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The Impact of Reverse Remodeling on Long Term Survival in Mildly Symptomatic Heart Failure Patients Receiving Cardiac Resynchronization Therapy: Results from the REVERSE study

Running Title: Remodeling and Survival with CRT in Mild HF

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Abstract

Background: Cardiac resynchronization therapy (CRT) decreases mortality, improves functional status and induces reverse left ventricular (LV) remodeling in selected populations with heart failure (HF). The magnitude of reverse remodeling predicts survival with many HF medical therapies. However, there are little data assessing the impact of remodeling on long term survival with CRT.

Objective: To assess the impact of CRT induced reverse remodeling on long term survival in mild HF.

Methods: REVERSE was a multi-center, double-blind, randomized trial of CRT among patients with mild HF. Long-term follow-up for 5 years was pre-planned. The present analysis was confined to the 353 patients who were randomized to CRT ON with paired echocardiographic studies at baseline and 6 months post-implant. Left ventricular end systolic volume index

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(LVESVi) was measured by a core laboratory and was an independently powered endpoint of REVERSE.

Results: A 68% reduction in mortality was observed among patients with ≥15% decrease in LVESVi compared to the rest of the patients (p=0.0004). Multivariable analysis showed that the change in LVESVi was a strong independent predictor (p=0.0002) with a 14% reduction of mortality for every 10% decrease of LVESVi. Other remodeling parameters, including left ventricular end diastolic volume index and ejection fraction showed a similar relationship with mortality.

Conclusion: Change in left ventricular end systolic volume over 6 months of CRT is a strong independent predictor of long term survival in mild HF.

Clinical Trial Registration: URL: http://clinicaltrials.gov/ct2/show/NCT00271154. Unique identifier: NCT00271154.

Key Words: Cardiac Resynchronization Therapy, Heart Failure, ICD, Defibrillator, Remodeling

Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; CCS = clinical composite score; CRT = cardiac resynchronization therapy; EF = ejection fraction; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LV = left ventricle; LVEDD = left ventricular end-diastolic dimension; LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index; NYHA = New York Heart Association.

Introduction

Cardiac resynchronization therapy (CRT) improves functional status and cardiac function and decreases heart failure (HF) hospitalizations and mortality among HF patients with left

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ventricular systolic dysfunction and QRS prolongation[1-8]. Initially, CRT was applied to patients with advanced HF, but more recent studies have shown similar benefit among patients with milder HF[9-11]. The reverse remodeling response, as measured by left ventricular volumetric changes, has important prognostic significance in pharmacologic studies of HF, including randomized studies of angiotensin converting enzyme (ACE) inhibitors[12,13], angiotensin receptor blockers (ARB)[14], beta blockers[15,16], and with ivabradine[17]. There are many other studies in support of the beneficial action of pharmacologic agents to induce reverse remodeling in HF[18]. With regard to CRT, randomized trials showed that reverse remodeling predicts clinical outcomes and arrhythmia events[19,20]. However, the long-term impact of remodeling on mortality is less well-studied. Accordingly, the present analysis was designed to evaluate changes in left ventricular volume on all-cause mortality in the preplanned 5 year follow-up of the REVERSE Study.

Methods

The design and primary results of the REVERSE trial were published previously[9,21,22]. Briefly, eligible patients had American College of Cardiology/American Heart Association Stage C, New York Heart Association (NYHA) Class I (previously symptomatic, currently asymptomatic) or NYHA Class II (mildly symptomatic). Patients were required to be in sinus rhythm with QRS duration ≥120 ms, a left ventricular ejection fraction (EF) ≤40%, and a left ventricular end-diastolic dimension (LVEDD) ≥55 mm.[24]. The Ethics Committee of each center approved the study protocol, and all patients gave written informed consent.

Patients were enrolled between September, 2004 and September, 2006. All patients underwent implantation of a CRT system (device and leads), with or without implantable cardioverter defibrillator (ICD) capabilities, based on standard clinical criteria. Patients who had

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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 primary endpoint of REVERSE was the clinical composite score (CCS) measured at 12 months[21,25]. Following the randomization period, CRT was programmed ON in all patients through 5 years post-implant to assess the long-term impact of this therapy.

Echocardiograms were obtained at baseline (prior to implant) and after 6 months of randomization with CRT turned off temporarily. Data were analyzed in one of two core laboratories (Philadelphia, USA and Pavia, Italy) blinded to clinical data. LV dimensions were recorded with 2D-directed M-mode echocardiography at the tips of the mitral valve leaflets. Echocardiograms were digitized to obtain LV volumes by Simpson's method of discs, as recommended by the American Society of Echocardiography[26], from which LVEF was calculated. Change in LV end-systolic volume, indexed by body surface area (LVESVi), was the pre-defined and independently powered secondary endpoint of REVERSE. Additional echocardiographic measures included LV end-diastolic volume index (LVEDVi) and EF. Further details of the echocardiographic protocol have been published previously[21].

