BENEFIT OF CRT IN MILDLY SYMPTOMATIC HEART FAILURE
RECENT DATA FROM MADIT-CRT AND RAFT

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POINTS FOR DISCUSSION

- Reverse remodeling and subsequent outcomes
- Effect in subgroups
- Effect on ventricular and atrial tachyarrhythmias
REVERSE REMODELING AND DYSSYNCHRONY
● 1820 ICM/NICM pts:
  ➢ EF ≤ 30%
  ➢ QRS ≥ 130 msec
  ➢ NYHA I/II

● Randomization:
  ➢ CRT-D vs. ICD-only
  ➢ 3:2 ratio

● Outcome:
  ➢ HR=0.66 (p=0.001)
MADIT-CRT: ECHO RESPONSE
Solomon et al et al. Circulation, 2010

- Improvement at 1 yr:
  - LVEDV
  - LVESV
  - LAV
  - LVEF

![Graph showing percent and absolute improvement in LVEDV, LVESV, LA volume, and LVEF. P = 0.0001 for all comparisons.]
### MADIT-CRT: ECHO RESPONSE AND SUBSEQUENT CLINICAL RESPONSE

**Solomon et al et al. Circulation, 2010**

<table>
<thead>
<tr>
<th>Primary End Point of First Occurrence of Heart Failure or Death</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Treatment and Ischemic Status</td>
</tr>
<tr>
<td>Percent improvement in end-diastolic volume (per 10% decrease)</td>
<td>0.61 (0.51, 0.71)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percent improvement in end-systolic volume (per 10% decrease)</td>
<td>0.72 (0.65, 0.80)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increase in ejection fraction (per 5 percentage points increase)</td>
<td>0.61 (0.50, 0.73)</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MADIT-CRT: LEFT ATRIUM AND SUBSEQUENT CLINICAL OUTCOME

Goldenberg et al. Unpublished
MADIT-CRT: RIGHT VENTRICULAR REMODELING

![Graph showing RV fractional area change at one year (%)]
MADIT-CRT: DYSSYNCHRONY
Solomon et al. European Heart Journal, 2011
MADIT-CRT: DYSSYNCHRONY

A

Favours CRT
Favours ICD
Interaction P-value

LBBB
Non-LBBB
P=0.001

Female
Male
P=0.23

Ischaemic
Non-Ischaemic
P=0.003

QRS>150ms
QRS<150ms
P<0.001

B

Favours CRT
Favours ICD
Interaction P-value

LBBB
Non-LBBB
P<0.001

Female
Male
P=0.19

Ischaemic
Non-Ischaemic
P=0.002

QRS>150ms
QRS<150ms
P=0.001
CLINICAL EFFICACY IN SUBGROUPS
Differential clinical response:
- Gender
- QRS duration

Differential echo response:
- Ischemic vs. non-ischemic CMP
MADIT-CRT: QRS MORPHOLOGY

LBBB

RBBB

Non-LBBB

IVCD
### LBBB

<table>
<thead>
<tr>
<th>Age</th>
<th>No. Events/No. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>90/606</td>
</tr>
<tr>
<td>&gt;65</td>
<td>15/67</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16/507</td>
</tr>
<tr>
<td>Female</td>
<td>69/394</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
</tr>
<tr>
<td>Ischemic I</td>
<td>31/413</td>
</tr>
<tr>
<td>Ischemic II</td>
<td>113/920</td>
</tr>
<tr>
<td>Nonischemic II</td>
<td>109/718</td>
</tr>
<tr>
<td>QRS Duration</td>
<td></td>
</tr>
<tr>
<td>&lt;150 msec</td>
<td>76/300</td>
</tr>
<tr>
<td>&gt;150 msec</td>
<td>170/921</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
</tr>
<tr>
<td>≤35%</td>
<td>52/105</td>
</tr>
<tr>
<td>&gt;35%</td>
<td>201/1104</td>
</tr>
<tr>
<td>LVEDV</td>
<td></td>
</tr>
<tr>
<td>≤240 ml</td>
<td>126/660</td>
</tr>
<tr>
<td>&gt;240 ml</td>
<td>127/614</td>
</tr>
<tr>
<td>LVESV</td>
<td></td>
</tr>
<tr>
<td>≤170 ml</td>
<td>118/564</td>
</tr>
<tr>
<td>&gt;170 ml</td>
<td>131/620</td>
</tr>
<tr>
<td>All Patients</td>
<td>255/1281</td>
</tr>
</tbody>
</table>

