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)

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Background—Cardiac resynchronization therapy (CRT) decreases mortality, improves functional status, and induces reverse left ventricular remodeling in selected populations with heart failure. These benefits have been noted with both CRT-pacemakers as well as those devices with defibrillator backup (CRT-D). However, there are little data comparing mortality between these 2 device types.

Methods and Results—REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) was a multicenter, randomized trial of CRT among patients with mild heart failure. Long-term annual follow-up for 5 years was preplanned. The present analysis was confined to the 419 patients who were randomized to active CRT group. CRT-pacemakers or CRT-D devices were implanted based on national guidelines at the time of enrollment, with 74 patients receiving CRT pacemaker devices and the remaining 345 patients receiving CRT-D devices. After 12 months of CRT, changes in the clinical composite score, left ventricular end systolic volume index, 6-minute walk time, and quality of life indices were similar between CRT pacemaker and CRT-D patients. However, long-term follow-up showed lower mortality in the CRT-D group. Specifically, multivariable analysis showed that CRT-D (hazard ratio, 0.35; P=0.003) was a strong independent predictor of survival. Female sex, longer unpaced QRS duration, and smaller baseline left ventricular end systolic volume index also were also associated with better survival.

Conclusions—REVERSE demonstrated that the addition of implantable cardioverter-defibrillator therapy to CRT is associated with improved long-term survival compared with CRT pacing alone in mild heart failure.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique Identifier: NCT00271154.

Key Words: cardiac resynchronization therapy ■ defibrillators, implantable ■ heart failure
Methods
The design and primary results of the REVERSE trial were published previously. 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) HF for ≥3 months before enrollment. Patients were required to be in sinus rhythm with QRS duration ≥120 ms, an ejection fraction ≤40%, and an LV end-diastolic dimension ≥55 mm measured by transthoracic echocardiography. All patients were receiving optimal medical therapy, and patients requiring pacing for bradycardia indications were excluded.

All patients underwent implantation of a CRT system (device and leads), with or without ICD capabilities, based on standard clinical criteria at the time of enrollment. Enrollment occurred in the United States, Canada, and Europe from September 2004 to September 2006. Patients who underwent successful implantation (N=610) were randomly assigned in a 2:1 fashion to active CRT (CRT ON) or to a control group (CRT OFF).

The primary end point of REVERSE was the clinical composite score measured at 12 months. Using this end point, patients were classified into 1 of 3 response groups: worsened, unchanged, or improved. Patients were judged to be worsened if they died, were hospitalized for worsening HF, crossed over to or permanently discontinued double-blind treatment because of worsening HF, or demonstrated worsening in NYHA class or moderate-to-marked worsening of patient global assessment. Patients were judged to be improved if they had not worsened and demonstrated improvement in NYHA class or moderate-to-marked improvement in patient global assessment. Patients who were not worsened or improved were classified as unchanged.

Change in LV end systolic volume, indexed by body surface area (LVESVi), was the predefined and independently powered secondary end point of REVERSE. Other secondary end points also assessed at 1 year included quality of life assessments and 6-minute hall walk times. Echocardiograms were obtained at baseline and after 12 months of randomization. Data were analyzed in 1 of 2 core laboratories 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 method of discs, as recommended by the American Society of Echocardiography. Long-term follow-up of this cohort was preplanned to allow assessment of the sustained benefit and cost-effectiveness of therapy. This included annual follow-up visits for 5 years. All-cause 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. Only those patients randomized to CRT ON are included; the CRT OFF group was programmed after the randomization period, which confounds the interpretation of long-term survival in this group. Adverse events were also evaluated by the independent events committee. A complication required invasive intervention or resulted in loss of device function but excluded device replacements because of normal battery depletion.

