 months after active CRT (CRT-ON). For the echocardiography procedure, CRT was temporarily inactivated. Collected data were analyzed by 1 of 2 core laboratories blinded to group assignment. For each patient, the paired left ventricular end-systolic volume (LVESV) measurements at baseline and 6 months post-CRT implant were compared. Patients were classified into 1 of 4 CRT response categories based on the change in LVESV post-CRT (expressed as a percent change): Worsened (any increase), Stabilized (0 to $\leq 15\%$ reduction), Responder (>15 to $<30\%$ reduction), and Super Responder ($\geq 30\%$ reduction).

Endpoints

The primary endpoint for this analysis was all-cause mortality. Additional endpoints include a composite measure of time to first heart failure hospitalization or all-cause mortality, as well as improvement in patient-reported health status (KCCQ overall score), quality of life (MLHFQ), and exercise capacity (6MWT).

Statistical analysis

Baseline variables were compared between groups using ordered univariate logistic regression for continuous variables and chi-square tests for dichotomous variables. P-values less than 0.05 were considered statistically significant. The distribution of responder groups between CRT-ON and CRT-OFF was compared using the chi-square test. All-cause mortality and the composite endpoint with first heart-failure hospitalization were analyzed using Cox proportional hazards models, with LVESV responder group as the independent variable, along with adjustment for statistically significant baseline variables by including them as covariates in the model (age, sex, ischemic/non-ischemic, CRT-P/CRT-D, LBBB/non-LBBB, LVEF, QRS duration, and diabetes).

A total of 4 Cox models were created: A 4-level LVESV responder group model and a 2-level (worsened vs. the rest) for each of the two endpoints. Mean changes from baseline for KCCQ, MLHFQ, and 6MWT variables were compared between groups using a repeated measures linear regression, including all time points where there was a value, with LVESV responder group as an independent variable, along with time and their interaction, and adjusting for statistically significant baseline variables by including them as covariates.

Results

Patients, Baseline Characteristics, and LVESV Responder Groups

Among the 419 patients randomized to the CRT-ON group, six patients died prior to the 6-month follow up and 60 other patients were excluded due to missing or inadequate paired LVESV measurements. Accordingly, 353 patients were included in the current analysis. Based on the percent change in paired baseline to 6-month LVESV measurements, there were 99 (28%) super responders, 84 (24%) responders, 81 (23%) stabilized, and 89 (25%) worsened patients. Table 1 shows baseline characteristics of each group. The super responder group had a higher percentage of females, non-ischemic cardiomyopathy, LBBB-morphology, and longer baseline QRS duration. In contrast, the worsened group had a higher percentage of males, ischemic cardiomyopathy, non-LBBB morphology, and higher baseline LVEF. A comparison of distribution of response groups for the CRT-ON and CRT-OFF cohorts is shown in Table 2. There was a highly significant difference between groups with more responders and super responders and fewer stabilized and worsened subjects ($p < 0.0001$) among the CRT-ON group as compared to the CRT-OFF group. This finding supports that responder classification was not simply due to baseline characteristic, but strongly dependent on the presence of CRT.

Mortality and HF Hospitalization

Of the 353 patients, 27 (7.6%) exited prior to 60-months post-implant. Fifteen of the 27 remained in the study at least 3 years. All these exited patients were censored at the time of exit in the survival analyses. There was a total of 45 deaths (12.7%) during the 6-month to 5-year follow up period. Mortality rates at 60 months post-implant were 6.1% for super responders, 7.9% for responders, 10.6% for stabilized, and 29.8% for worsened. After adjusting for baseline variables, mortality was significantly different between the subgroups ($p=0.02$; Figure 1). There was, however, no difference in survival among the super responder, responder, and stabilized subgroups (adjusted $p=0.87$), supporting the concept that patients considered stabilized are a distinct cohort with 5-year mortality rate lower than the worsened group but statistically similar to the responder groups.

For the composite endpoint (time to first heart failure hospitalization or all-cause mortality), a trend towards a difference in event rates at 5 years was observed (adjusted $p=0.09$; Figure 2). Comparing the worsened group to the other 3 groups combined, the heart failure hospitalization or all-cause mortality rates at 60 months post-implant were 39.3% and 19.2%, respectively (adjusted $p=0.06$). The responder event rate was numerically higher than the stabilized or super responder rate. None of these differences were statistically significant, which may reflect the relatively low event rates in these groups of mild heart failure patients.

Patient-Reported Health Status, Quality of Life and Exercise Capacity

The relationship between the magnitude of LV remodeling and the change in patient-reported health status (KCCQ overall summary scores) is shown in Figure 3. At each time point post-randomization, there was an improvement in KCCQ overall summary scores. The amount of

improvement was incremental with increased magnitude of LV remodeling. Moreover, the magnitude of this improvement was very large compared with standard criteria for clinically meaningful differences.¹⁶ This trending relationship was consistent over the 5-year follow up period. Even when adjusted for baseline variables, the interaction between LVESV group and time was significant ($p=0.02$), indicating that the groups are changing differently over time.

Similar results were observed with the MLHFQ (Figure 4). The super responder group had the largest mean improvement in MLHFQ score, with a consistent 10+ point group average above baseline throughout the study period. The responder group had a larger mean improvement in MLHFQ scores than that of the stabilized or worsened group throughout the study period, despite some decreases over time. Although the stabilized group had a mean improvement in MLHFQ score equivalent to that of the worsened group at 6 months, at all subsequent follow-ups the MLHFQ score averages were numerically higher in the stabilized group. After adjusting for baseline covariates, the interaction between LVESV group and time was statistically significant ($p=0.02$).

The relationship between the magnitude of LV remodeling and the change in exercise capacity (distance walked during a 6MWT) is shown graphically in Figure 5. The interaction between LVESV group and time was not statistically significant ($p=0.79$). However, improvement in 6MWT was better in the super responder group than others. A test comparing the super responders vs. the other 3 groups, adjusting for time and baseline variables was statistically significant ($p=0.03$).

Discussion

Our findings indicate that preventing further increase in LVESV by CRT was associated with reduced mortality. Secondly, improvement in functional measures by CRT was associated with LV reverse remodeling response. These results support consideration of functional and mortality endpoints to assess CRT efficacy and provides further evidence the dichotomous ‘responder and non-responder’ classification should be modified.