Patients were actively 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 each death was adjudicated by an independent adverse events adjudication committee to classify the cause of death by standard criteria.

For the initial analysis of the effect of LVESVi change on mortality, patients were divided into two groups using the commonly used cutoff of a 15% decrease of volume that was prespecified in REVERSE[19,21]. Subsequent analyses separated the changes into quartiles or

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treated LVESVi change as a continuous variable to allow more detailed assessment of the response.

Data Analysis

Continuous variables are summarized with mean and standard deviation; categorical variables with counts and percentages. Time to event analyses used Kaplan-Meier estimates and the log-rank test. Cox proportional hazards regression was used to compute hazard ratios (HR) and assess influence of covariates. Time 0 in these analyses was the date of the 6-month follow-up visit. Subjects were censored using the date of the latest case report form. The covariate analysis of LVESVi (treated as a continuous variable) was performed using Cox proportional hazards methods. A p-value <0.05 was considered statistically significant and p-values were not adjusted for multiple comparisons.

Results

Patient Population

Of the 610 patients in REVERSE, 419 were randomized to CRT ON. In this group, 66 subjects were not included in the present analysis for the following reasons: six subjects died prior to their 6-month follow-up, 3 subjects missed their 6-month follow-up, and 57 subjects had inadequate echocardiograms for adequate LVESVi measurement at baseline (23), 6 months (24), or both (8). Thus, there were 353 patients included in the present study. Of note, there were no statistically significant differences ($p<0.05$) in baseline characteristics between the included and excluded subjects. The 353 patients averaged 4.6 years of implanted follow-up time.

Baseline characteristics of the patient population are presented in Table 1. This was a typical population of mild HF patients receiving CRT. They were predominately late middle age men

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with a majority having ischemic heart disease and an underlying left bundle branch block on the unpaced ECG.

Reverse Remodeling

The echocardiographic measures of reverse remodeling were assessed after 6 months of CRT. LVESVi decreased by an average of 14.9 ± 27.5 ml/m^2, LVEDVi decreased 15.8 ± 32.4 ml/m^2, and the EF increased 3.6 ± 8.3% in this cohort. As shown previously, all of these changes were highly significant compared with the unpaced CRT OFF group[9]. The pre-specified remodeling endpoint in this study was a reduction of LVESVi. A reduction of at least 15% was reached by 183 (52%) subjects. There were some important clinical differences between subjects with a > 15% change in LVESVi and those who did not reach this endpoint; these results are shown in Table 1. Those patients with significant remodeling were more likely to be female, have non-ischemic cardiomyopathy, and have a typical left bundle branch block (LBBB). In addition, the unpaced QRS duration was longer.

Survival with CRT

The REVERSE cohort was followed for 5 years as a pre-planned extension phase of the randomized portion of the trial[27]. Such long-term follow-up allows for the assessment of mortality, which was low as expected over the first 1-2 years in patients with mild heart failure[9-11]. The mortality curves for the subgroups with and without significant reductions in LVESVi are presented in Figure 1. The curves begin to separate about 15 months after the 6-month follow-up, and they continue to be separate over the full duration of follow-up. The Hazard Ratio is 0.32 (p=0.0004) indicating a 68% lower mortality rate in subjects who achieved the remodeling endpoint (> 15% reduction in LVESVi). It is noteworthy that the estimated long-term mortality was very low (6.9%) in the subgroup with significant remodeling despite severe

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systolic dysfunction and QRS prolongation at baseline. Table 2 lists the adjudicated causes of death within the two groups. The subgroup achieving the remodeling endpoint had a lower rate of death in all categories, including sudden and non-sudden cardiac death.

Although a decrease of LVESVi > 15% is commonly used to define an echocardiographic remodeling response to CRT, this arbitrary cutoff could affect the results. Therefore, the response was subdivided in quartiles to evaluate the effect on remodeling more accurately. The largest remodeling response (quartile 4) was a > 32.1% reduction of LVESVi, whereas patients with an increase of LVESVi despite CRT constituted quartile 1. These results are shown in Figure 2. There was again a very significant effect of change of LVESVi on mortality ($p<0.0001$) with the lowest mortality among subjects with the largest reduction and a very high mortality among subjects with an increase in LV volume at 6 months.

Current guidelines strongly recommend CRT in mild heart failure only for patients with LBBB[28]\; accordingly, the analysis was repeated in subgroups based on QRS morphology. These results are presented separately in Figure 3 for the LBBB (n=217) and non-LBBB (n=133) cohorts. The p-values within both groups were significant indicating that change in LVESVi is a significant factor in predicting future mortality in both LBBB and non-LBBB patients.

As noted previously, there were some important clinical differences between the subjects in the different remodeling subgroups, so a multi-variable analysis was performed. For this analysis, the change in LVESVi was treated as a continuous variable. These results are shown in Table 3. After adjusting for important covariates, remodeling was a strong independent predictor ($p=0.0002$) with a 14% reduction of mortality for every 10% decrease of LVESVi. The other significant predictors of mortality were baseline LVESVi, QRS duration, device type (CRT-D or

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CRT-P), and sex with better survival in subjects with smaller left ventricular volume, longer QRS duration, CRT-D recipients, and women.

