

# Randomized Trial of Cardiac Resynchronization in Mildly Symptomatic Heart Failure Patients and in Asymptomatic Patients With Left Ventricular Dysfunction and Previous Heart Failure Symptoms

Cecilia Linde, MD, PhD,\* William T. Abraham, MD, FACC,† Michael R. Gold, MD, PhD,‡ Martin St. John Sutton, MD,§ Stefano Ghio, MD,¶ Claude Daubert, MD,|| on behalf of the REVERSE (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) Study Group  
*Stockholm, Sweden; Columbus, Ohio; Charleston, South Carolina; Philadelphia, Pennsylvania; Pavia, Italy; and Rennes, France*

- Objectives** We sought to determine the effects of cardiac resynchronization therapy (CRT) in New York Heart Association (NYHA) functional class II heart failure (HF) and NYHA functional class I (American College of Cardiology/American Heart Association stage C) patients with previous HF symptoms.
- Background** Cardiac resynchronization therapy improves left ventricular (LV) structure and function and clinical outcomes in NYHA functional class III and IV HF with prolonged QRS.
- Methods** Six hundred ten patients with NYHA functional class I or II heart failure with a QRS  $\geq 120$  ms and a LV ejection fraction  $\leq 40\%$  received a CRT device ( $\pm$  defibrillator) and were randomly assigned to active CRT (CRT-ON; n = 419) or control (CRT-OFF; n = 191) for 12 months. The primary end point was the HF clinical composite response, which scores patients as improved, unchanged, or worsened. The prospectively powered secondary end point was LV end-systolic volume index. Hospitalization for worsening HF was evaluated in a prospective secondary analysis of health care use.
- Results** The HF clinical composite response end point, which compared only the percent worsened, indicated 16% worsened in CRT-ON compared with 21% in CRT-OFF (p = 0.10). Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index ( $-18.4 \pm 29.5$  ml/m<sup>2</sup> vs.  $-1.3 \pm 23.4$  ml/m<sup>2</sup>, p < 0.0001) and other measures of LV remodeling. Time-to-first HF hospitalization was significantly delayed in CRT-ON (hazard ratio: 0.47, p = 0.03).
- Conclusions** The REVERSE (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) trial demonstrates that CRT, in combination with optimal medical therapy ( $\pm$  defibrillator), reduces the risk for heart failure hospitalization and improves ventricular structure and function in NYHA functional class II and NYHA functional class I (American College of Cardiology/American Heart Association stage C) patients with previous HF symptoms. (REsynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction [REVERSE]; NCT00271154). (J Am Coll Cardiol 2008; 52:1834–43) © 2008 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) with or without an implantable cardioverter-defibrillator (ICD) improves quality of life, functional status, exercise capacity, morbidity, and mortality in New York Heart Association (NYHA)

functional class III and ambulatory class IV heart failure (HF) patients with left ventricular (LV) systolic dysfunction

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From the \*Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden; †Division of Cardiovascular Medicine and the Davis Heart and Lung Research Institute, Ohio State University, Columbus, Ohio; ‡Division of Cardiology, Medical University of South Carolina, Charleston, South Carolina; §University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; ¶Poli-clinico San Matteo, Pavia, Italy; and the ||Département de Cardiologie, CHU, Rennes, France. Dr. Linde reports research grants, speaker honoraria, and consulting fees from Medtronic and speaker honoraria and consulting fees from St. Jude Medical. Dr. Abraham reports research grants, speaker honoraria, and consulting

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and a prolonged QRS duration (1–5). Resynchronization therapy also progressively improves LV structure and function in these patients (6), raising the possibility that CRT might delay disease progression in HF patients with less severe symptoms through LV reverse remodeling. Two small studies in NYHA functional class II patients support this hypothesis (7,8); however, both of these studies were only 6 months in duration and neither study included asymptomatic patients with systolic dysfunction.

We report the results of the REVERSE (REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction) trial, a randomized, double-blind trial of CRT in patients with asymptomatic and mildly symptomatic heart failure and a prolonged QRS interval.

## Methods

**Patient population.** Eligible patients had American College of Cardiology/American Heart Association Stage C (9), NYHA functional class I (previously symptomatic, currently asymptomatic) or NYHA functional class II (mildly symptomatic) HF for at least 3 months before enrollment. Patients were required to be in sinus rhythm with QRS duration  $\geq 120$  ms, to have a LV ejection fraction (EF)  $\leq 40\%$ , and to have a LV end-diastolic diameter  $\geq 55$  mm as measured by echocardiography. All patients were receiving optimal medical therapy for HF (9,10), including stable doses of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and a beta-blocker for at least 3 months. Patients were excluded if in the 3 months before enrollment they were classified as NYHA functional class III or IV or had been hospitalized for HF. Those in need of cardiac pacing, those who had been paced from a previous device, or those with permanent or persistent atrial arrhythmias also were excluded. Other reasons for exclusion have been published previously (11). The ethics committee of each center approved the protocol, and all patients gave written informed consent.

**Study design and procedures.** Patients meeting the entry criteria underwent evaluations at baseline: NYHA functional class, quality of life assessment (Minnesota Living with Heart Failure Questionnaire [12] and the Kansas City Cardiomyopathy Questionnaire [13]), 6-min walk test, 12-lead electrocardiogram (for QRS duration), and 2-dimensional Doppler-flow echocardiography (to assess ventricular structure and function and the degree of mitral regurgitation).