### Non-LBBB

<table>
<thead>
<tr>
<th>Age</th>
<th>No. Events/No. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>48/244</td>
</tr>
<tr>
<td>&gt;65</td>
<td>76/292</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>111/477</td>
</tr>
<tr>
<td>Female</td>
<td>51/59</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
</tr>
<tr>
<td>Ischemic I</td>
<td>22/120</td>
</tr>
<tr>
<td>Ischemic II</td>
<td>69/214</td>
</tr>
<tr>
<td>Nonischemic II</td>
<td>86/102</td>
</tr>
<tr>
<td>QRS Duration</td>
<td></td>
</tr>
<tr>
<td>&lt;150 msec</td>
<td>71/343</td>
</tr>
<tr>
<td>&gt;150 msec</td>
<td>51/193</td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
</tr>
<tr>
<td>≤35%</td>
<td>12/31</td>
</tr>
<tr>
<td>&gt;35%</td>
<td>130/502</td>
</tr>
<tr>
<td>LVEDV</td>
<td></td>
</tr>
<tr>
<td>≤240 ml</td>
<td>61/315</td>
</tr>
<tr>
<td>&gt;240 ml</td>
<td>61/218</td>
</tr>
<tr>
<td>LVESV</td>
<td></td>
</tr>
<tr>
<td>≤170 ml</td>
<td>62/232</td>
</tr>
<tr>
<td>&gt;170 ml</td>
<td>59/230</td>
</tr>
<tr>
<td>All Patients</td>
<td>122/536</td>
</tr>
</tbody>
</table>
1798 ICM/NICM pts:
- EF ≤ 30%
- QRS ≥ 120 msec
- NYHA II/III

Randomization:
- CRT-D vs. ICD-only
- 1:1 ratio

Outcome:
- HR=0.68 (p<0.001)
Differences in clinical response:

- QRS duration
- QRS morphology
- Gender
CLASS I

1. CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, (546,547) III, or ambulatory IV (542–545); symptoms on GDMT. (Level of Evidence: A for NYHA class III/IV; Level of Evidence: B for NYHA class II)

CLASS IIa

1. CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT (542–544,546–548). (Level of Evidence: B)

2. CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT (542–544,547). (Level of Evidence: A)
Individual factors may contribute differently to the clinical response to CRT

Echocardiographic response correlated with clinical response in MADIT-CRT

Combined assessment of factors associated with a favorable echo response can identify patients who derive clinical benefit from CRT-D
STUDY DESIGN

**Step I: Derivation Analyses**
Identification of response factors

- **Sample:** CRT-D patients with paired echo data
- **Available:** 718 patients (101 events)
- **Unavailable:** 371 pts (87 events)

**Identification of 7 echo response factors to CRT-D**

**Step II: Construction of response score**

**Step III: Validation Analyses**
(yield of response score for assessment of clinical CRT-D benefit)

- **Sample:** All study patients with complete baseline data
- **Available:** 1761 patients (367 events)
- **Unavailable:** 59 patients (10 events)

**Evaluation of CRT-D vs. ICD reduction in clinical events by response score**

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Fig. 1: Study Design: Flow-Diagram*
## STEP I: FACTORS ASSOCIATED WITH ECHO RESPONSE TO CRT-D*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Incremental Response (SE)</th>
<th>P-value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>-2.9% (1.0%)</td>
<td>0.003</td>
<td>2</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>-4.2% (0.9%)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>QRS ≥ 150 msec</td>
<td>-2.7% (0.9%)</td>
<td>0.003</td>
<td>2</td>
</tr>
<tr>
<td>LBBB</td>
<td>-3.4% (1.0%)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Prior HF hospitalization</td>
<td>-1.9% (0.8%)</td>
<td>0.02</td>
<td>1</td>
</tr>
<tr>
<td>Baseline LAV &lt;40 ml/m²</td>
<td>-4.2% (1.1%)</td>
<td>&lt;0.001</td>
<td>3</td>
</tr>
<tr>
<td>Baseline LVEDV ≥ 125 ml/m²</td>
<td>-5.6% (1.0%)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
</tbody>
</table>