Analyses were also performed with other remodeling parameters. The results for LVEDVi are shown in Panel A of Figure 4 and they are strikingly similar to the results for LVESVi. The survival curves grouped by changes in LVEF are shown in Panel B. Again, there is a strong relationship between the magnitude of change of EF and long-term mortality with CRT.

Discussion

The primary result of the present analysis is that the change in LVESVi with CRT was a strong independent predictor of long-term mortality in mild HF. Specifically, among subjects with a > 15% reduction of LVESVi after 6-months of CRT, all-cause mortality was 1.6% annually. This was a 68% lower mortality relative with the rest of the cohort. A more detailed analysis of response identified a very high risk cohort with further LV dilation with CRT, which constituted about 25% of the population. Mortality was more than 4-fold greater in this subgroup (29.8% vs 6.9% for > 15% reduction of LVESVi). Finally, the magnitude of other echocardiographic measures of remodeling (LVEDVi and EF) also showed strong relationships with long term survival.

The impact of LV volumetric changes on mortality has been assessed previously in both pharmacologic and CRT studies. In SOLVD Treatment, subjects receiving enalapril had a mean 12.3% reduction in LVESVi. Correspondingly, those patients in the active drug arm had a 16% relative risk reduction in mortality[19,29]. Other studies of ACE inhibitors or ARBs have consistently shown the important prognostic value of echocardiographic volumetric changes on long term outcomes and survival[14,18]. Studies of carvedilol have also shown an association

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between reverse remodeling and reduced mortality[15,16]. Similar findings were shown with ivabradine therapy among patients already on betablocker therapy[17]. Interestingly, an increase in mortality has been observed in pharmacologic treatment that increases LV volumes. This was shown in the ibopamine trial[25]. These findings are supported further by a recent meta-analysis comprising 30 mortality studies, 25 drug/device therapies and 88 remodeling trials of these therapies in HF patients. Short term LV remodeling was associated with lower mortality[18] with more pronounced mortality effects among patients with greater reductions in LV volumes.

CRT and betablockers are linked to the greatest magnitude of left ventricular reverse remodeling compared to other heart failure drug therapies[18]. More than 95% of patients in more recent randomized clinical trials of CRT have been on betablockers[10-12]. Reverse remodeling by beta blockade is dependent on dose[15]. In REVERSE, 60% were on at least 50% of guideline-indicated dose and 30% on target dose[31]. As CRT can be used as further therapy in addition to beta blockade, this combination may be the most potent in terms of reverse remodeling which is reflected in our results. To our knowledge, REVERSE is the first study to show that reverse remodeling by a non-pharmacological HF therapy is an independent predictor of long term survival.

With regard to previous studies of CRT, several studies demonstrated a relationship between remodeling and composite endpoints including survival. Ypenburg et al[26] reported a relationship between the extent of LV volume changes and mortality and heart failure hospitalizations. Similarly, Yu et al[27] showed that a reduction in LVESV of 10% significantly lowers the risk of mortality and heart failure events. Finally, analysis of the MADIT CRT study showed a reduction of the composite endpoint of HF hospitalization and survival in both the CRT and ICD groups[29]. The present results suggest that large reductions of LVESVi are associated with

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decreases of both non-sudden and sudden death. The impact of reverse remodeling on HF mortality is not surprising given the associations of remodeling with reductions of HF hospitalization noted above. LV volumetric changes have also been shown to decrease ventricular arrhythmia in both the REVERSE[19] and MADIT CRT[35] studies, so again it follows that a reduction of sudden death may be expected long term. There was also an apparent decrease in non-cardiac death. Whether this was due to the identification of a sicker subgroup of patients more prone to die from the sequela of HF, such as renal failure or infection, or to mortality classification difficulties cannot be determined from these results.

The impact of reverse remodeling on long term mortality was noted for the non-LBBB subgroups. This is particularly interesting, as current guidelines do not recommend CRT for these patients with mild HF on the results of large randomized trials[10,11]. The remodeling response is much smaller in non-LBBB subjects[36-38], which is consistent with poorer outcomes. However, the present results indicate improved survival in those subjects who have a significant decrease in LVESVi with CRT. Further study is needed to assess if there are predictors of a good remodeling response in the non-LBBB cohort who may benefit from CRT.