Data Analysis
Continuous variables are summarized with mean and SD; categorical variables with counts and percentages. Comparisons of variables between patients with CRT with and without ICD use Student t test (assuming unequal sample size and unequal variance) and Fisher exact test. The clinical composite score was analyzed as a 3-category variable using Fisher exact test. The time to event analysis used the Kaplan–Meier method, the log-rank test to compare curves, and Cox proportional hazards regression to compute hazard ratios (HR) and assess influence of covariates. Covariates were chosen before analysis by the authors as commonly known influences of mortality. The appropriate/inappropriate episode analyses also used Kaplan–Meier methods for rate estimates. The multivariable analysis used the full model including all covariates of interest. Displayed survival curves were ended once <20 patients remain at risk, although all data are included in the log-rank test and Cox proportional hazards models. Complication rates were compared using Fisher exact test. 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 and are the subjects of this analysis. Of this cohort, 74 received CRT-P devices, and the remaining 345 received CRT-D devices. Demographic and other characteristics of these 2 subgroups are presented in Table 1. Of note, there were some important clinical differences between the groups. Patients receiving CRT-P devices were less likely to have ischemic heart disease and more likely to have a left bundle–branch block morphology on their unpaced ECG. In addition, patients with CRT-D had a larger baseline LV end systolic volume, a lower mean LV ejection fraction and more often had right bundle–branch block; and intraventricular conduction disturbance.

Clinical Outcomes
The primary end point in REVERSE was the clinical composite score measured at 12 months. The overall distribution of the clinical composite score improved with CRT. Results of the device subgroups are shown in Figure 1; the distributions were similar for the patients programmed to CRT ON with both groups having >50% classified as improved and <20% worsened (P=0.89 comparing CRT-P and CRT-D). The powered secondary end point in REVERSE was the change in LVESVi≥12 months. These data are presented in Figure 2. It can be seen that the baseline LVESVi was larger in the CRT-D patients as noted above. However, both groups had marked reductions of LV volumes with CRT (P<0.0001 in both cases). The magnitude of the reverse remodeling response was similar, with mean reduction of LVESVi of 18.6±21.3 mL/m² in patients with CRT-P and 18.3±30.4 mL/m² in patients with CRT-D (P=0.92).

There were several other secondary end points collected in REVERSE, which are shown in Table 2. The 6-minute hall
walk distances improved ≈20 m in both groups at 1 year, again with no statistically significant difference between CRT-P and CRT-D patients (P=0.82). There were 2 different QOL indices measured in this study. Quality of life measured with both the Minnesota Living with Heart Failure and the Kansas City Cardiomyopathy scores improved to a similar extent with CRT.

The REVERSE cohort was followed for 5 years as a preplanned extension of the randomized portion of the trial. Such long-term follow-up allows for the assessment of mortality, which was low as expected during the first 1 to 2 years in patients with mild HF. The mortality curves for the CRT-P and CRT-D groups are presented in Figure 3. The curves separate early, and they continue to be separate for the full duration of follow-up. The HR is 0.66 indicating a 34% lower mortality rate in patients with CRT-D. However, this difference did not reach statistical significance (P=0.18).

As noted previously, there were some important clinical differences between the 2 groups. Accordingly, a multivariable analysis was performed to assess the independent impact of device type on mortality. The variables used and results of the multivariable analysis are shown in Table 3. After adjusting for important covariates, device type was a strong independent predictor (HR, 0.35; P=0.003) with improved survival among patients with CRT-D. The other significant predictors of mortality were baseline LVESVi, QRS duration, and sex with better survival in patients with smaller LV volume, longer QRS duration, and women. There was a strong trend for improved survival with younger age. Whereas the improved survival among women was not surprising, the magnitude of this effect (HR, 0.07) was large. This was attributable to the fact that only 1 of 92 women in the study died during the 5-year follow-up. To ensure that the significance of device type was not because of this unusually large effect, the multivariable analysis was rerun without sex as a covariate. Device type was still highly significant (HR, 0.40; P=0.008).

Ventricular tachycardia/ventricular fibrillation episodes were adjudicated through the randomized period of the study in the CRT-D group. During 24 months, 18.7% of patients with CRT-D had an appropriate, treated ventricular tachycardia/ventricular fibrillation episode. There were 307 ventricular tachycardia/ventricular fibrillation episodes with 54 (17.6%) terminated with shocks and the remaining 253 treated by ATP. Inappropriate shocks for non–ventricular tachycardia/ventricular fibrillation episodes occurred in 8.0% of patients >2 years.

