LV remodeling in heart failure

• Cardiac remodeling can be defined as progressive increases in size and changes in shape resulting in deterioration of function of the heart after cardiac injury.
• It is secondary to genome expression, molecular, cellular, and interstitial changes after the initial insult.
• It is the final common pathway toward the development of decompensating heart failure.
Gradual increases in left ventricular end-diastolic and end-systolic volumes, wall thinning, and a change in chamber geometry to a more spherical, less elongated shape.
Conclusions
In patients with normal systolic function, conventional right ventricular apical pacing resulted in adverse left ventricular remodeling and in a reduction in the left ventricular ejection fraction; these effects were prevented by biventricular pacing.
LV remodeling in heart failure

<table>
<thead>
<tr>
<th>Cardiac resynchronization therapy</th>
<th>LVEDD (mm)</th>
<th>LVESD (mm)</th>
<th>LVESVI (ml/m²)</th>
<th>LVEDVI (ml/m²)</th>
<th>EF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72.7 ± 9.2</td>
<td>71.6 ± 9.1</td>
<td>100 ± 36</td>
<td>129 ± 37</td>
<td>21.7 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>70 ± 10</td>
<td>-3.5</td>
<td>67 ± 12</td>
<td>121 ± 45</td>
<td>28.1 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>74 ± 10</td>
<td>67 ± 12</td>
<td>58 ± 12</td>
<td>121 ± 45</td>
<td>28.1 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>63 ± 10</td>
<td>58 ± 12</td>
<td>85 ± 29</td>
<td>119 ± 37</td>
<td>29 ± 6</td>
</tr>
<tr>
<td></td>
<td>116 ± 43</td>
<td>85 ± 29</td>
<td>119 ± 37</td>
<td>19 ± 5</td>
<td>29 ± 6</td>
</tr>
</tbody>
</table>

LVEDD, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea; CSA, central sleep apnea; n.a., not available.
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

For patients who have left ventricular ejection fraction (LVEF) less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, cardiac resynchronization therapy (CRT) with or without an ICD is indicated for the treatment of New York Heart Association (NYHA) functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.

For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.

For patients with LVEF less than or equal to 35% with NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy and who have frequent dependence on ventricular pacing, CRT is reasonable.

CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing.

CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
whether prophylactic CRT in combination with an ICD (CRT–ICD) would reduce the risk of death or nonfatal heart-failure events (whichever came first) in patients with an ejection fraction of 30% or less, a QRS duration of 130 msec or more, and NYHA class I or II symptoms, as compared with patients receiving only an ICD.

MADIT-CRT

**DESIGN**

North-America
1283 patients
(100 centres)

Europe
597 patients
(20 centres)

Inclusion period
22/12/2004 → 23/04/2008

1820 patients
(110 centres)

Randomisation
2 : 3

731 ICD
VVI 40 / DDD 40

1089 CRT–D
DDD 40

Clinical and device evaluation at 1 mo, then every 3-mo; Echocardiography at 1-yr

Primary end-point:
Time to all-cause death or first HF event

Intention to treat analysis; Echo corelab
MADIT CRT: Primary endpoint
Time to death or first heart failure event

Mean f/u time: 26 months


MADIT CRT: Secondary endpoint
Reverse remodeling at 1-year

Conclusion

This study provides evidence that preventive CRT–ICD therapy decreases the risk of heart-failure events in vulnerable patients with ischemic or nonischemic heart disease who have minimal heart-failure symptoms but a wide QRS complex.
**Purpose and Design**

- To evaluate the long-term benefits of CRT in the 262 European patients included in *REVERSE* and prospectively followed for 24 months

- Randomized, double-blind, parallel-arm controlled clinical trial

**Inclusion Criteria**

- NYHA Class II or I (previously symptomatic)
- \( \text{QRS} \geq 120 \ \text{ms} \)
- \( \text{LVEF} \leq 40\%; \ \text{LVEDD} \geq 55 \ \text{mm} \)
- Optimal medical therapy (OMT)
- Without permanent cardiac pacing
- With or without an ICD indication
End Points

- **Primary: HF Clinical Composite Response**, comparing the proportion of patients worsened in CRT OFF vs. CRT ON groups
  - Composite includes: all-cause mortality, HF hospitalizations, crossover due to worsening HF, NYHA class, and the patient global assessment assessed in double blind manner

- **Prospectively Powered Secondary:**
  - LV End Systolic Volume Index (LVESVi)
  - comparing CRT OFF vs. CRT ON subjects
  - LVESVi assessed by core labs (1 in Europe, 1 in U.S)