There are several clinical implications of these data. First, the present findings confirm that echocardiographic measures of remodeling are an important endpoint for CRT response. Such responses at 6 months are a strong predictor of mortality, so this should be considered as an endpoint for studies designed to optimize CRT, as it would save considerable sample size and time over studies using mortality as an endpoint. Second is the observation that further LV dilation despite CRT is a very poor prognostic sign with a high mortality. These patients should be considered for intervention including alternative advanced heart failure therapy optimization of programming parameters, lead repositioning or even discontinuation of CRT. Finally, the

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clinical predictors of long term mortality with CRT are very similar to the predictors of clinical response in mild HF[9-11,35-37]. Specifically, in addition to the change of LVESVi, women, increased unpaced QRS duration, CRT-D devices, and smaller LV volumes were associated with lower mortality. CRT-D had been previously shown to be associated with reduced mortality[39], while the other factors were shown to be associated with reduced HF hospitalizations[9-11].

This study should be interpreted in the face of several methodological limitations. The REVERSE study was double-blinded only during the randomized phase including the echocardiographic assessment. It is conceivable that this affected treatment at different phases of the study. In addition, titration of medications was discouraged during the randomized phase and this may affect long-term outcome. Finally, this study only evaluated subjects with mild HF.

Conclusions

In summary, in the long-term follow-up of REVERSE patients with CRT, reverse remodeling, as defined as a > 15% reduction of LVESVi was associated with a 68% mortality reduction. Analysis adjusting for baseline covariates showed a 14% reduction in mortality for every 10% change in LVESVi. Finally, the subgroup of patients who continue to remodel despite CRT (LVESVi increases) have a markedly increased mortality.

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References

1. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing

ACCEPTED MANUSCRIPT

in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-880.

2. Abraham WT, Fisher WG, Smith AL, et al. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
3. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;40:111-118.
4. Higgins SL, Hummel JD, Niazi IK, Giudici MC, Worley SJ, Saxon LA, Boehmer JP, Higginbotham MB, De Marco T, Foster E, Yong PG. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;42:1454-1459.
5. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, Canby RC, Schroeder JS, Liem LB, Hall S, Wheelan K; Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003; 289:2685-2694.
6. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.

Accepted manuscript

7. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.

8. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;27:1928-1932.

9. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52:1834-1843.

10. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-1338.

11. 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.

12. Konstam MA, Kronenberg MW, Rousseau MF, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinen D. Effects of the angiotensin converting enzyme inhibitor, enalapril, on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. *Circulation* 1993;88:2277-83.

Accepted manuscript

13. Konstam MA, Patten RD, Thomas I, et al. Effects of losartan and captopril on left ventricular volumes in elderly patients with heart failure: results of the ELITE ventricular function substudy. *Am Heart J* 2000;139:1081-7.

14. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Randomised trial of losartan versus captopril on mortality in patients with symptomatic heart failure: the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; 355:1582-7.

15. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA investigators. *Circulation* 1996;94:2807-2816.

16. Colucci WS, Kolias TJ, Adams KF, Armstrong WF, Ghali JK, Gottlieb SS, Greenberg B, Klibaner MI, Kukin ML, Sugg JE; REVERT Study Group. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. *Circulation* 2007;116:49-56.

17. Tardif JC, O´Meara EO, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Swedberg K; SHIFT Investigators. Effects of selective heart rate reduction with ivabradine on left ventricular remodeling and function: results from the SHIFT echocardiography substudy. *Eur Heart J* 2011;32:2507-2515.

18. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug and device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2010;56:392-406.

Accepted manuscript

19. Gold MR, Linde C, Abraham WT, Gardiwal A, Daubert JC. The impact of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in mild heart failure. *Heart Rhythm* 2011;8:679-684.

20. Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, Foster E, Huang DT, Klein HU, Zareba W, Eldar M, Goldenberg I. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2011;57:2416-23.

21. Linde C, Gold M, Abraham WT, Daubert JC, for the REVERSE Study Group. 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.

22. Daubert JC, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Török T, Linde C; REVERSE Study Group. 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 REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial. *J Am Coll Cardiol* 2009;54:1837-1846.

23. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL. 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

Accepted manuscript

Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *J Am Coll Cardiol* 2002;40:1703-1719.

24. 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.
25. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;7:176-182.
26. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
27. Linde C, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, Daubert C; REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of Cardiac Resynchronization Therapy in mild heart failure: Five year Results from the REsynchronization reverses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Eur Heart J* 2013;34:2592-9.
28. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2013;61(3):e6-75.
29. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991:325:293-302.

Accepted manuscript

30. Packer, Milton MD, Califf, Krum H, McMurray JJ, Rouleau JL, Swedberg K. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002;106:920-926.

31. Linde CM, Gold M, Abraham WT, Daubert JC, on behalf of the REVERSE Study Group. Baseline characteristics of patients randomised in REsynchronization reverses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Congest Heart Fail* 2008;14:66-74.

32. Rousseau MF, Konstam MA, Benedict CR, Donckier J, Galanti L, Melin J, Kinan D, Ahn S, Ketelslegers JM, Pouleur H. Progression of left ventricular dysfunction secondary to coronary artery disease, sustained neurohormonal activation and effects of ibopamine therapy during long-term therapy with angiotensin-converting enzyme inhibitor. *Am J Cardiol* 1994;73:488-93.

33. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;53:483-90.

34. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;112:1580-6.

35. Solomon SD, Foster E, Bourgoun M, Shah A, Viloria E, Brown MW, Hall WJ, Pfeffer MA, Moss AJ; MADIT-CRT Investigators. Effect of cardiac resynchronization therapy on reverse remodeling and relation to outcome: multicenter automatic defibrillator implantation trial: cardiac resynchronization therapy. *Circulation* 2010;122:985-92.

Accepted manuscript

36. Sutton MSJ, Ghio S, Plappert T, Tavazzi L, Scelsi L, Daubert C, Abraham WT, Gold MR, Hassager C, Herre JM, Linde C; REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) Study Group. Cardiac resynchronization induces major structural and functional reverse remodeling in patients with New York heart association class I/II heart failure. *Circulation* 2009;120:1858-1865.

37. Goldenberg I, Moss AJ, Hall W, et al. Predictors of Response to Cardiac Resynchronization Therapy in the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;124:1527-36.

38. Gold MR, Thebault C, Linde C, Abraham WT, Gerritse B, Ghio S, St John Sutton M, Daubert JC. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure. Results from the resynchronization reverses remodeling in systolic left ventricular dysfunction (REVERSE) study. *Circulation* 2012;126:822-829.

39. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, Cerkvenik J, Linde C. Implantable Defibrillators Improve Survival in Patients With Mildly Symptomatic Heart Failure Receiving Cardiac Resynchronization Therapy: Analysis of the Long-Term Follow-Up of Remodeling in Systolic Left Ventricular Dysfunction (REVERSE). *Circ Arrhythm Electrophysiol*. 2013;6(6):1163-1168.

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Clinical Perspective

Pharmacologic therapies for systolic heart failure (HF) that are associated with reverse left ventricular remodeling produce a mortality benefit. In the present study, the long term effect of reverse remodeling on mortality with cardiac resynchronization therapy (CRT) was assessed. A 15% or greater reduction of LVESVi, which is the standard measure of remodeling with CRT, was associated with a 68% all-cause mortality reduction. Similar results were observed with other remodeling parameters, including a reduction of LVEDVi or an increase of ejection fraction. Equally important, the subgroup of patients who continue to remodel despite CRT have a markedly increased mortality. These findings indicate that reverse remodeling should be a goal of CRT therapy and is an appropriate short term (6 months) endpoint for interventions to optimize this treatment. Such interventions include physiologic measures to optimize LV lead position or programmed pacing parameters. However, continued LV dilation with CRT is a marker of a poor prognosis and warrants aggressive treatment, such as alternative HF therapies or considering inhibiting CRT.

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Tables

Table 1. Baseline Patient Characteristics

	LVESVi Change at 6 Months			
	Increased or decreased <15% (n=170)	**Decreased ≥15% (n=183)**	**All Patients (n=353)**	**p-value**
Age, mean (yrs)	63.8 ± 9.4	62.2 ± 11.5	63.0 ± 10.6	0.15
Male (%)	87.1	66.7	76.5	<0.0001
Ischemic etiology (%)	68.8	45.4	56.7	<0.0001
CRT-D (%)	88.8	76.0	82.2	0.002
NYHA II (%)	79.4	83.1	81.3	0.41
LBBB	47.3	75.7	62.0	
RBBB	14.2	3.3	8.6	<0.0001
IVCD	38.5	21.0	29.4	
LVEF (%)	26.4 ± 7.3	27.2 ± 6.7	26.8 ± 7.0	0.26
LVESVi (ml/m^2)	97.9 ± 35.7	100.8 ± 33.9	99.4 ± 34.7	0.42
QRS (ms)	148 ± 20	157 ± 21	153 ± 20	<0.0001
Diabetes (%)	25.9	18.0	21.8	0.09
ACE Inhibitor or ARB (%)	95.9	96.7	96.3	0.78
Beta-blocker (%)	94.1	95.6	94.9	0.63
Diuretics (%)	80.6	78.7	79.6	0.69

Continuous variables are represented by mean ± standard deviation. Student's t-test or Fisher's exact test are used to test for statistical significance between groups in the first 2 columns. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CRT-D, cardiac resynchronization therapy with implantable defibrillators; CRT-P, CRTpacemakers; LBBB, left bundle–branch block; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; NYHA, New York Heart Association; and RBBB, right bundle–branch block.