Previous results challenged the classification of CRT response using the clinical composite or reverse remodeling endpoints to divide patients dichotomously into either responders or non-responders.^{9, 10} Treating response as a continuum of care without dichotomization has been emphasized more recently based on a growing body of evidence in favor of this approach.⁸ Moreover, it is now clear that stabilizing heart failure with CRT, even if the traditional endpoints of responder are not met, is associated with reduced mortality compared with those who continue to worsen.^{9, 10} However, little is known about whether normalization or near normalization of LV function (i.e. super responder) is associated with better survival or fewer heart failure hospitalizations.¹² In addition, the effect of CRT response classification on functional endpoints, such as exercise capacity or quality of life, are not well studied.

We report **4 major findings**. **First**, mortality is higher among patients who continue to remodel despite CRT (worsened subgroup), whereas there are no significant differences among subjects who stabilize, respond, or super respond. This difference persisted over five years despite adjustments of patient characteristics. **Second**, heart failure hospitalizations also show similar event rates in all groups, but with a higher rate among the worsened subgroup. **Third**, changes in quality of life generally follow a continuum with separation between the groups clear by one year and persisting throughout the duration of study follow-up, though the stabilized group improvement was similar to the worsened group. After a potential placebo effect initially,

exercise capacity improvement seems to be restricted to super responders, though factors other than cardiac function may be contributing to the decline in hall walk distance over time. **Fourth**, simple clinical predictors of the 4 categories of response are associated with distinct clinical “phenotypes.” Specifically, gender, etiology of heart failure, baseline QRS morphology and QRS duration are significantly different between groups (Table 2), which extends this well documented relationship with binary classifications of response.

Quality of life, health care status, and exercise capacity were some of the first endpoints assessed with early CRT clinical trials.^{1, 2} However, these “softer” endpoints were considered less important when studies with longer follow-up evaluated mortality and heart failure hospitalization as primary endpoints.⁴⁻⁶ Moreover, there is concern of a placebo effect of device implantation, which may over-estimate benefit.^{20, 21} This is unlikely to be contributing to the outcome of the present study, as REVERSE was a double-blind study during the randomization phase with device implantation in both groups. Thus, the changes noted in the first year of follow-up were during a period when the differences between groups were already evident. Furthermore, it is now clear that optimizing the care of CRT patients should not only include prolonging life and reducing hospitalization, but also improving functional status and quality of life.⁸

An intriguing and important aspect of our results was the disparate effect of the magnitude of reverse remodeling on different endpoints. Only those patients who worsened with CRT, as measured by continued increase of LVESV, had a higher mortality and more frequent heart failure hospitalizations. This could be interpreted as indicating that simply preventing continued remodeling is a sufficient goal for CRT. However, quality of life and patient-reported health status continued to improve further as more reverse remodeling occurred. These results provide

strong support for maximizing CRT response rather than simply avoiding further remodeling.

The results of 6-minute hall walk were more complex only showing a clear improvement among super responders. This may reflect factors other than heart failure status, such as orthopedic issues or the ageing process, which may have a larger impact on this parameter.

This study should be interpreted in light of certain methodologic limitations. First, all analyses were post-hoc. Second, REVERSE included only patients with mild heart failure with a lower mortality rate than more advanced heart failure patients, so the results cannot be extrapolated to such patients. However, a more recent analysis of patients with advanced heart failure showed that stabilized patients have a lower mortality and heart failure hospitalization rate than those who worsen, although responders did better than those who stabilized. Super responders and other endpoints were not evaluated in that study.⁹ Third, group classification was based on echocardiographic measures which may be less reproducible than some other imaging modalities. However, the concordance correlation coefficient in REVERSE was very high (0.90) for LVESVi.²² This analysis focused on the change in LVESV, a measure routinely used in CRT trials and a prospectively powered endpoint of the REVERSE study. However no additional echocardiographic measures (e.g., LVEF) were used. Fourth, the number of events was relatively small, which may have led to inadequate statistical power to show differences in some of the analyses. Although CRT response is noted to be greatest among patients with LBBB, responder groups were under-powered to compare LBBB to non-LBB (data not shown). Finally, enrollment in REVERSE occurred during a time when only bipolar left ventricular leads were available, and techniques were not available to maximize lead position. More recent advances in technology, programming, and medical therapy are likely to improve CRT outcomes.²³⁻²⁵

Conclusion

The study provides further evidence that CRT patients with stabilized disease progression have very low mortality and heart failure hospitalization rates in mild heart failure compared to those who worsen. Thus, they should not be considered non-responders. This was reinforced in a cohort of more advanced heart failure.¹⁵ Stratification of patients into multiple cohorts based on the magnitude of response provides a better estimation of the clinical benefit of CRT. This stratification should also better inform clinical resource allocation, with demand increasing as the magnitude of CRT response decreases. Patients who continue to remodel (or worsen) have poor outcomes and need intensification of care to improve therapy (e.g., repositioning leads, inactivating CRT, and optimizing programming and medical therapy), while clinical resource utilization may be reduced for patients with a maximal reverse remodeling (or super-response). Maximizing the reverse remodeling response is an important goal for heart failure management, as a larger response is associated with improved quality of life, health status, and exercise capacity.

Acknowledgements

The authors thank Randy Crossland, PhD and Dedra Fagan, PhD of Medtronic for assistance in the preparation of this manuscript.

Funding: The REVERSE trial was supported by Medtronic, Inc.

References

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. 2001;344:873-880. <https://doi.org/10.1056/nejm200103223441202>.
2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med*. 2002;346:1845-1853. <https://doi.org/10.1056/NEJMoa013168>.
3. Abraham WT, Young JB, León AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation*. 2004;110:2864-2868. <https://doi.org/10.1161/01.Cir.0000146336.92331.D1>.
4. 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;350:2140-2150. <https://doi.org/10.1056/NEJMoa032423>.
5. 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;352:1539-1549. <https://doi.org/10.1056/NEJMoa050496>.
6. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385-2395. <https://doi.org/10.1056/NEJMoa1009540>.
7. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *Jama*. 2003;289:2685-2694. <https://doi.org/10.1001/jama.289.20.2685>.