After baseline evaluation, patients underwent implantation of a CRT system (device and leads), with or without ICD capabilities. Within 21 days of informed consent, patients who had undergone successful implantation were randomly assigned in a 2:1 fashion to active CRT (CRT-ON) or to control (CRT-OFF) for 12 months. Thereafter, all patients were recommended to be programmed to CRT-ON, except in Europe, where patients were to remain in their assigned group for 24 months so that we could

assess the health economic outcomes of early CRT intervention. Randomization occurred in permuted blocks within centers. Those assigned to CRT-ON were programmed to a mode that paced both ventricles and inhibited atrial pacing unless the intrinsic rate was  $\leq 35$  beats/min, and those assigned to CRT-OFF had the device programmed to inhibit atrial or ventricular pacing unless the intrinsic rate was  $\leq 35$  beats/min. The atrioventricular delay was optimized by echocardiography (11).

Patients were evaluated at 1, 3, 6, and 12 months. During the randomized phase, patients were blinded to their randomization assignment and blinded personnel (heart failure staff who were managing patients' heart failure) administered quality of life questionnaires, patient global assessment, NYHA functional classification, 6-min walk test, and physical examination. Unblinded personnel (i.e., electrophysiologist staff) performed device interrogation and programming, 12-lead electrocardiogram, echocardiography, and pacemaker follow up data. The echocardiography recordings were evaluated by core labs who were not informed of randomization assignments. All patients underwent a full echocardiogram at 12 months, programmed to the CRT mode to which they were randomized, followed by a limited echocardiogram with patients programmed in the opposite CRT mode. For those assigned to CRT-ON, a 10-min CRT washout period was required before obtaining the limited echocardiogram with CRT programmed off.

Investigators were asked to report all adverse events, which were classified for HF and system relatedness by an independent Adverse Event Advisory/Endpoint Committee (AEAC) blinded to treatment modality. An unblinded independent Data Monitoring Committee consisting of 3 physician-scientists and a statistician reviewed accumulating adverse events, hospitalization, and mortality data to monitor for safety issues.

Crossover from the assigned mode was prohibited before the 12-month assessment, except for patients assigned to either group who experienced chronic worsening of heart failure to NYHA functional class III or class IV. Such crossovers required prior discussion between the responsible blinded site investigator and a member of the REVERSE Steering Committee and were allowed only as a last resort.

**End points and statistical analysis.** The primary end point of the study was the HF clinical composite response (11,14). Using this end point, we classified patients into 1 of 3 response groups at 12 months after randomization: worsened, unchanged, or improved. Patients were judged to be worsened if they died, were hospitalized (at any time during

## Abbreviations and Acronyms

<b>AEAC</b> = Adverse Event Advisory/Endpoint Committee
<b>CRT</b> = cardiac resynchronization therapy
<b>HF</b> = heart failure
<b>ICD</b> = implantable cardioverter-defibrillator
<b>LV</b> = left ventricular
<b>LVESVI</b> = left ventricular end-systolic volume index
<b>NYHA</b> = New York Heart Association

the 12 months) because of or associated with worsening HF, crossed over or permanently discontinued double-blind treatment because of worsening HF at any time during the 12 months, demonstrated worsening in NYHA functional class at their 12-month visit, or reported moderately or markedly worse heart failure symptoms compared to before CRT implant (Patient Global Assessment) when asked at the 12-month follow-up. Patients were judged to be improved if they had not worsened and had demonstrated improvement in NYHA functional class at 12 months and/or reported moderately or markedly improved heart failure symptoms at the 12-month follow-up. Patients who were not worsened or improved were classified as unchanged. Hospitalizations and crossovers only contributed to the end point if the AEAC verified their relatedness to HF. Because asymptomatic patients (NYHA functional class I) were included in the study and their NYHA status could not improve, the percent of patients worsened was used to compare the efficacy of CRT between study groups.

The left ventricular end-systolic volume index (LVESVI) was the prospectively powered secondary end point. This was measured as the absolute change between baseline and 12 months for comparison between the 2 randomized groups. The 12-month echocardiographic measurements were made with CRT programmed off, irrespective of the treatment assignment, with the same parameters in the full echocardiographic protocol for CRT-OFF patients and a limited echocardiographic protocol for CRT-ON patients. In CRT-ON patients these measurements were recorded after a 10-min washout period. Two core laboratories for echocardiography, 1 in the U.S. and 1 in Europe, performed all echocardiographic measurements.

All end points were analyzed according to the intention-to-treat principle; patients who crossed over were analyzed in their original treatment assignment. All *p* values reported are nominal, and all statistical tests are 2-sided. The study had a statistical power of 80% to detect an absolute difference of 12.1% in worsened HF clinical composite responses between the 2 groups with 512 randomized patients. The study had 80% power to detect a difference of 8.11 ml/m<sup>2</sup> change in LVESVI between the 2 groups with 483 randomized patients. We used the larger of 512 and 483; therefore, the prespecified study sample size was 683 enrolled patients based on an assumed attrition rate of 25% from enrollment to randomization. For the pre-specified analysis of the primary end point, the percent of patients worsened was used to compare the efficacy of CRT between study groups with the chi-square test. Kaplan-Meier analysis was used to analyze all-cause mortality and time to first heart failure hospitalization. Time 0 was the date of randomization and patients not experiencing an event were censored at 12 months. The log-rank test was used to assess significance in both cases. Complication rates were compared with the chi-square test. The difference in incidence of ventricular arrhythmias was tested with the Comparison of Incidence Rates (Large Sample Test) (15). Other sec-

ondary end points were compared with the 2-sample *t*-test, comparing the differences from baseline to 12 months (11). For the HF clinical composite response (% worsened) odds ratio figure, 95% Wald confidence limits are reported. Analyses were conducted with SAS software (version 9.1, SAS Institute, Cary, North Carolina). There were no interim analyses of the efficacy data and, therefore, the data monitoring committee had no pre-specified stopping rules.

