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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

(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 $\geq 15\%$ 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

ventricular systolic dysfunction and QRS prolongation¹⁻⁸. Initially, CRT was applied to patients with advanced HF, but more recent studies have shown similar benefit among patients with milder HF⁹⁻¹¹. 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 ivabradine¹⁷. There are many other studies in support of the beneficial action of pharmacologic agents to induce reverse remodeling in HF¹⁸. 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) $\leq 40\%$, 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

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 Echocardiography²⁶, 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 previously²¹.

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

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

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/m², LVEDVi decreased 15.8 ± 32.4 ml/m², and the EF increased $3.6 \pm 8.3\%$ in this cohort. As shown previously, all of these changes were highly significant compared with the unpaced CRT OFF group⁹. 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 trial²⁷. 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 failure⁹⁻¹¹. 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

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 LBBB²⁸; 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

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

between reverse remodeling and reduced mortality^{15,16}. Similar findings were shown with ivabradine therapy among patients already on betablocker therapy¹⁷. Interestingly, an increase in mortality has been observed in pharmacologic treatment that increases LV volumes. This was shown in the ibopamine trial²⁵. 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 mortality¹⁸ 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 therapies¹⁸. More than 95% of patients in more recent randomized clinical trials of CRT have been on betablockers¹⁰⁻¹². Reverse remodeling by beta blockade is dependent on dose¹⁵. In REVERSE, 60% were on at least 50% of guideline-indicated dose and 30% on target dose³¹. 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 al²⁶ reported a relationship between the extent of LV volume changes and mortality and heart failure hospitalizations. Similarly, Yu et al²⁷ 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 groups²⁹. The present results suggest that large reductions of LVESVi are associated with

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 REVERSE¹⁹ and MADIT CRT³⁵ 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 subjects³⁶⁻³⁸, 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

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 mortality³⁹, while the other factors were shown to be associated with reduced HF hospitalizations⁹⁻¹¹.

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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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.

Tables

Table 1. Baseline Patient Characteristics

	LVESVi Change at 6 Months			p-value
	Increased or decreased <15% (n=170)	Decreased ≥15% (n=183)	All Patients (n=353)	
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.

Table 2. Causes of Death

			Increased or decreased <15% (n=170)	Decreased ≥15% (n=183)
Sudden			6 (3.5%)	1 (0.5%)
Cardiac	Non-	Heart failure	9 (5.3%)	5 (2.7%)
	sudden	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%)