8. Mullens W, Auricchio A, Martens P, et al. Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care: A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. *Eur J Heart Fail.* 2020;22:2349-2369. <https://doi.org/10.1002/ejhf.2046>.
9. Chung ES, Gold MR, Abraham WT, et al. The Importance of Early Evaluation after Cardiac Resynchronization Therapy to Redefine Response: Pooled Individual Patient Analysis from Five Prospective Studies. *Heart Rhythm.* 2021. <https://doi.org/10.1016/j.hrthm.2021.11.030>.
10. Gold MR, Rickard J, Daubert JC, Zimmerman P, Linde C. Redefining the Classifications of Response to Cardiac Resynchronization Therapy: Results From the REVERSE Study. *JACC Clin Electrophysiol.* 2021;7:871-880. <https://doi.org/10.1016/j.jacep.2020.11.010>.
11. van Bommel RJ, Bax JJ, Abraham WT, et al. Characteristics of heart failure patients associated with good and poor response to cardiac resynchronization therapy: a PROSPECT (Predictors of Response to CRT) sub-analysis. *Eur Heart J.* 2009;30:2470-2477. <https://doi.org/10.1093/eurheartj/ehp368>.
12. Steffel J, Ruschitzka F. Superresponse to cardiac resynchronization therapy. *Circulation.* 2014;130:87-90. <https://doi.org/10.1161/circulationaha.113.006124>.
13. Linde C, Gold M, Abraham WT, Daubert JC. Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic left ventricular dysfunction with previous symptoms or mild heart failure--the RESynchronization reVERses Remodeling in Systolic left vEntricular

dysfunction (REVERSE) study. *Am Heart J*. 2006;151:288-294.

<https://doi.org/10.1016/j.ahj.2005.03.002>.

14. 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;52:1834-1843.

<https://doi.org/10.1016/j.jacc.2008.08.027>.

15. 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;54:1837-1846. <https://doi.org/10.1016/j.jacc.2009.08.011>.

16. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. *Circulation: Cardiovascular Quality and Outcomes*. 2015;8:469-476. <https://doi.org/doi:10.1161/CIRCOUTCOMES.115.001958>.

17. Gregoratos G, Abrams J, Epstein AE, et al. ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices--summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Am Coll Cardiol*. 2002;40:1703-1719. [https://doi.org/10.1016/s0735-](https://doi.org/10.1016/s0735-1097(02)02528-7)

[1097\(02\)02528-7](https://doi.org/10.1016/s0735-1097(02)02528-7).

18. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Update of the guidelines on sudden cardiac death of the European Society of Cardiology. *Eur Heart J*. 2003;24:13-15. [https://doi.org/10.1016/s0195-0668x\(02\)00809-6](https://doi.org/10.1016/s0195-0668x(02)00809-6).
19. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22:1527-1560. <https://doi.org/10.1053/euhj.2001.2783>.
20. Sohaib SM, Chen Z, Whinnett ZI, et al. Meta-analysis of symptomatic response attributable to the pacing component of cardiac resynchronization therapy. *Eur J Heart Fail*. 2013;15:1419-1428. <https://doi.org/10.1093/eurjhf/hft139>.
21. Thibault B, Ducharme A, Harel F, et al. Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex ≥ 120 milliseconds. *Circulation*. 2011;124:2874-2881. <https://doi.org/10.1161/circulationaha.111.032904>.
22. St John Sutton M, Linde C, Gold MR, et al. Left Ventricular Architecture, Long-Term Reverse Remodeling, and Clinical Outcome in Mild Heart Failure With Cardiac Resynchronization: Results From the REVERSE Trial. *JACC Heart Fail*. 2017;5:169-178. <https://doi.org/10.1016/j.jchf.2016.11.012>.
23. Chun KH, Oh J, Yu HT, et al. The role of sacubitril/valsartan in the management of cardiac resynchronization therapy non-responders: a retrospective analysis. *ESC Heart Fail*. 2020. <https://doi.org/10.1002/ehf2.12988>.
24. Kydd AC, Khan FZ, Watson WD, Pugh PJ, Virdee MS, Dutka DP. Prognostic benefit of optimum left ventricular lead position in cardiac resynchronization therapy: follow-up of the TARGET Study Cohort (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy). *JACC Heart Fail*. 2014;2:205-212. <https://doi.org/10.1016/j.jchf.2013.11.010>.

- 384 25. Singh JP, Cha YM, Lunati M, et al. Real-world behavior of CRT pacing using the
385 AdaptivCRT algorithm on patient outcomes: Effect on mortality and atrial fibrillation
386 incidence. *J Cardiovasc Electrophysiol*. 2020;31:825-833.
387 <https://doi.org/10.1111/jce.14376>.

388 **Tables**389 **Table 1: Baseline Characteristics**

	Super Responder (n=99)	Responder (n=84)	Stabilized (n=81)	Worsened (n=89)	P-value
Age, mean (yrs.)	60.6 ± 11.7	64.1 ± 11.0	62.9 ± 9.2	64.6 ± 9.6	0.02
Male (%)	61.6	72.6	84.0	89.9	<0.0001
Ischemic etiology (%)	37.4	54.8	63.0	74.2	<0.0001
CRT-D (%)	73.7	78.6	93.8	84.3	0.004
NYHA II (%)	80.8	85.7	79.0	79.8	0.68
LBBB	81.6	68.7	51.9	43.2	<0.0001
LVEF (%)	25.8 ± 6.0	27.2 ± 6.7	27.1 ± 6.7	28.8 ± 6.9	0.004
LVESVi (ml/m²)	104.0 ± 34.3	97.1 ± 33.1	100.7 ± 37.0	95.2 ± 34.5	0.14
QRS (ms)	160.3 ± 21.2	153.4 ± 19.8	149.0 ± 18.1	147.0 ± 21.1	<0.0001
Diabetes (%)	17.2	19.1	17.3	33.7	0.02
ACE Inhibitor or ARB (%)	97.0	96.4	93.8	97.8	0.56
Beta-blocker (%)	96.0	95.2	92.6	95.5	0.75
Diuretics (%)	81.8	75.0	80.3	80.9	0.68

Values are presented as mean ± standard deviation or as percentage where appropriate.