## Results

**Study population.** Patients were enrolled at 73 centers; 37 in the U.S., 1 in Canada, and 35 in Europe. Enrollment began in September 2004 and ended in September 2006. A total of 684 patients were enrolled in the study, with 648 completing a baseline assessment, 642 undergoing attempted CRT implant, and 621 being successfully implanted. The average time from implant to randomization was 4.8 days. Eleven of the 621 patients were not randomized because of the following reasons: inclusion criteria not met, complete heart block, atrial arrhythmias, LV lead dislodgment, loss of capture, death, heart failure status (*n* = 2), and surgical epicardial LV lead use (*n* = 3), leaving 419 randomized to CRT-ON and 191 randomized to CRT-OFF.

As previously described (16), baseline characteristics were similar in the 2 groups (Table 1). Almost all patients (97%) were on either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker and on a beta-blocker (95%). Thirty-five percent were receiving beta-blockers in target dose and 60% were receiving at least 50% of target dose according to current HF guidelines (10). The mean LVEF was 26.7 ± 7.0% and the mean LV end-diastolic diameter was 66.9 ± 8.9 mm. The mean QRS duration was 153 ± 22 ms. A CRT-ICD was implanted in 83% of successfully implanted patients and a CRT device in 17%, with no significant differences between randomization groups on the basis of device type (Table 1). The overall implantation success rate was 97%.

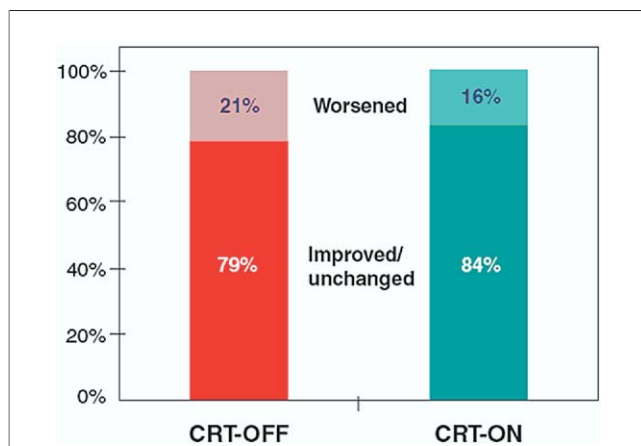
**Effects on primary and secondary end points.** Of the 419 patients assigned to CRT-ON, 16% worsened in their HF clinical composite response at 1 year compared with 21% of the 191 patients randomized to CRT-OFF (*p* = 0.10) (Fig. 1). The reasons for patients receiving a score of worsened, improved, or unchanged are listed in Table 2. Paired LVESVI data were available in 487 of 610 patients (80%). The reasons for missing data were an unreadable echocardiogram at baseline (*n* = 42) or 12 months (*n* = 53), echocardiographic examination not performed at baseline (*n* = 3) or at the 12-month visit (*n* = 14; 1 due to missing full echocardiogram, 10 due to missing limited echocardiograms, and 3 due to missing full and limited echocardiograms), and because of patient death before the 12-month visit (*n* = 11). The LVESVI improved (−18.4 ± 29.5 ml/m<sup>2</sup>) in the CRT-ON group (*n* = 324) compared with the CRT-OFF group (−1.3 ± 23.4 ml/m<sup>2</sup>; *n* = 163; *p* < 0.0001) (Fig. 2). The observed reduction in LVESVI in

**Table 1 Patient Baseline Characteristics in the CRT-OFF and CRT-ON Groups**

Parameter	CRT-OFF (n = 191)	CRT-ON (n = 419)	p Value
Age, yrs	61.8 ± 11.6	62.9 ± 10.6	0.26
Gender, male (%)	152 (80)	327 (78)	0.75
NYHA functional class II, n (%)	159 (83)	344 (82)	0.82
Ischemic, n (%)	97 (51)	236 (56)	0.22
Diabetic, n (%)	46 (24)	91 (22)	0.53
ACE inhibitors, n (%)	151 (79)	330 (79)	1.00
ARBs, n (%)	39 (20)	88 (21)	0.91
ACE inhibitors or ARBs, n (%)	186 (97)	404 (96)	0.63
Beta-blockers, n (%)	179 (94)	401 (96)	0.32
At least 50% of target dose of beta-blockers, n (%)	114 (60)	255 (61)	0.79
100% of target dose of beta-blockers, n (%)	62 (32)	153 (37)	0.36
Diuretics, n (%)	148 (77)	339 (81)	0.33
Intrinsic QRS width, ms	154 ± 24	153 ± 21	0.41
LV ejection fraction, %	26.4 ± 7.1	26.8 ± 7.0	0.50
LV end-diastolic dimension, cm	7.0 ± 0.9	6.9 ± 0.9	0.65
LV end-systolic dimension, cm	5.8 ± 1.1	5.7 ± 1.0	0.63
LV end-systolic volume, cm <sup>3</sup>	203 ± 91	197 ± 74	0.42
LV end-diastolic volume, cm <sup>3</sup>	272 ± 102	268 ± 89	0.60
LV mass, g	274 ± 78	269 ± 76	0.57
Interventricular mechanical delay, ms	33.6 ± 36.4	33.9 ± 40.1	0.94
Glomerular filtration rate, ml/min	89.6 ± 36.4	84.2 ± 31.3	0.08
Heart rate, beats/min	68.2 ± 10.9	66.9 ± 10.3	0.17
Supine systolic blood pressure, mm Hg	123.4 ± 19.0	125.2 ± 18.6	0.25
Supine diastolic blood pressure, mm Hg	72.0 ± 12.0	72.2 ± 10.8	0.82
Weight, kg	87.5 ± 18.8	85.1 ± 17.8	0.12
Minnesota Living With Heart Failure Score	28.8 ± 21.7	27.0 ± 20.1	0.32
Kansas City Cardiomyopathy Questionnaire Overall Summary Score	70.7 ± 22.1	73.7 ± 19.0	0.14
6-min hall walk, m	388 ± 132	399 ± 125	0.34
CRT-ICD implanted, n (%)	163 (85)	345 (82)	0.41