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Table 2. Causes of Death

			Increased or decreased <15% (n=170)	Decreased ≥15% (n=183)
Cardiac	Sudden		6 (3.5%)	1 (0.5%)
	Non-sudden	Heart failure	9 (5.3%)	5 (2.7%)
		Non-HF	0 (0.0%)	1 (0.5%)
Non-cardiac			16 (9.4%)	5 (2.7%)
Unknown			2 (1.2%)	0 (0.0%)
Total			33 (19.4%)	12 (6.6%)

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Table 3 Multi-variable Analysis of Mortality >6 Months after CRT

Parameter	Comparison	Hazard Ratio	95% CI	P-value
% Change in LVESVi over 6 Months	Per 10%	0.86	0.79-0.93	0.0002
Age	Per 10 years	1.33	0.94-1.87	0.11
Sex	Female vs Male	0.09	0.01-0.65	0.02
Ischemic	Ischemic vs Non-ischemic	1.53	0.65-3.60	0.33
Baseline LVESVi	Per 10 ml/m^2	1.16	1.07-1.26	0.0003
Baseline QRS Duration	Per 10 ms	0.83	0.70-0.99	0.04
LBBB	LBBB vs Non-LBBB	0.56	0.28-1.15	0.11
Baseline NYHA	Class I vs Class II	0.71	0.32-1.54	0.38
Diabetic	Yes vs No	0.86	0.42-1.76	0.68
Device Type	CRT-P vs. CRT-D	2.74	1.29-5.81	0.009

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Figure Legends

Figure 1. Kaplan-Meier curves of mortality for the subgroup with changes in LVESVI > 15% after 6 months of CRT and the rest of the cohort.

Figure 2. Kaplan-Meier curves of mortality for quartiles based on percentage changes in LVESVi after 6 months of CRT.

Figure 3. Kaplan-Meier curves of mortality for quartiles based on percentage changes in LVESVi after 6 months of CRT, examining LBBB and non-LBBB subgroups.

Figure 4. Kaplan-Meier curves of mortality for quartiles based on reverse remodeling changes after 6 months of CRT. Panel A: LVEDVi. Panel B; LVEF

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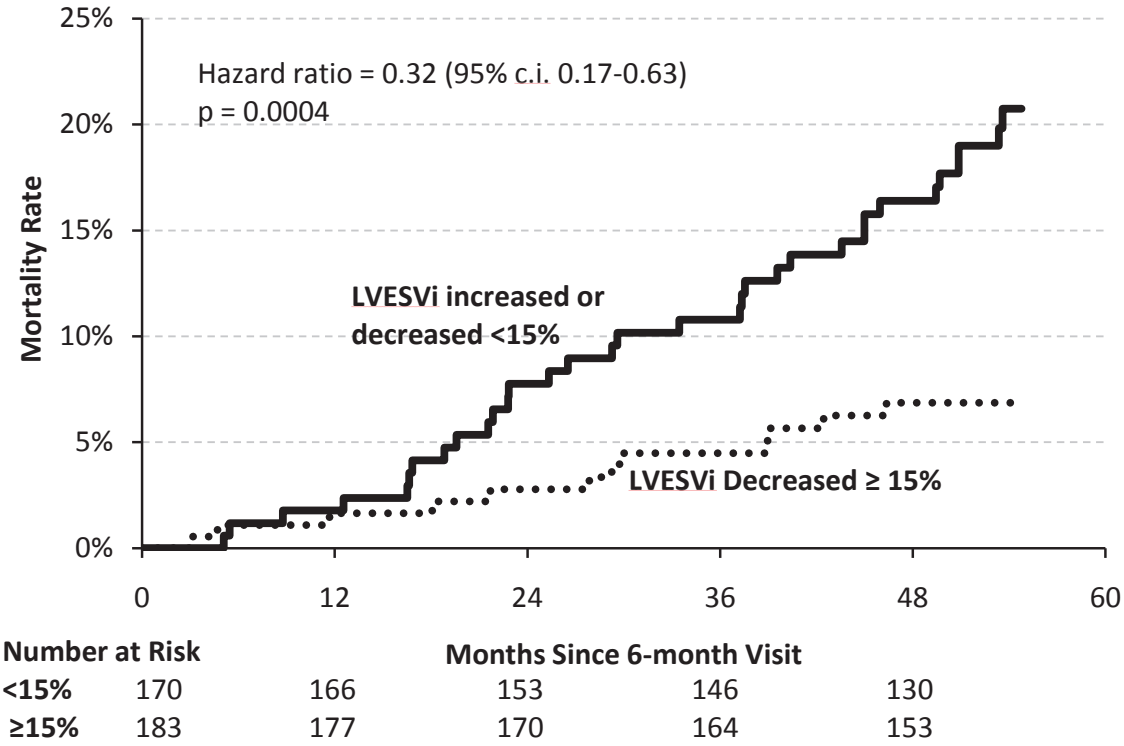