CRT-D = cardiac resynchronization therapy with defibrillator; NYHA II = New York Heart Association Class II; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

391 **Table 2: Distribution of all REVERSE patients by LVESV response classification.**

	CRT OFF (n=191)	CRT ON (n=419)	P-value
Super Responder	15 (9.0%)	99 (28.0%)	<0.0001
Responder	21 (12.6%)	84 (23.8%)	
Stabilized	67 (40.1%)	81 (22.9%)	
Worsened	64 (38.3%)	89 (25.2%)	
Missing LVESV at baseline or 6 months	24	66	

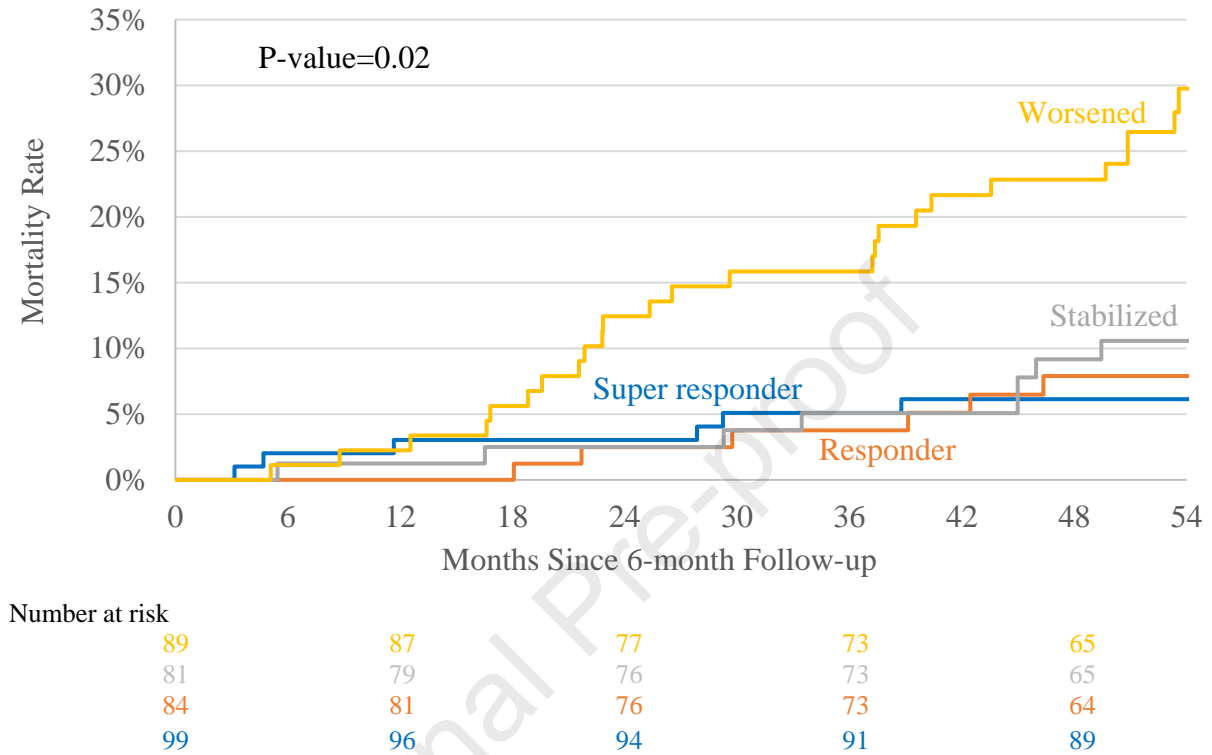
Values are presented as n (percentage).

CRT= Cardiac Resynchronization Therapy; LVESV= left ventricular end-systolic volume

392

Figures

Figure 1: Mortality rate by 6-month LVESV Responder Classification



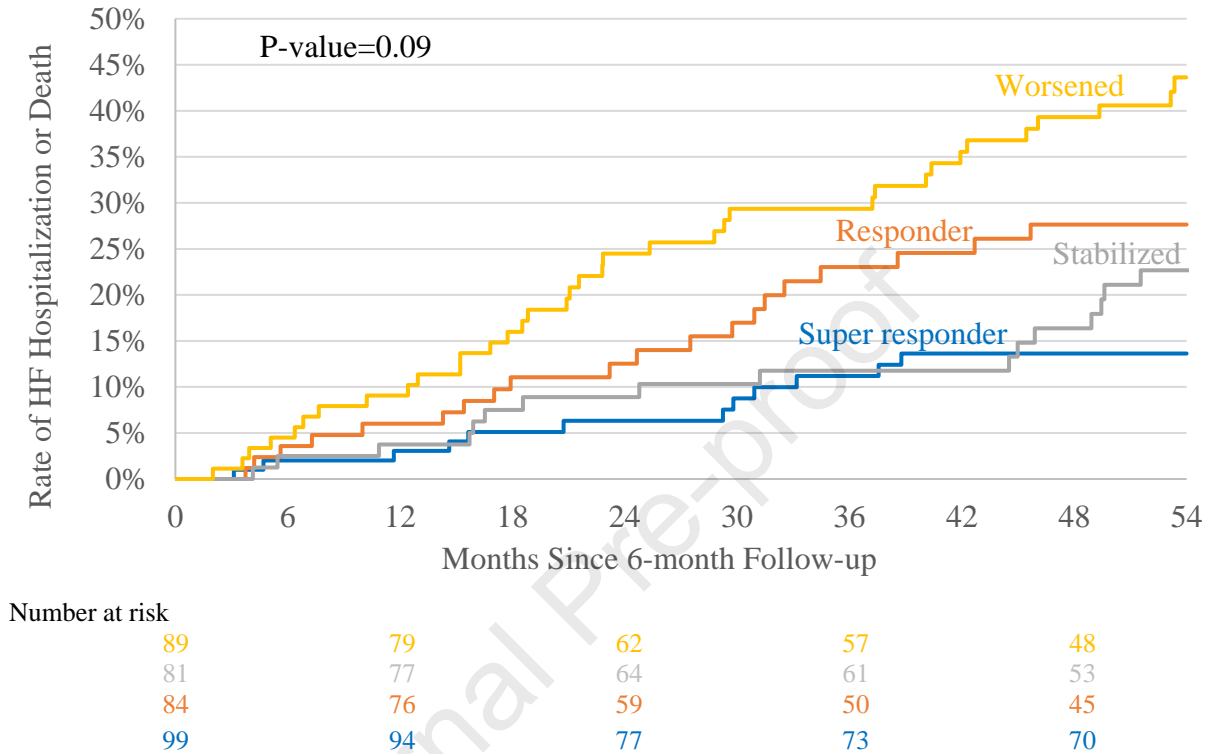
Cox Proportional Hazard Model Covariate Information					
Parameter	Reference value	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age		0.14	1.026	0.992	1.061
Sex	Male	0.02	12.177	1.612	92.004
Ischemic	No	0.60	0.796	0.336	1.886
Device Type	CRT-P	0.11	1.837	0.874	3.861
Morphology	LBBB	0.18	0.604	0.290	1.256
LVEF		0.08	0.959	0.915	1.005
QRS Duration		0.10	0.986	0.969	1.003
Diabetes	No	0.60	1.204	0.605	2.398
LVESV Group	Super	0.04	0.376	0.144	0.977

Cox Proportional Hazard Model Covariate Information					
Parameter	Reference value	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LVESV Group	Responder	0.02	0.334	0.133	0.839
LVESV Group	Stabilized	0.02	0.369	0.163	0.834

396

397 Kaplan-Meier analysis of death occurring after 6 months based on LVESV change from baseline
398 to 6 months. The overall p-value in the graph is adjusted for age, sex, ischemic/non-ischemic,
399 CRT-P/CRT-D, LBBB/non-LBBB, LVEF, QRS duration, and diabetes, and, using a Cox model,
400 tests whether LVESV group affects mortality. Covariate information from the Cox model is
401 shown beneath the graph.