p values are 2-sided and were calculated with the Fisher exact test or the 2-sample t-test.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CRT-ICD = cardiac resynchronization therapy-implantable cardioverter-defibrillator; LV = left ventricular; NYHA = New York Heart Association.



**Figure 1 The Heart Failure Clinical Composite Response**

The primary end point, comparing the proportion of worsened subjects at 12 months ( $p = 0.10$ ). CRT-OFF = control patients; CRT-ON = patients receiving cardiac resynchronization therapy.

CRT-ON patients was 3 times greater in the nonischemic group ( $-29.8 \pm 30.5$  ml/m<sup>2</sup>;  $n = 142$ ) than in patients with an ischemic etiology of HF ( $-9.5 \pm 25.5$  ml/m<sup>2</sup>;  $n = 182$ ), but was of similar magnitude in patients in NYHA functional class I ( $-15.4 \pm 27.6$  ml/m<sup>2</sup>) and NYHA functional class II ( $-19.1 \pm 30.0$  ml/m<sup>2</sup>) HF. The difference in the change in LVESVI between CRT-ON and CRT-OFF was statistically significant in all the subgroups analyzed (Fig. 3). Other measures of reverse remodeling also improved significantly with active CRT (Fig. 2). The interventricular mechanical delay was significantly reduced after 12 months in CRT-ON compared with CRT-OFF ( $-13.0 \pm 43.2$  ms in CRT-ON,  $n = 276$ , vs.  $0.2 \pm 34.0$  ms in CRT-OFF,  $n = 140$ ;  $p = 0.0007$ ). The effect of CRT on the HF clinical composite response in various subgroups was evaluated (Fig. 4) with the use of odds ratios. The overall odds ratio for the study was 0.70 in favor of CRT-ON. The point estimates for nearly all subgroups favored CRT-ON, demonstrating consistent results across the study population.

The change in the 6-min walk distance at 12 months ( $12.7 \pm 102.4$  m in CRT-ON vs.  $18.7 \pm 105.2$  m in CRT-OFF;  $p = 0.52$ ) and quality of life by the Minnesota score ( $-8.4 \pm 17.1$  in CRT-ON vs.  $-6.7 \pm 15.9$  in

**Table 2** HF Clinical Composite Response Details in the CRT-OFF and CRT-ON Groups

Clinical Composite Response Detail	CRT-OFF (n = 191)	CRT-ON (n = 419)
Worsened, n (%)	41 (21)	67 (16)
Death	3 (2)	9 (2)
Hospitalization due to or associated with worsening HF	14 (7)	12 (3)
Crossover due to worsening HF	5 (3)	1 (<1)
Worsened patient global assessment and NYHA functional class	0 (0)	2 (<1)
Worsened NYHA functional class only	18 (9)	40 (10)
Worsened patient global assessment only	1 (1)	3 (1)
Improved, n (%)	76 (40)	228 (54)
Improved on patient global assessment and NYHA functional class	11 (6)	69 (16)
Improved NYHA functional class only	28 (15)	59 (14)
Improved patient global assessment only	37 (19)	100 (24)
Unchanged	74 (39)	124 (30)