Study Schematic

- Baseline Assessment
- Successful CRT Implant
- Randomized 1:2
- CRT OFF (OMT ± ICD) 1
- CRT ON (OMT ± ICD) 2
- 12 Months: North American randomization complete (CRT recommended in all pts)
- 24 Months: European randomization complete (CRT recommended in all pts)
**Enrollment and Randomization**

- 642 Implant Attempts
- 621 Successful CRT Implants (97%)
- 610 Patients Randomized
  - U.S. 343 (56%); Europe 262 (43%); Canada 5 (<1%)

**Main Study: 12-Month**

**Clinical Composite Response**
- Pre-Specified Analysis
  - Proportion Worsened
  - CRT OFF: 21% Worsened, 16% Unchanged, 54% Improved
  - CRT ON: 39% Unchanged, 30% Improved
  - P=0.10

**Powered Secondary Objective**
- 12 Month Change in LVESVi
  - CRT OFF: Δ=-1.3
  - CRT ON: Δ=-18.4
  - P<0.0001

(C Linde et al, JACC 2008; 52: 1834-1843)
**Enrollment and Randomization**

- 621 Successful CRT Implants (97%)
- 610 Patients Randomized
  - U.S. 343 (56%)
  - Europe 262 (43%)
  - Canada 5 (<1%)
- CRT OFF 191 Patients
- CRT ON 419 Patients
- 262 patients (Europe) followed for 24 months
- CRT OFF 82 Patients
- CRT ON 180 Patients
- 42 ineligible or withdrew
- 11 exits after successful implant

**Primary End Point: Clinical Composite Response**

- Entire distribution analysis of worsened, unchanged and improved: P=0.0006
- CRT OFF:
  - Worsened: 34%
  - Improved/Unchanged: 66%
  - Entire distribution analysis: P=0.01
- CRT ON:
  - Worsened: 19%
  - Improved/Unchanged: 81%
  - Entire distribution analysis: P=0.0006

C Daubert et al. JACC 2009
Primary End Point
Clinical Composite Response
% worsened over time

Worsening attributed to death or HF hospitalization in 68% of worsened patients in the CRT OFF group

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>US/Can N=348</th>
<th>Europe N=262</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean) yrs</td>
<td>63.4 ± 11.3</td>
<td>61.3 ± 10.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Ischemic</td>
<td>63%</td>
<td>44%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA II</td>
<td>82%</td>
<td>83%</td>
<td>0.75</td>
</tr>
<tr>
<td>ICD</td>
<td>95%</td>
<td>68%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EF</td>
<td>26.3 ± 7.2</td>
<td>27.1 ± 6.8</td>
<td>0.16</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>65.5 ± 8.4</td>
<td>68.8 ± 9.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>151 ± 21</td>
<td>156 ± 23</td>
<td>0.008</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>96%</td>
<td>94%</td>
<td>0.13</td>
</tr>
<tr>
<td>ACE-i/ARB</td>
<td>95%</td>
<td>&gt;99%</td>
<td>0.0003</td>
</tr>
<tr>
<td>6-min. Walk (m)</td>
<td>363 ± 134</td>
<td>439 ± 103</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
**Powered Secondary End Point: LVESVi**

- CRT OFF
- CRT ON
- P<0.0001

P-value compares 24-month changes.

-C Daubert et al JACC 2009

**Other Remodeling Parameters**

- LVEDVi (ml/m^2)
- LVEF (%)

P-values compare 24-month changes.

-C Daubert et al JACC 2009
Other Secondary Endpoints

- **Minnesota Living with HF Score**
  - CRT OFF vs. CRT ON
  - P-values compare 24-month changes.

- **Six-minute Hall Walk (m)**
  - CRT OFF vs. CRT ON
  - P-values compare 24-month NYHA.

- **NYHA Class**
  - % Class I or II
  - P=0.17

Time to First HF Hospitalization or Death

- **Percentage Hospitalized for HF or Died**
  - CRT OFF vs. CRT ON
  - HR (95%CI): 0.38 (0.20-0.73)
  - P=0.003

- **Number at Risk**
  - CRT OFF: 82, 79, 76, 70, 39
  - CRT ON: 180, 176, 173, 168, 77

C Daubert et al. JACC 2009
**Conclusion**

Together with MADIT CRT, the 24 month results of the European cohort of REVERSE show that CRT is beneficial in mildly symptomatic HF patients on optimal medical therapy, by improving:

- clinical outcome (CCR or HF events)
- ventricular structure and function

CRT may modify disease progression in mildly symptomatic HF patients with broad QRS.

**THANK YOU**