Figure 2: Rate of Heart Failure Hospitalization or Mortality by 6-month LVESV Responder Classification



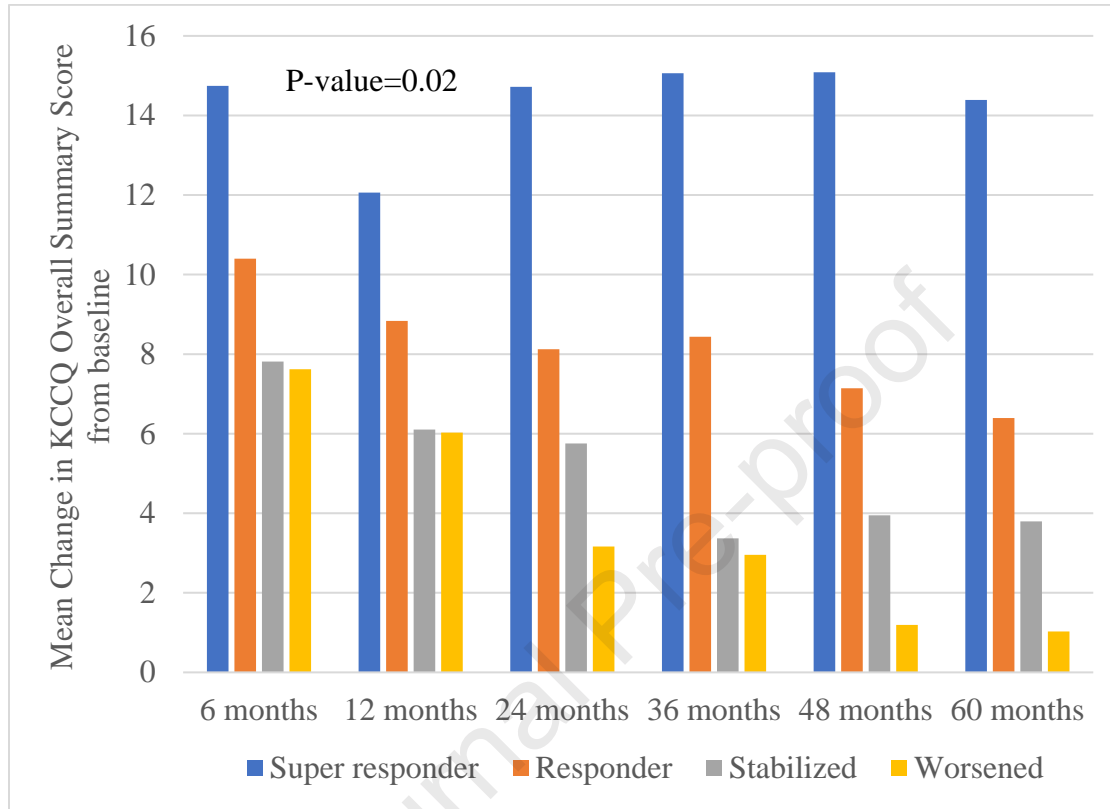
Cox Proportional Hazard Model Covariate Information					
Parameter	Reference value	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age		0.52	1.008	0.984	1.032
Sex	Male	0.10	1.833	0.895	3.756
Ischemic	No	0.34	0.733	0.389	1.381
Device Type	CRT-P	0.35	1.318	0.743	2.337
Morphology	LB BB	0.006	0.463	0.267	0.803
LVEF		0.007	0.953	0.920	0.987
QRS Duration		0.04	0.987	0.974	1.000
Diabetes	No	0.35	0.793	0.489	1.287
LVESV Group	Super	0.07	0.532	0.266	1.066

Cox Proportional Hazard Model Covariate Information					
Parameter	Reference value	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
LVESV Group	Responder	0.68	0.883	0.491	1.586
LVESV Group	Stabilized	0.03	0.515	0.279	0.949

Kaplan-Meier analysis of time to first heart failure hospitalization or all-cause death occurring after 6 months based on LVESV change from baseline to 6 months. The overall p-value in the graph is adjusted for age, sex, ischemic/non-ischemic, CRT-P/CRT-D, LBBB/non-LBBB, LVEF, QRS duration, and diabetes, and, using a Cox model, tests whether the LVESV responder group affects HF hospitalization + all-cause death. Covariate information from the Cox model is shown beneath the graph.