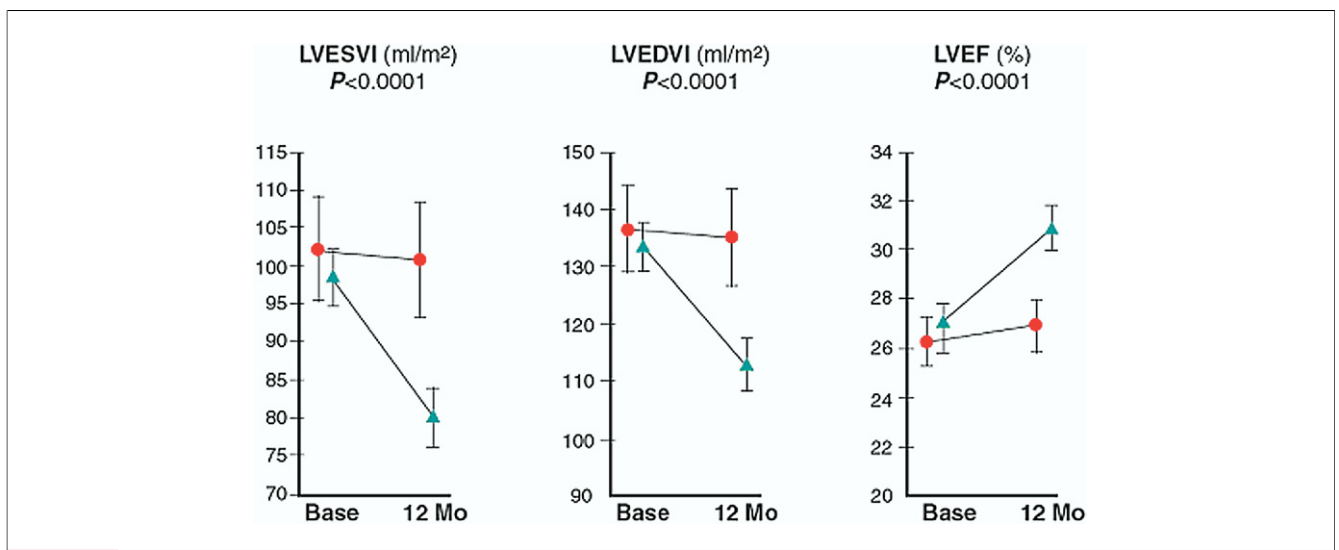
Data in the table are listed in hierarchical order (subjects are included only in one subcategory). HF = heart failure; other abbreviations as in Table 1.

CRT-OFF;  $p = 0.26$ ) and the Kansas City score ( $8.7 \pm 17.8$  in CRT-ON vs.  $8.5 \pm 16.1$  in CRT-OFF,  $p = 0.91$ ) did not improve with CRT. There were 196 adjudicated episodes of ventricular tachycardia or ventricular fibrillation (0.57 per year in 54 of 345 CRT-ICD patients) in CRT-ON and 114 episodes (0.70 per year in 24 of 163 CRT-ICD patients) in CRT-OFF ( $p = 0.09$  favoring CRT-ON).

There were 222 hospitalizations during the 12-month follow-up period. There were 17 HF-related hospitalizations in the CRT-ON group ( $n = 419$ ) and 15 in the CRT-OFF group ( $n = 191$ ). The time-to-first HF hospitalization was significantly delayed in the CRT-ON group (hazard ratio: 0.47,  $p = 0.03$ ) (Fig. 5). There were 12 deaths from the time of randomization through the 1-year follow up. The mortality rate was 2.2% at 12 months for the

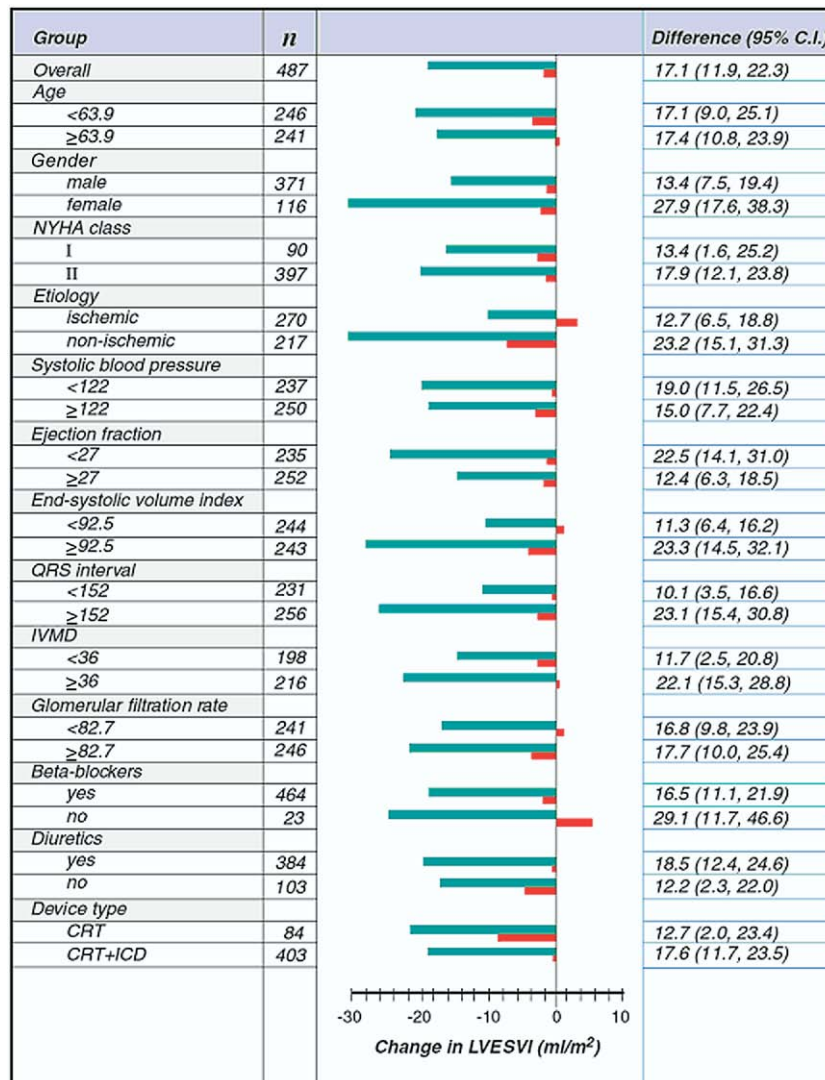
CRT-ON group and 1.6% for the CRT-OFF group ( $p = 0.63$ ). Deaths were adjudicated to be due to progressive HF ( $n = 3$ ), documented arrhythmias ( $n = 2$ ), gastrointestinal bleeding, renal cancer, aspiration pneumonia, pulmonary fibrosis, and electromechanical dissociation. No cause was able to be determined for 2 deaths. Nine of the deaths were not related to the therapy, procedure, or system and such relatedness was unknown for 3 deaths.