Number at Risk					
<15%	170	166	153	146	130
≥15%	183	177	170	164	153

Fig 1

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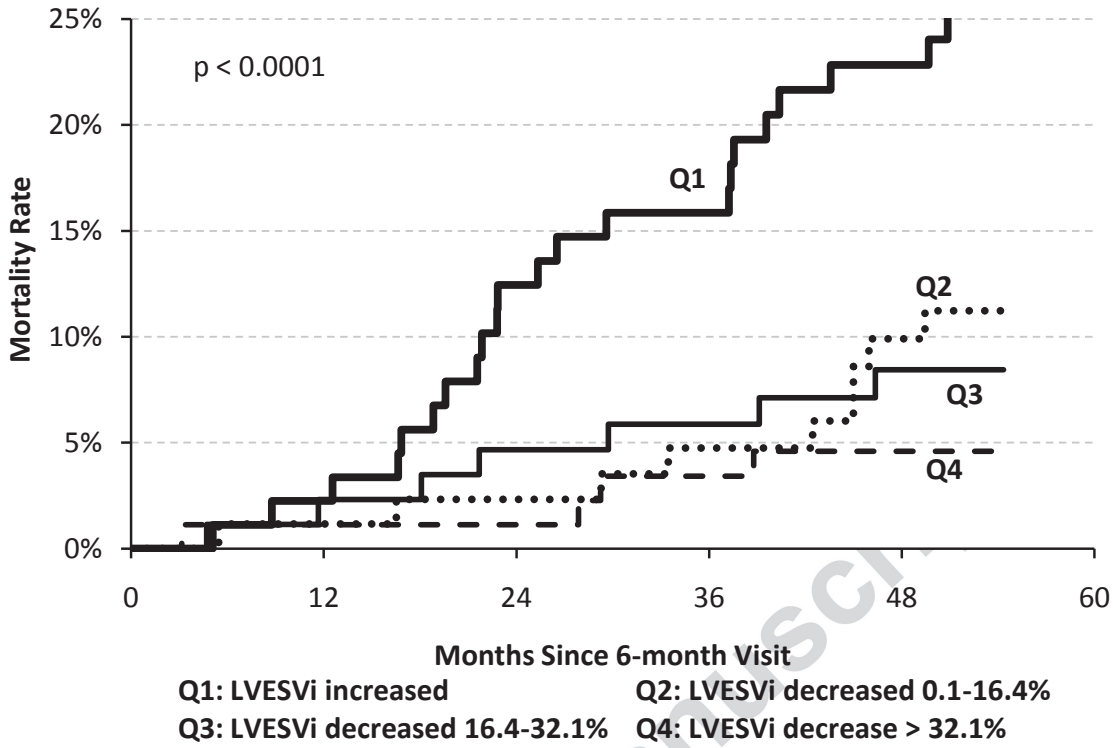

Fig 2

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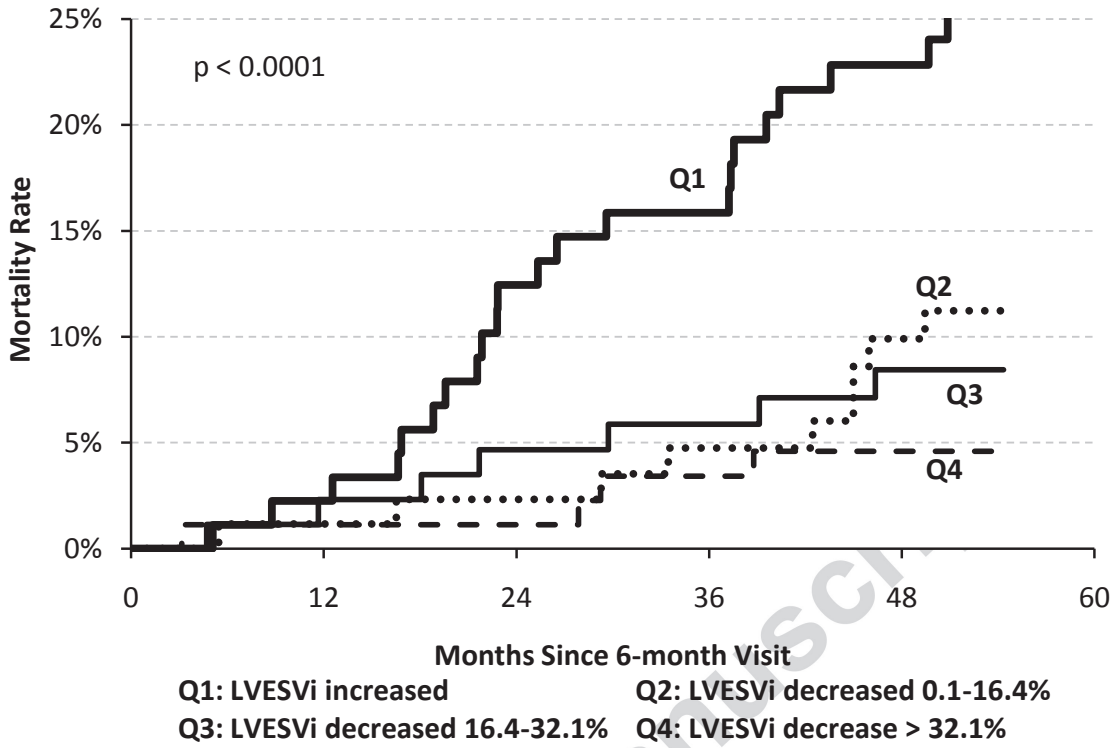