The cause of death and adverse events were evaluated by an independent events committee. Overall, there were 13 (17.6%) deaths among patients with CRT-P and 40 (11.6%) among patients with CRT-D. The classifications of deaths are presented in Table 4 along with the percentage of patients dying from each cause. Patients with CRT-D had lower incidences of sudden death as well as noncardiac death, although the small numbers in each group preclude any meaningful statistical comparisons. Among the 74 patients with CRT-P, 21 patients (28%) had 25

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**Table 2. Change in Secondary End Points From Baseline to 12 Months**

<table>
<thead>
<tr>
<th></th>
<th>CRT-P (N=74)</th>
<th>CRT-D (N=345)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six-minute hall walk, m</td>
<td>21.1±105.1 (68)</td>
<td>18.1±97.6 (325)</td>
<td>0.82</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure Score</td>
<td>−8.2±14.3 (70)</td>
<td>−8.4±17.7 (316)</td>
<td>0.92</td>
</tr>
<tr>
<td>Kansas City Cardiomyopathy Score</td>
<td>5.7±16.6 (35)</td>
<td>9.0±17.9 (308)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Variables are represented by mean±SD (n). Student t test is used to test for statistical significance. Negative values represent improvement in the Minnesota Living with Heart Failure Score. CRT-D indicates cardiac resynchronization therapy with implantable defibrillators; and CRT-P, CRT-pacemakers.

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**Figure 1.** Clinical composite score at 12 months. CRT-D indicates cardiac resynchronization therapy with implantable defibrillators; and CRT-P, CRT-pacemakers.

**Figure 2.** Change in left ventricular end systolic volume index (LVESVi) from baseline to 12 months. CRT-D indicates cardiac resynchronization therapy with implantable defibrillators; and CRT-P, CRT-pacemakers.

**Figure 3.** Mortality >5 years of follow-up. CI indicates confidence interval; CRT-D, cardiac resynchronization therapy with implantable defibrillators; and CRT-P, CRT-pacemakers.
Table 3. Multivariable Analysis of Mortality Rate >5 Years Using the Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Baseline Parameters</th>
<th>Units/Level</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device type</td>
<td>CRT-D</td>
<td>0.35</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>Per 10 y</td>
<td>1.33</td>
<td>0.08</td>
</tr>
<tr>
<td>LVEF</td>
<td>Per 10%</td>
<td>0.92</td>
<td>0.74</td>
</tr>
<tr>
<td>QRS duration</td>
<td>Per 10 ms</td>
<td>0.81</td>
<td>0.008</td>
</tr>
<tr>
<td>LVESVI</td>
<td>Per 10 mL/m²</td>
<td>1.17</td>
<td>0.0003</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>0.07</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>1.04</td>
<td>0.90</td>
</tr>
<tr>
<td>Ischemic</td>
<td>Yes</td>
<td>1.78</td>
<td>0.15</td>
</tr>
<tr>
<td>NYHA class</td>
<td>I</td>
<td>0.82</td>
<td>0.57</td>
</tr>
<tr>
<td>LBBB</td>
<td>Yes</td>
<td>0.66</td>
<td>0.22</td>
</tr>
</tbody>
</table>

CRT-D indicates cardiac resynchronization therapy with implantable defibrillators; LBBB, left bundle–branch block; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end systolic volume index; and NYHA, New York Heart Association.

Complications related to the implant, system, or therapy during the course of follow-up. In the 345-patient CRT-D group, 119 patients (34%) had 191 related complications. During the 5-year follow-up, right ventricular lead complications were higher in the CRT-D group (76 complications in 63 of 335 patients; 18.3%) than the CRT-P group (5 complications in 5 of 74 patients; 6.8%) with a P value of 0.01. The CRT-D complications were largely because of failure of Fidelis leads.