**Complications.** An adverse event that resulted in invasive intervention or the termination of significant device function regardless of other treatments was classified as a complication. During or just before implantation there were 26 procedure or system-related complications among the 642 patients (i.e., the perioperative complication rate was 4%) who underwent an implant attempt, including adverse drug reaction ( $n = 4$ ), pneumothorax



**Figure 2** Mean LVESVI, LVEDVI, and LVEF at Baseline and 12 Months in the CRT-OFF and CRT-ON Groups

Error bars represent 95% confidence intervals. Red circles = CRT-OFF ( $n = 163$ ); green triangles = CRT-ON ( $n = 324$ ). CRT = cardiac resynchronization therapy; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; other abbreviations as in Figure 1.



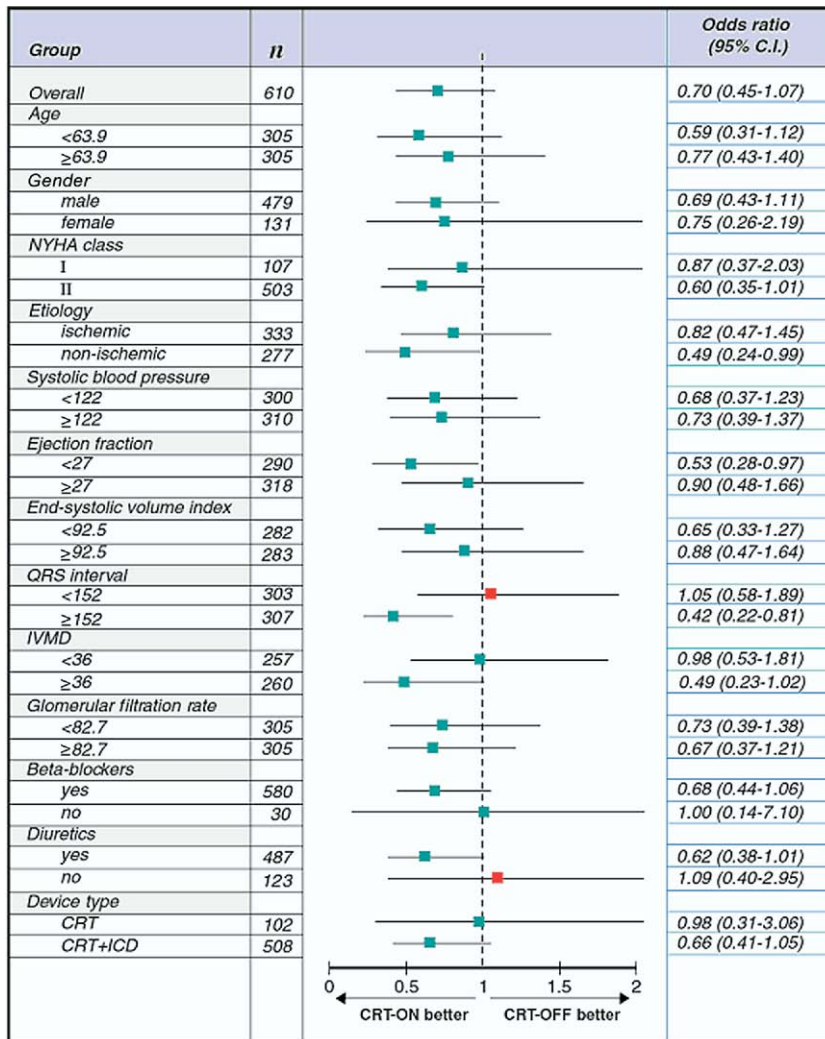
**Figure 3** Effect of CRT on LVESVI

An analysis of the mean change in LVESVI ( $\text{ml}/\text{m}^2$ ) from baseline to 12 months is shown. The difference (CRT-OFF – CRT-ON) in the mean changes, along with its 95% confidence interval, is shown for each subgroup. Confidence intervals that do not include 0 indicate statistical significance ( $p < 0.05$ ). The subgroups of age, systolic blood pressure, ejection fraction, end-systolic volume index, QRS width, interventricular mechanical delay, and glomerular filtration rate are divided according to the median value in the study sample. **Green bars** = CRT-ON; **red bars** = CRT-OFF. ICD = implantable cardioverter-defibrillator; IVMD = interventricular mechanical delay; NYHA = New York Heart Association; other abbreviations as in Figure 2.

( $n = 4$ ), atrial fibrillation or flutter ( $n = 4$ ), coronary sinus dissection ( $n = 3$ ), pulmonary edema ( $n = 2$ ), ventricular fibrillation ( $n = 2$ ), complete heart block ( $n = 2$ ), cardiac tamponade ( $n = 1$ ), pericardial effusion ( $n = 1$ ), electromechanical dissociation ( $n = 1$ ), hypotension ( $n = 1$ ), and increased defibrillation threshold ( $n = 1$ ). Twenty-five of the 26 complications were resolved within 28 days of onset.