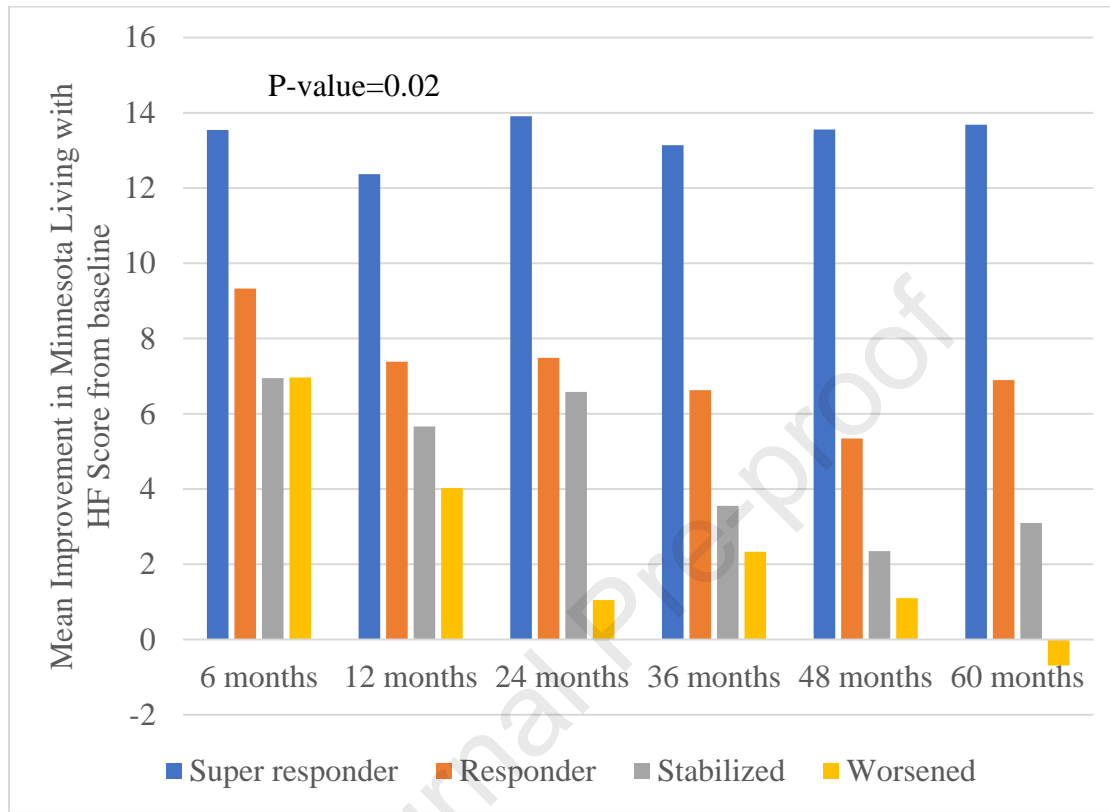
Figure 3: Change in KCCQ overall summary scores by 6-month LVESV Responder

Classification



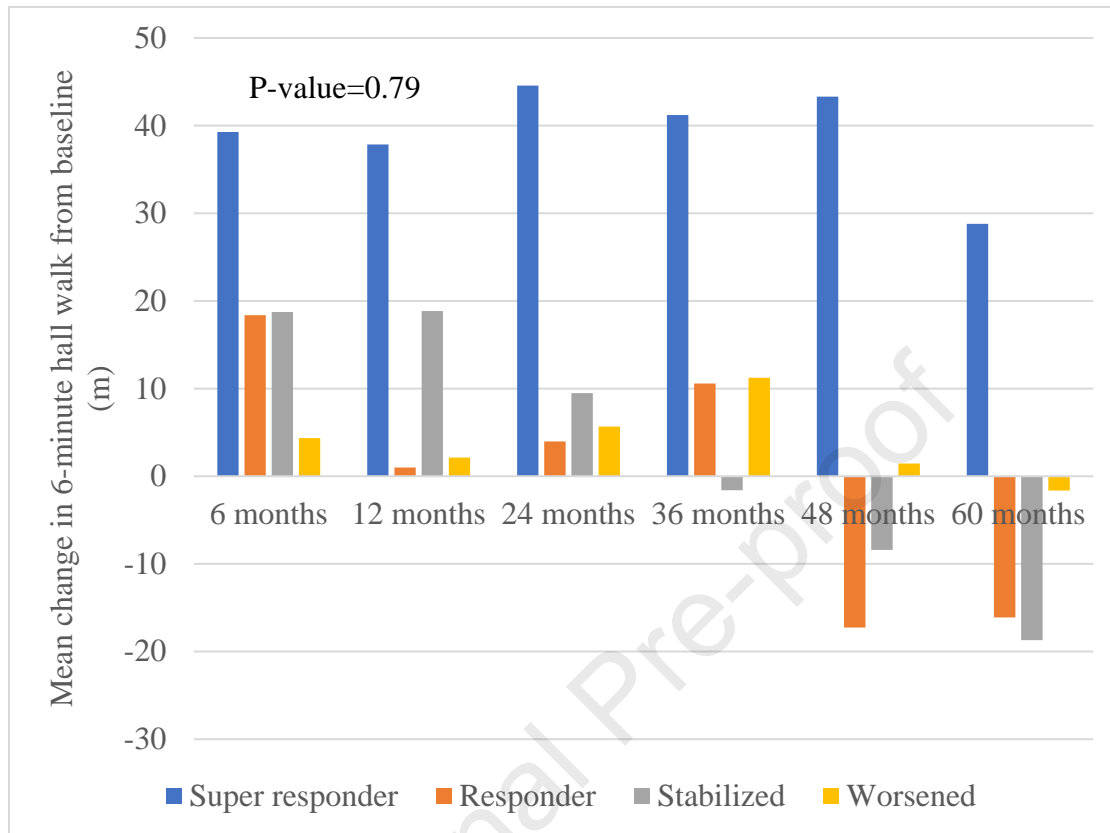
The p-value is the interaction between LVESV group and time in a repeated measures analysis adjusted for age, sex, ischemic/non-ischemic, CRT-P/CRT-D, LBBB/non-LBBB, LVEF, QRS duration, and diabetes.

Figure 4: Change in Minnesota Living with Heart Failure scores by 6-month LVESV Responder Classification