Fig 3

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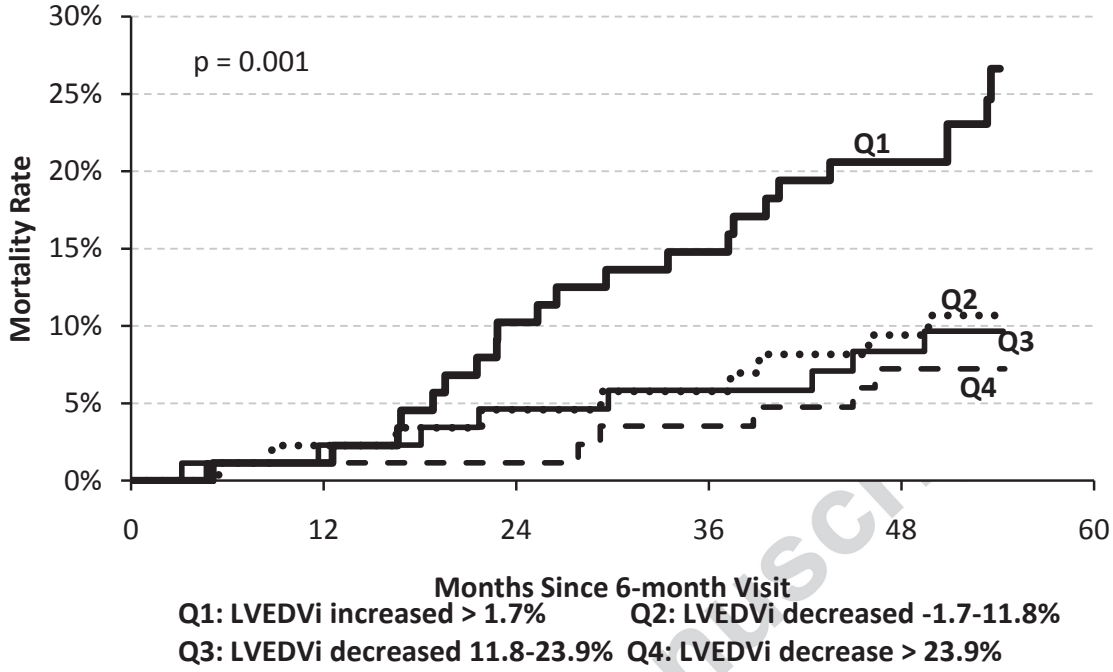
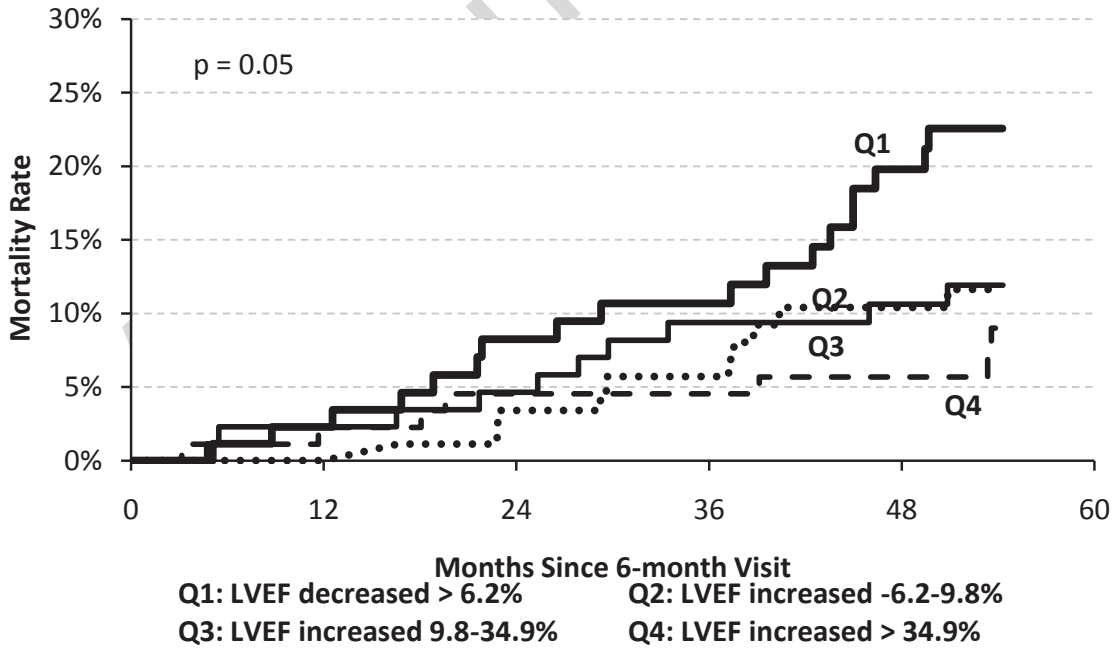
Panel A



Panel B



Changes in LVEF are relative changes.

Fig 4