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

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

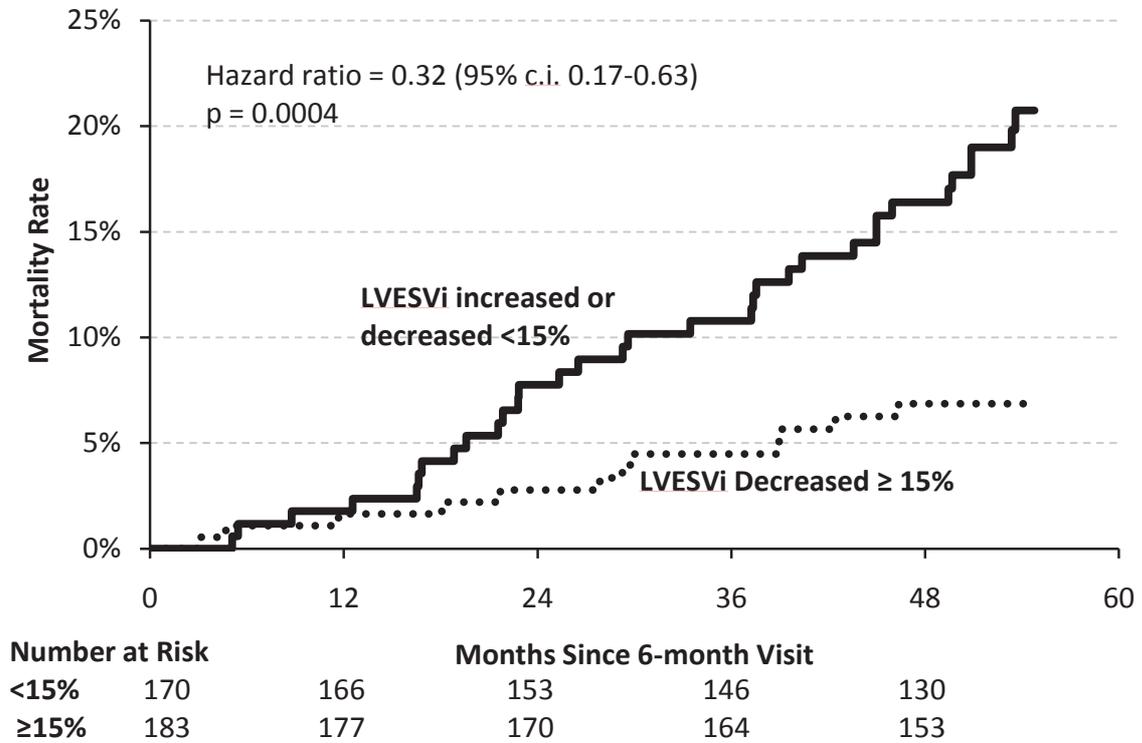