Discussion

The primary results of the present analysis suggest that the addition of ICD therapy to CRT (CRT-D) reduces long-term mortality compared with CRT pacing alone. Multivariable analysis demonstrated a highly significant 65% reduction of mortality rates with CRT-D during the 5-year follow-up. The improvements at 1 year in clinical outcomes, echocardiographic volumetric changes, quality of life, and exercise capacity were similar between groups, suggesting that the survival benefit of CRT-D devices was independent of the effects of biventricular pacing, which was programmed similarly for both groups. CRT has been shown to improve functional status, reduce HF hospitalizations, promote reverse remodeling, and decrease all-cause mortality. These benefits were demonstrated in prospective randomized trials of both CRT-P and CRT-D devices, but no study has been powered to compare these devices directly. COMPANION randomized patients with severe HF to CRT-P, CRT-D, or optimal medical therapy. The composite primary end point of all-cause hospitalization or mortality was similar among the CRT groups. Only the CRT-D group was associated with significant decrease in all-cause mortality at 1 year compared with optimal medical therapy (P=0.003), whereas the 24% relative risk reduction in the CRT-P arm was only borderline significant (0=0.059). Moreover, sudden cardiac death was significantly reduced by CRT-D only during the 16 months follow-up. To our knowledge, REVERSE and COMPANION are the only prospective, randomized, multicenter trials that included both CRT-P and CRT-D devices.

The allocation of device type (CRT-P versus D) was not randomized in this trial but rather was determined by local guidelines at the time of enrollment. This resulted as expected in some important clinical differences between the groups. For instance, patients with ejection fraction >35% do not meet primary prevention ICD guidelines, and those with nonischemic cardiomyopathy were less likely to qualify for ICD backup early in the study enrollment. As a result, patients receiving CRT-P devices were less likely to have ischemic heart disease and more likely to have a left bundle–branch block morphology on their unpaced ECG, which are factors associated with better outcomes. In contrast, CRT-D patients had a larger baseline LV end systolic volume, a lower mean LV ejection fraction, and more often had right bundle–branch block, which are factors associated with worse outcome. These differences, mostly favoring CRT-P in expected survival prompted the adjustment for covariates in the multivariate analysis that led to the primary results. The other clinical predictors of improved mortality in the multivariate analysis were not surprising. These include baseline LVESVI, QRS duration, and sex. As expected, there was a strong trend for an effect of age on survival.

The results of several observational studies suggested improved survival with CRT-D devices. The European CRT Survey was a prospective, multinational, observational study. This study showed that CRT-P was independently associated with higher mortality, as well as atrial fibrillation, and advanced HF; 2 comorbidities excluded in REVERSE. There were trends for improved survival in women and with longer QRS duration, similar to the present study. Follow-up was much shorter for this study and was intended to evaluate 1-year outcomes with CRT. Auricchio et al performed a retrospective analysis of consecutive patients at several European Centers with longer follow-up. CRT-D was associated with a 20% reduction in mortality, which did not reach statistical significance in multivariate analysis. Finally, Morani et al recently showed that CRT-D reduced mortality compared with CRT-P in an Italian registry of patients with predominately advanced HF.

Compared with the studies noted above, REVERSE showed a greater benefit of CRT-D with relevance to mortality reduction. One possible explanation for the larger effect of ICD therapy may be the patient population enrolled in REVERSE. This was the only study of those evaluating both device types that was restricted to patients with mild HF. Pharmacological studies of HF show that the proportion of sudden death decreases and that of HF death increases as NYHA class increases. Consistent with this observation, subgroup analysis of Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed that a mortality benefit of ICD therapy was observed in NYHA II but not NYHA III patients. Extrapolating these effects to the CRT population suggest that a greater benefit for ICD backup may be present in mild HF.

