CRT Produces Long-term Improvements in Disease Progression in Mildly Symptomatic Heart Failure Patients: Five-year results from the RESynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study

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On Behalf of the REVERSE Study Group
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Acknowledgments

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Sponsor
Medtronic Inc.

Trial Registration
ClinicalTrials.gov ID NCT00271154
REVERSE Purpose and Design of main study

- To determine the effects of CRT with or without an ICD on disease progression over 12 months in patients with asymptomatic and mildly symptomatic heart failure and ventricular dysynchrony

- Randomized, double-blind, parallel-controlled clinical trial
REVERSE Study Design

Baseline
NYHA Class II or I (previously symptomatic), NSR, QRS \( \geq 120 \) ms, LVEF \( \leq 40\% \), LVEDD \( \geq 55 \) mm, without bradycardia, with or without ICD indication, on optimal medical therapy

All receive implant attempt

Successful CRT Implant

1:2 randomization

Randomized

**CRT OFF**
(OMT or OMT+ICD)

1, 3, 6, 12 Months

**Patients and clinicians managing HF are blinded**

**CRT ON**
(CRT+OMT or CRT+OMT+ICD)

1, 3, 6, 12 Months

At 1 Year in US and 2 yrs in Europe, all patients have CRT ON continued yearly follow-up over 5 yrs
End Points of main study

- **Primary**: HF Clinical Composite proportion of patients worsened in CRT OFF vs. CRT ON groups

- **Prospectively Powered Secondary**: Left Ventricular End Systolic Volume Index (LVESVi) comparing CRT OFF vs. CRT ON assessed by core labs

- **Other Secondary endpoints**: 6´walk, QoL, NYHA class, total mortality and HF hospitalizations adjudicated by DSMB for HF relatedness
** Primary Objective:**
Clinical Composite Score

- **Improved:** 40%
- **Unchanged:** 39%
- **Worsened:** 21%

**CRT OFF**

- **P=0.10**

**CRT ON**

- **54%**

**Powered Secondary Objective:**
Change in LVESVi

- **CRT OFF**
  - Δ = -1.3
  - **P<0.0001**

- **CRT ON**
  - Δ = -18.4

Long term (5 years) study Purpose

To evaluate if benefits in reverse remodeling, functional status, mortality, and HF hospitalizations are maintained over time in the 419 pts assigned to CRT ON
Methods of present 5 year follow up

- Yearly assessment of
- 6 min walk, QoL and NYHA class
- Echo-data by core lab
- HF related hospitalizations and mortality
- Serious adverse events – LV lead related

- As part of pre-specified substudy
Patients were followed annually at years 2, 3, 4, and 5.
Flow Diagram

684 Patients enrolled in REVERSE

419 Subjects randomized to CRT ON
- 419 Received CRT
- 0 Did not receive CRT

87 Did not complete study
- 53 Death
- 24 Withdrew consent
- 6 Lost to follow-up
- 3 Study device explanted, not replaced
- 1 Heart transplant

12 Permanently Discontinued CRT
- 4 Diaphragmatic stimulation
- 3 Worsening heart failure
- 2 Patient request
- 1 RV lead damage
- 2 Unknown

419 Analyzed
- 0 Excluded from analysis

684 Excluded
- 74 Not randomized
  - 33 Not meeting inclusion criteria
  - 6 Declined to participate
  - 21 Unsuccessful implant
  - 14 Other reasons
- 191 Randomized to CRT OFF

0 Did not receive CRT

0 Excluded from analysis
### Patient Characteristics

**CRT ON (n=419)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (yrs)</td>
<td>62.9 ± 10.6</td>
</tr>
<tr>
<td>Male (%)</td>
<td>327 (78.0%)</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>236 (56.3%)</td>
</tr>
<tr>
<td>CRT-D (%)</td>
<td>345 (82.3%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26.8 ± 7.0*</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.9 ± 0.9</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>152.8 ± 21.0</td>
</tr>
<tr>
<td>NYHA II (%)</td>
<td>344 (82.1%)</td>
</tr>
<tr>
<td>ACE Inhibitor or ARB (%)</td>
<td>404 (96.4%)</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>401 (95.7%)</td>
</tr>
</tbody>
</table>

*2 patients missing data
**LV Reverse Remodeling**

![Graph showing LV Reverse Remodeling](image)

- **LVESVI** and **LVEDVI** changes over months since randomization.
- Numbers are changes from baseline.
- Error bars represent 95% confidence intervals.
Total Mortality

% Mortality

Months Since Implant

Error bars represent 95% confidence intervals

5 yr 13.5%
Mortality and First HF Hospitalization

Error bars represent 95% confidence intervals

% With HF Hospitalization or Death

0 12 24 36 48 60

Months Since Randomization

5-yr 28.1 %
Clinical Measurements

Numbers in yellow are mean changes from baseline

**Minnesota score**
-10 -8 -8 -6 -7

**Kansas city score**
+11 +9 +8 +8 +7 +7

**Six minute walk**
+23 +19 +19 +19 +17 +1
Evolution of NYHA Class

% of Patients

Months Since Randomization

n 0 1 3 6 12 24 36 48 60

419 414 410 409 405 390 370 338 314
Adverse Effects:
LV Lead Related Complications

% of Patients with an LV Lead-related Complication

Months Since Implant

Number remaining
419  371  356  337  316  171

0%  10%  20%  30%  40%
Conclusions

CRT produced sustained reverse remodeling accompanied by low mortality and need for heart failure hospitalizations.

Benefits of CRT persisted indicating that CRT attenuates disease progression in mildly symptomatic heart failure patients with wide QRS over at least 5 years.