Fig 1

Accepted

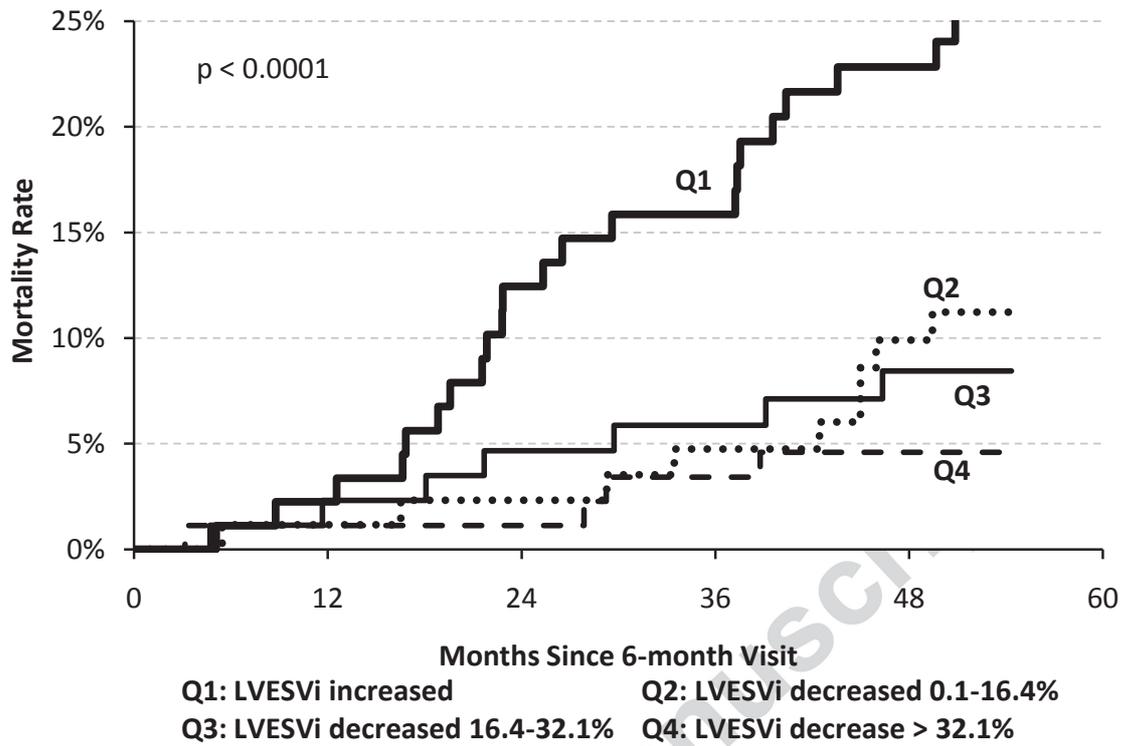


Fig 2

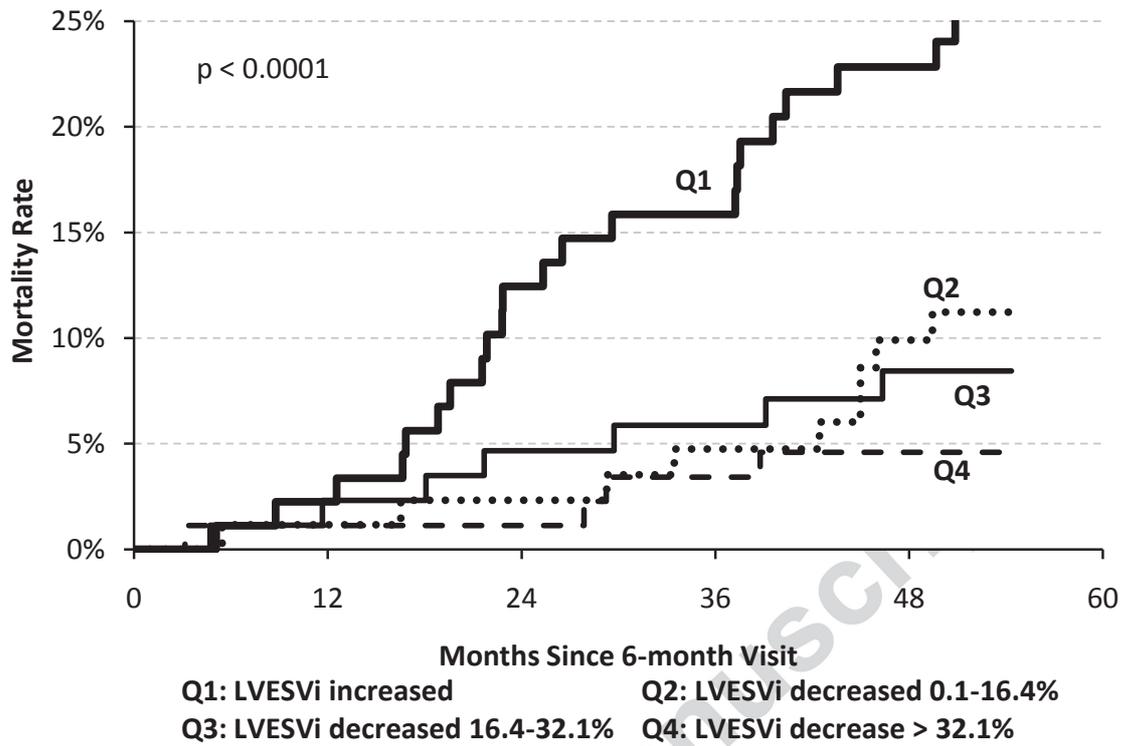