After implantation and during the 12-month follow-up, 101 of the 621 successfully implanted patients experienced a total of 138 procedure or system-related complications (i.e., the post-operative procedure or system-related complication

rate was 16%). There was no statistically significant difference in complication rates between CRT-ON and CRT-OFF patients during the first 12 months of randomization ( $p = 0.64$ ). Of the 138 complications, the most common postimplant complications were lead dislodgements (left ventricular  $n = 41$ , right ventricular  $n = 15$ , and right atrial  $n = 10$ ), inappropriate device irritation of tissue (e.g., diaphragmatic nerve stimulation,  $n = 14$ ), atrial fibrillation or flutter ( $n = 8$ ), implant site hematoma ( $n = 5$ ), hypotension ( $n = 4$ ), and pericardial effusion ( $n = 4$ ). At the time of database closure, 128 (93%) of post-implant complications were resolved (66% within 3 weeks of onset),



**Figure 4** Effect of CRT on the Heart Failure Clinical Composite Response of Worsened in Subgroups

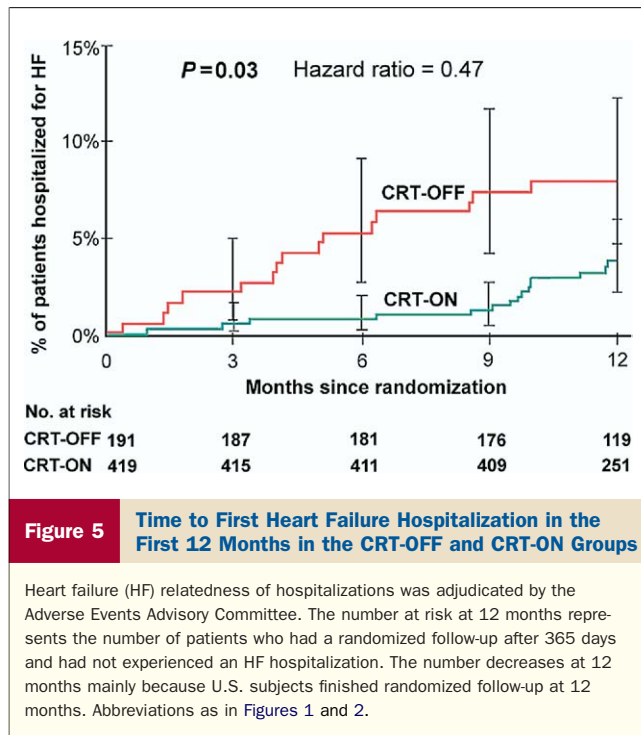
Analysis of the percentage worsened in the heart failure clinical composite response using odds ratios and 95% confidence intervals is shown. Lower odds ratios favor CRT-ON. An odds ratio of 0.5 means the odds of a patient being in worsened condition are half as high in the CRT-ON group as the CRT-OFF group. The subgroups of age, systolic blood pressure, ejection fraction, end-systolic volume index, QRS width, interventricular mechanical delay, and glomerular filtration rate are divided according to the median value in the study sample. Because of missing baseline data, not all subgroup numbers equal a total of 610. Abbreviations as in Figures 1, 2, and 3.

7 were ongoing, 2 were unresolved with no further actions expected, and one resulted in death.

Because the majority of REVERSE patients were implanted with CRT-ICD devices, the primary incremental risk for CRT or CRT-ICD therapy over ICD therapy alone is the LV lead and CRT therapy. That is, because most of these patients had a clinical indication for ICD therapy (17) and were to be subjected to the risks of ICD implantation, the incremental risk of LV lead implantation and CRT itself was analyzed. Among the 621 successfully implanted patients during the first 12 months, there was one CRT therapy-related complication in which cardiac failure was resolved by turning CRT off. There were 66 LV lead-related complications among 59 patients (i.e., the LV lead related complication rate was 10%) which required reopera-

tion in 48 patients (8% of successfully implanted patients). The most common events in the 66 LV lead related complications were LV lead dislodgements (n = 41), diaphragmatic stimulation (n = 14), and subclavian vein thrombosis (n = 3). In 86% of cases, these LV lead complications were resolved without untoward clinical effects.

**Crossovers and patient compliance.** The 12-month follow-up was completed by 594 of the surviving 598 patients (99%). No randomized patients were lost to follow-up or exited from the study. There were 20 permanent crossovers in 12 months. Six patients crossed over from CRT-ON to CRT-OFF due to worsening HF (n = 2), diaphragmatic nerve stimulation (n = 2), persistent atrial fibrillation (n = 1), and incorrect programming (n = 1).



**Figure 5** Time to First Heart Failure Hospitalization in the First 12 Months in the CRT-OFF and CRT-ON Groups

Heart failure (HF) relatedness of hospitalizations was adjudicated by the Adverse Events Advisory Committee. The number at risk at 12 months represents the number of patients who had a randomized follow-up after 365 days and had not experienced an HF hospitalization. The number decreases at 12 months mainly because U.S. subjects finished randomized follow-up at 12 months. Abbreviations as in Figures 1 and 2.

Fourteen patients crossed over from CRT-OFF to CRT-ON due to worsening HF (n = 12), patient unwillingness to remain in the assigned mode (n = 1), and inadvertent erroneous programming (n = 1). Of the 14 crossovers investigators indicated were due to worsening HF, the AEAC adjudicated 13 as being due to HF. Of these, 6 patients received a worsened score in the HF clinical composite as a result of the crossover (Table 2); the others were hospitalized for HF before their crossover.