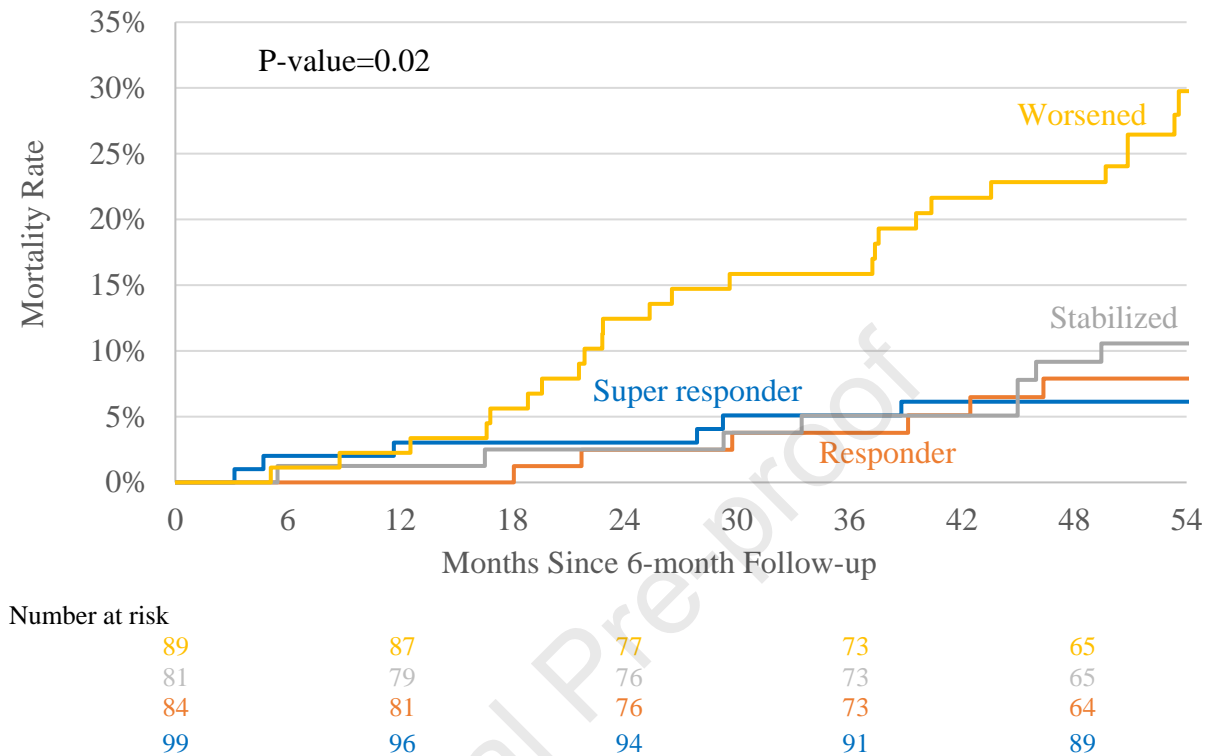


The p-value is the interaction between LVESV group and time in a repeated measures analysis adjusted for age, sex, ischemic/non-ischemic, CRT-P/CRT-D, LBBB/non-LBBB, LVEF, QRS duration, and diabetes.

Figure 5: Change in 6MWT results by 6-month LVESV Responder Classification



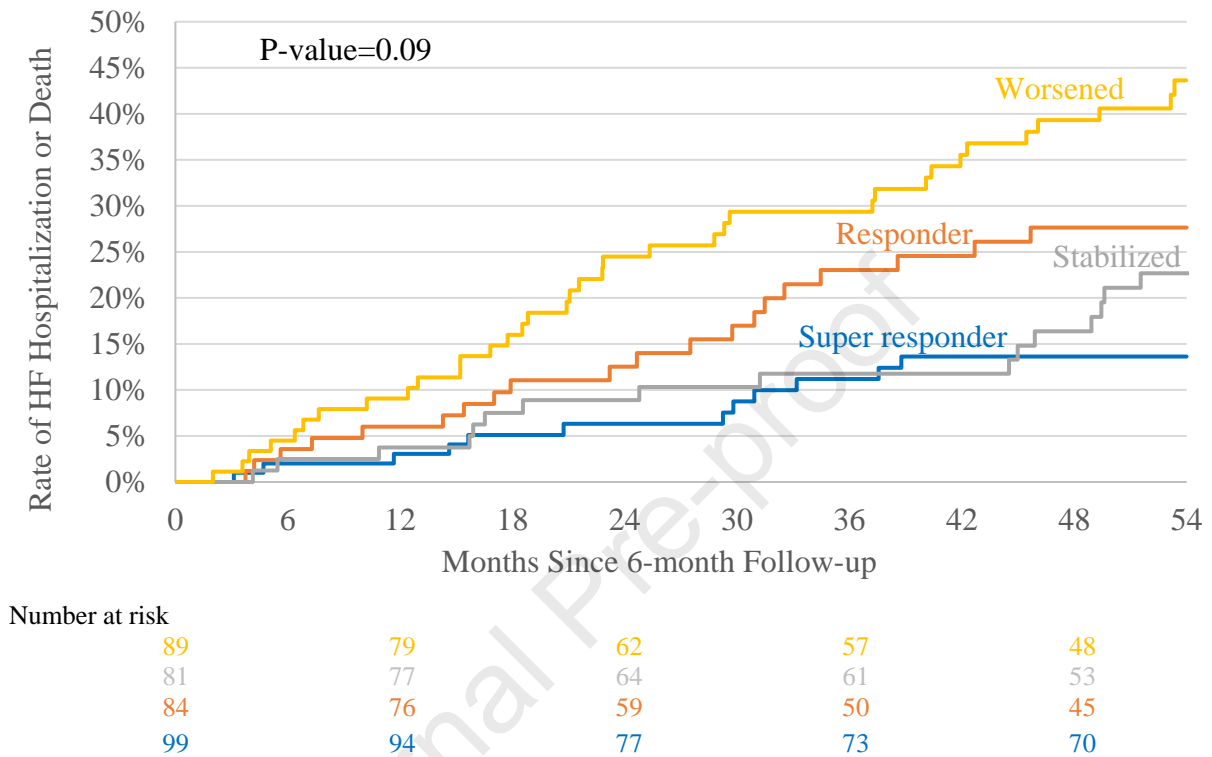
The p-value is the interaction between LVESV group and time in a repeated measures analysis adjusted for age, sex, ischemic/non-ischemic, CRT-P/CRT-D, LBBB/non-LBBB, LVEF, QRS duration, and diabetes.

Figure 1: Mortality rate by 6-month LVESV Responder Classification

Cox Proportional Hazard Model Covariate Information					
Parameter	Reference value	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age		0.14	1.026	0.992	1.061
Sex	Male	0.02	12.177	1.612	92.004
Ischemic	No	0.60	0.796	0.336	1.886
Device Type	CRT-P	0.11	1.837	0.874	3.861
Morphology	LBBB	0.18	0.604	0.290	1.256
LVEF		0.08	0.959	0.915	1.005
QRS Duration		0.10	0.986	0.969	1.003
Diabetes	No	0.60	1.204	0.605	2.398
LVESV Group	Super	0.04	0.376	0.144	0.977
LVESV Group	Responder	0.02	0.334	0.133	0.839
LVESV Group	Stabilized	0.02	0.369	0.163	0.834

Figure 2: Rate of Heart Failure Hospitalization or Mortality by 6-month LVESV Responder

Classification



Cox Proportional Hazard Model Covariate Information					
Parameter	Reference value	P-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age		0.52	1.008	0.984	1.032
Sex	Male	0.10	1.833	0.895	3.756
Ischemic	No	0.34	0.733	0.389	1.381
Device Type	CRT-P	0.35	1.318	0.743	2.337
Morphology	LBBB	0.006	0.463	0.267	0.803
LVEF		0.007	0.953	0.920	0.987
QRS Duration		0.04	0.987	0.974	1.000
Diabetes	No	0.35	0.793	0.489	1.287
LVESV Group	Super	0.07	0.532	0.266	1.066
LVESV Group	Responder	0.68	0.883	0.491	1.586
LVESV Group	Stabilized	0.03	0.515	0.279	0.949