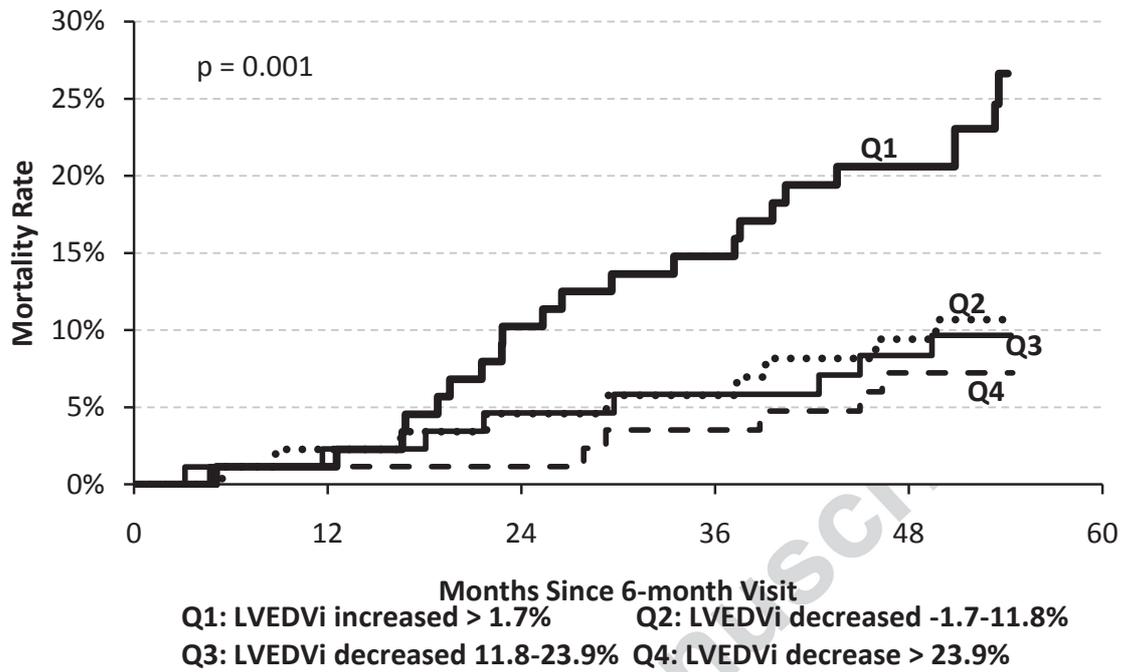
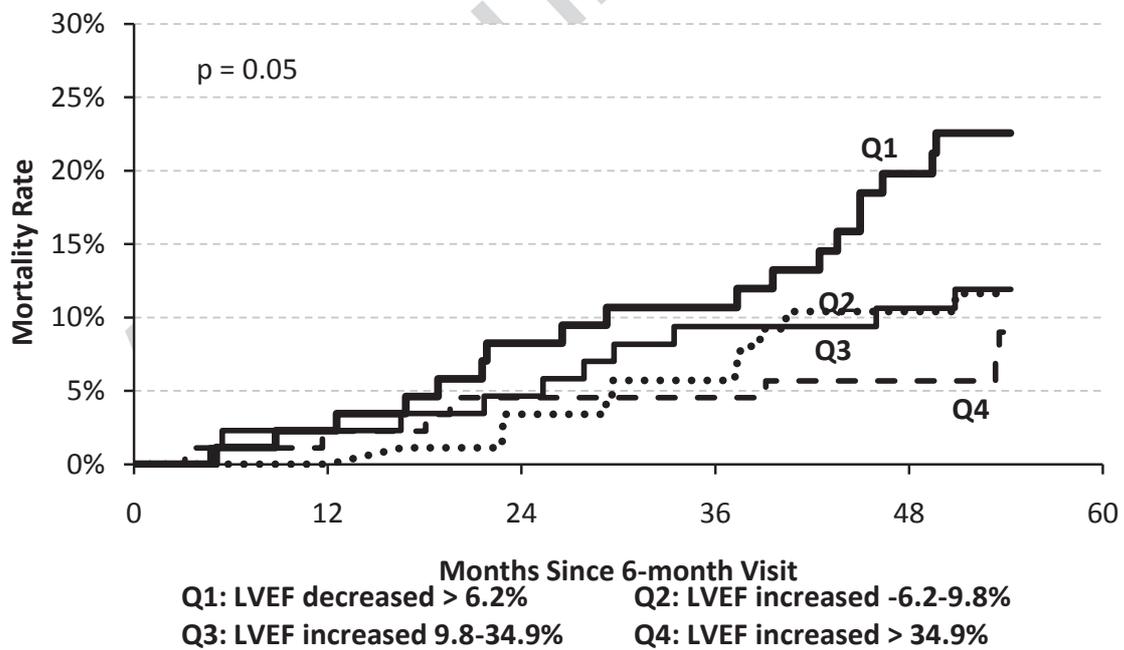


Fig 3

Panel A



Panel B



Changes in LVEF are relative changes.

Fig 4