Table 4. Causes of Death

<table>
<thead>
<tr>
<th>Cardiac Causes</th>
<th>CRT-P (N=74)</th>
<th>CRT-D (N=345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden</td>
<td>4 (5%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Nonsudden</td>
<td>3 (4%)</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>6 (8%)</td>
<td>16 (5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

CRT-D indicates cardiac resynchronization therapy with implantable defibrillators; and CRT-P, CRT-pacemakers.
noted in the present analysis. It is noteworthy that although most patients in REVERSE received concomitant ICDs, the guidelines for primary preventive ICDs were not identical between the countries included in this trial, as a lower percentage of Europeans patients received a CRT-D. In contrast, the use of HF medication, which also reduces the risk of sudden cardiac death, was excellent and nearly identical between geographic regions.

Adjudication of the etiology of deaths showed lower rates of sudden death with ICD backup, although this did not account for the full benefit of CRT-D therapy observed. Although the incremental benefit of CRT-D compared with CRT-P should be primarily attributable to a reduction of tachyarrhythmia deaths, the classification of deaths in HF trials is often challenging. This is one reason why all-cause mortality is a more accepted end point to assess therapy benefit. The benefit of ICD backup in this study was offset in part by increased complications. The majority of complications noted in the CRT-D group were associated with the ICD lead. The predominate lead implanted in this study was Fidelis, which had a high rate of complication and is no longer commercially available. Presumably with more reliable ICD leads, system complications will be lower.

There are several clinical implications of these data. First, CRT-D devices should be considered in patients with mild HF, particularly those with good long-term life expectancy. Second, CRT-D cost-effectiveness compared with CRT-P may be more favorable in mild HF compared with that noted with patients with advanced HF. A more formal analysis of long-term data will be needed to assess this hypothesis. Finally, the clinical predictors of long-term mortality with CRT are similar to the predictors of echo-cardiographic or clinical response in mild HF. Specifically, woman, younger age, increased un paced QRS duration, and smaller LV volumes were associated with lower mortality.

This study should be interpreted in the face of several methodological limitations. Randomization was not stratified based on device type, and most of these analyses were performed post hoc. Also, the study was not powered to detect any clinically relevant difference between patients with CRT-P and those with CRT-D. The small number of deaths (13) in the CRT-P arm could confound results. Finally, this study only evaluated patients with mild HF so the results may not necessarily apply to patients with more severe HF.

Conclusions
In summary, in the long-term follow-up of REVERSE, a low all-cause mortality of <3% annually was noted in this mild HF cohort. Analysis adjusting for baseline covariates showed that the addition of ICD therapy to CRT (CRT-D) was associated with a significant 65% relative reduction of mortality. Women, longer QRS duration, and smaller baseline LV volumes were also independent predictors of lower mortality.

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Disclosures
Drs Gold, Linde, and Daubert served as consultants to and received research grants from Medtronic. Drs Gold and Linde

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CLINICAL PERSPECTIVE

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with heart failure, left ventricular systolic dysfunction, and QRS prolongation. Previous multicenter, randomized clinical trials demonstrated decreased mortality, improved functional status, and left ventricular remodeling with CRT. These benefits have been noted with both CRT-pacemakers (CRT-P) as well as those devices with defibrillator backup (CRT-D). CRT-P devices are less expensive and have less morbidity associated with their use, but they do not have therapy to protect from ventricular tachyarrhythmias. The Resynchronization reVeRses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial is 1 of only 2 multicenter studies to include both CRT-P and CRT-D subjects and the only study to include mild (New York Heart Association I and II) heart failure. Long-term (5-year) follow-up of this study showed lower mortality in the CRT-D group. Specifically, multivariable analysis demonstrated that CRT-D (hazard ratio, 0.35; P=0.003) was a strong independent predictor of survival. Female sex, longer unpaced QRS duration, and smaller baseline left ventricular end systolic volume index were also associated with better survival, which is consistent with previous studies of CRT. Whereas REVERSE demonstrated that the addition of implantable cardioverter-defibrillator therapy to CRT is associated with improved long-term survival compared with CRT pacing alone in mild heart failure, further cost-effectiveness analyses should help guide clinicians select the optimal therapy for patients.
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