Journal Pre-proof

Figure 3: Change in KCCQ overall summary scores by 6-month LVESV Responder

Classification

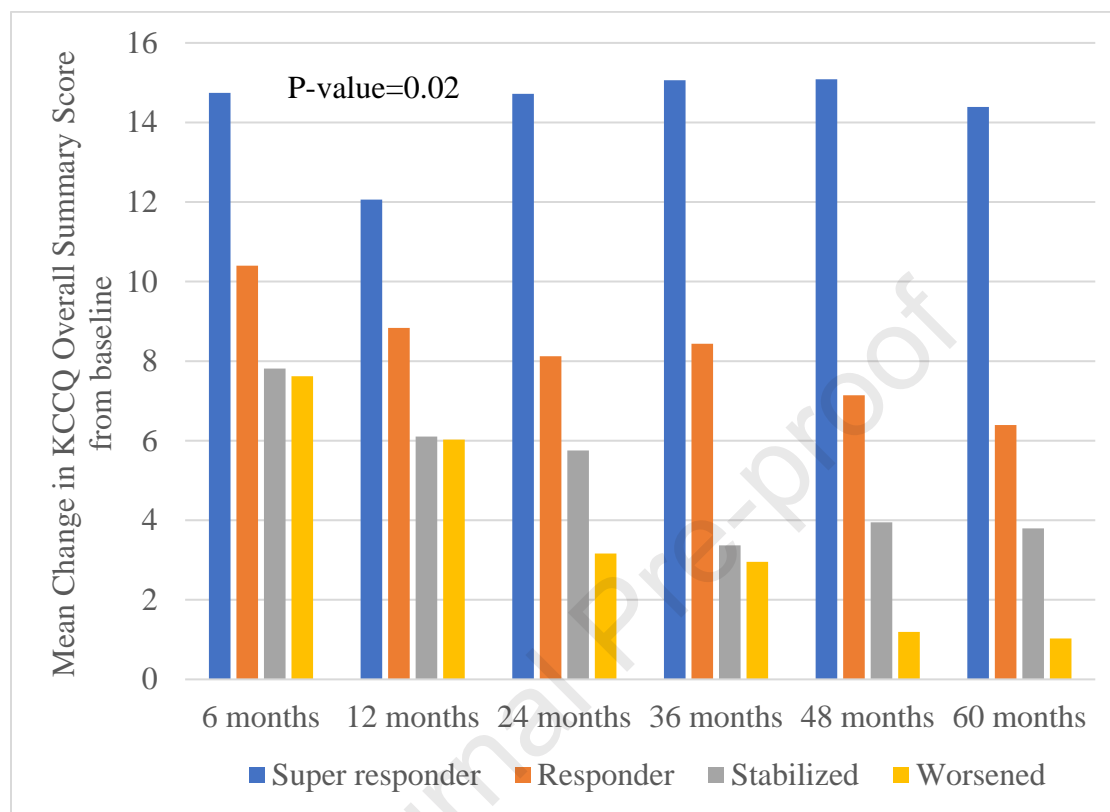


Figure 4: Change in Minnesota Living with Heart Failure scores by 6-month LVESV Responder Classification

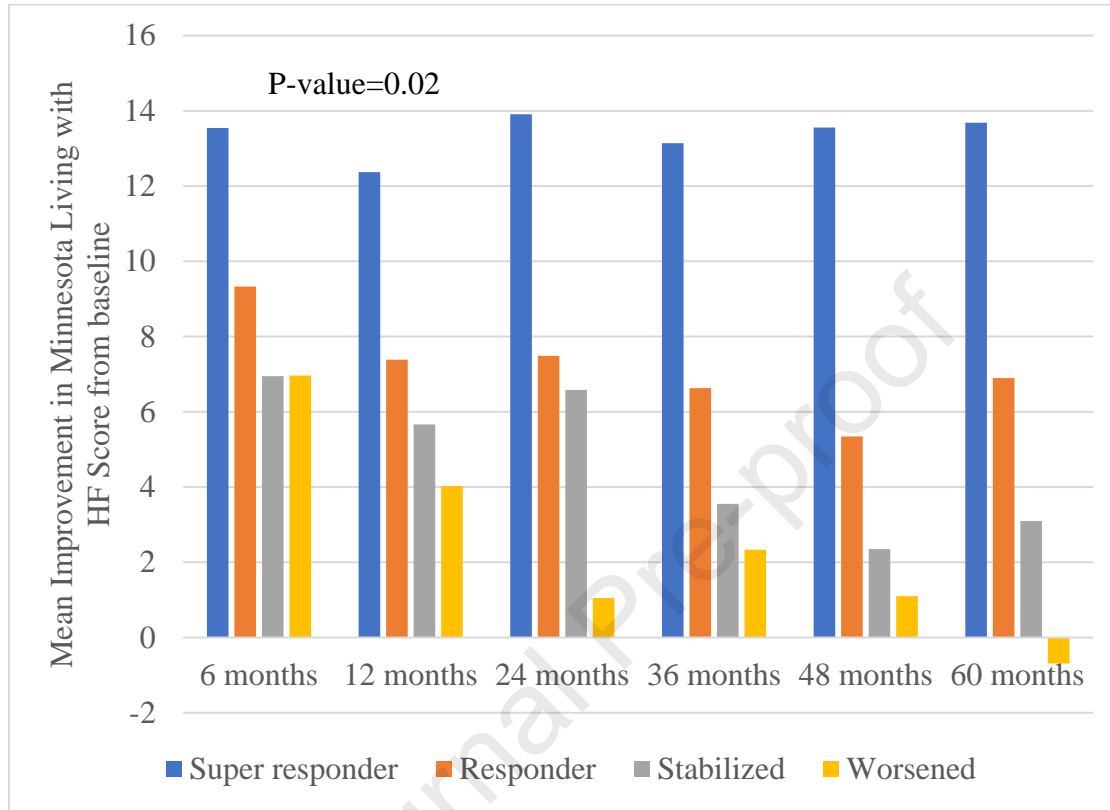


Figure 5: Change in 6MWT results by 6-month LVESV Responder Classification