## Discussion

The REVERSE trial shows for the first time in a large multicenter, randomized, double-blind study that CRT improves ventricular structure and function in patients with asymptomatic and mildly symptomatic heart failure. In contrast, the percent worsened in the composite primary end point compared with the percent unchanged or improved did not differ significantly. In addition, REVERSE demonstrates a significant reduction in HF morbidity defined as the need for hospitalization for worsening HF. Specifically, there was a statistically significant 53% relative risk reduction in time to first HF hospitalization associated with active CRT. Finally, REVERSE found no significant improvement in quality of life or exercise capacity with CRT. This latter finding is not surprising in a group of patients with little functional impairment at baseline.

The primary end point was chosen because it combines the occurrence of major events such as HF morbidity, HF hospitalization, and mortality with NYHA functional class and quality of life (14). It was thought to be more sensitive than conventional approaches in detecting the presence or

absence of a true treatment effect in CRT studies. Because the clinical event rate was expected to be lower in the REVERSE patient group than in moderate-to-severe HF patients, the composite was expected to be more sensitive than any of its individual parameters per se to detect a treatment difference by CRT. In previous studies in which authors used the clinical composite HF end point (14), the distribution of “worsened,” “unchanged,” and “improved” was compared. We used the clinical composite to assess changes in less symptomatic and even asymptomatic patients. Hence, we regarded both “unchanged” and “improved” as lack of disease progression and “worsened” as disease progress. Therefore, we analyzed the percent worsened as our primary end point. When this prespecified analysis plan was used, the study did not meet its primary end point (14). Nonetheless, the extent of reverse structural and functional remodeling in the present study was comparable with that of previous CRT studies in NYHA functional class III and class IV patients (2,4,5).

Importantly, more patients in the REVERSE trial than in these trials were on beta-blockers for at least 3 months before consent and, to a larger extent, at the target dose with no dose alterations allowed during the randomization phase unless medically necessary. This result suggests that CRT produces significant additive effects on ventricular remodeling that occur in addition to HF drug therapy. Reverse remodeling by CRT has previously been reported in smaller studies of NYHA functional class II HF patients with 6 months of follow-up (7,8). Thus, REVERSE extends these observations in a larger number of patients with more prolonged follow-up. This finding, along with the observation that reverse LV remodeling but not symptomatic improvement has been linked to better survival in another CRT study of 141 patients followed for 695 days (18), supports the improvement in clinical outcomes observed in REVERSE. It is possible that the 12-month observation period was too short to meet the clinical composite end point in the mildly symptomatic or asymptomatic patients in REVERSE. The 24-month study period in the European cohort may have important implications for other CRT studies in this population.

Overall, the mortality and hospitalization rates were low in the REVERSE trial. This is not surprising because the REVERSE patient population had asymptomatic or mildly symptomatic HF, which is known to be associated with low rates of morbidity and mortality (19). Moreover, REVERSE patients were younger, had a more narrow QRS width, and had greater adherence to present pharmacological HF guidelines at baseline than in most previous trials. Nonetheless, a clear clinical benefit on time to first HF hospitalization was found in association with active CRT in the present study. Although REVERSE was not designed as a morbidity and mortality trial, this observation could suggest that CRT in NYHA functional class I and II patients over a longer treatment period could provide benefits in morbidity and even in mortality. In the CARE



HF (CArdiac REsynchronization in Heart Failure) study of NYHA functional class III to IV patients, incremental benefits in mortality and cardiovascular hospitalizations were shown with a mean follow up period of 36 months by CRT, which was also demonstrated within the mildest subgroup (20,21). It remains to be demonstrated if this is true also in NYHA functional class I to II patients. The long-term effect of CRT on mortality and HF events is currently being investigated in the RAFT (Rythmol Atrial Fibrillation Trial) (22) and MADIT CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) (23) studies.

The benefits of CRT in the REVERSE patient population must be balanced against the risks. Because most patients in REVERSE had a primary preventive indication for an ICD (17), the added risk of implanting a CRT device is related to the LV lead. This risk was relatively low with a LV lead related complication rate of 10% over the 12 months of follow-up. The reoperation rate for LV lead-related complications was similar in the REVERSE trial (8%) to the CARE HF trial, where LV-lead related major adverse events prompted reoperations in nearly 7% of patients (24). The complication rate will be further assessed in the 24-month randomization period in the European cohort as it will be for the full 5-year follow up for all REVERSE patients. The 97% implant success rate was very high, representing an improvement in implantation technique and lead technologies compared with earlier CRT studies (2,3).

## Conclusions

We found that CRT reduces the risk for HF hospitalization and reverses LV remodeling over 12 months in patients with American College of Cardiology/American Heart Association Stage C, NYHA functional class I and Class II HF, raising the possibility that CRT might delay disease progression in HF patients with less severe symptoms through LV reverse remodeling.


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**Reprint requests and correspondence:** Dr. Cecilia Linde, Department of Cardiology, Karolinska University Hospital, S-17176 Stockholm, Sweden. E-mail: [cecilia.linde@ki.se](mailto:cecilia.linde@ki.se).

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- Key Words:** cardiac resynchronization therapy ■ heart failure ■ randomized controlled trial ■ biventricular pacing ■ reverse remodeling.
-  **APPENDIX**
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- For a list of the 73 centers who contributed to this study, please see the online version of this article.**