*Results are obtained from a best subsets analysis that included 25 prespecified clinical and echocardiographic candidate factors*
STEP II: CONSTRUCTION OF RESPONSE SCORE

- Response score range 0 to 14

- Pts categorized into approximate quartiles based on the distribution of the response scores:
  - Group 1 (n=391): Q1 score 0-4
  - Group 2 (n=401): Q2 score 5-6
  - Group 3 (n=469): Q3 score 7-8
  - Group 4 (n=500): Q4 score 9-14
PERCENT CHANGE IN LVEDV BY RESPONSE GROUP

P < 0.001
PERCENT CHANGE IN LVE SV BY RESPONSE GROUP

P < 0.001
CLINICAL BENEFIT BY SCORE GROUP

GROUP 1 (Q1 SCORE: 0-4)

GROUP 2 (Q2 SCORE: 5-6)

GROUP 3 (Q3 SCORE: 7-8)

GROUP 4 (Q4 SCORE ≥9)
<table>
<thead>
<tr>
<th>Response Groups</th>
<th>Score</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>P for Trend†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=1761)</td>
<td>0–14</td>
<td>0.62</td>
<td>0.51–0.77</td>
<td>&lt;0.001</td>
<td>NA</td>
</tr>
<tr>
<td>By response score quartile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n=391)</td>
<td>0–4</td>
<td>0.87</td>
<td>0.58–1.32</td>
<td>0.52</td>
<td>0.005</td>
</tr>
<tr>
<td>2 (n=401)</td>
<td>5–6</td>
<td>0.67</td>
<td>0.46–0.98</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>3 (n=469)</td>
<td>7–8</td>
<td>0.64</td>
<td>0.43–0.97</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>4 (n=500)‡</td>
<td>≥9</td>
<td>0.31</td>
<td>0.20–0.53</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>By individual response scores</td>
<td></td>
<td>0.87</td>
<td>0.81–0.96</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
LEAD POSITION IN MADIT-CRT
Singh et al. Circulation 2011

A

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral</td>
<td>381</td>
</tr>
<tr>
<td>Posterior</td>
<td>74</td>
</tr>
<tr>
<td>Anterior</td>
<td>95</td>
</tr>
</tbody>
</table>

B

- Lateral*: 56%
- Posterior*: 12%
- Anterior*: 18%
- All Apical: 14%

* Includes basal & mid-ventricular segments
LEAD POSITION IN MADIT-CRT
Singh et al. Circulation 2011

A

Heart failure only
Apical vs nonapical 1.55 (0.94–2.53) 0.083
Apical vs basal 2.20 (1.15–4.21) 0.018
Apical vs midventricular 1.38 (0.83–2.28) 0.214
Midventricular vs basal 1.60 (0.94–2.72) 0.086
Posterior vs anterior 1.11 (0.53–2.29) 0.787
Lateral vs anterior 0.99 (0.58–1.67) 0.985

Death
Apical vs nonapical 2.91 (1.42–5.97) 0.004*
Apical vs basal 5.27 (1.67–16.66) 0.005*
Apical vs midventricular 2.45 (1.17–5.14) 0.018*
Midventricular vs basal 2.15 (0.74–6.27) 0.161
Posterior vs anterior 0.51 (0.11–2.47) 0.404
Lateral vs anterior 0.79 (0.33–1.93) 0.506

B
Limitations

- No difference in echo response (somewhat better in apical)
- 110 pts with apical lead position; 24 HF/death events
- Endpoint driven primarily by mortality (total=10; noncardiac =4)
- Within CRT-D difference, without comparison to ICD group
REVERSE LV REMODELING AND SUBSEQUENT VENTRICULAR TACHYARRHYTHMIAS; Barsehshet/Goldenberg et al. JACC 2011

Unadjusted P<0.001

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Years</th>
<th>ICD 622</th>
<th>Low Response 220</th>
<th>High Response 529</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>497 (0.09)</td>
<td>182 (0.10)</td>
<td>451 (0.03)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>371 (0.13)</td>
<td>135 (0.14)</td>
<td>316 (0.05)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>263 (0.16)</td>
<td>67 (0.23)</td>
<td>203 (0.08)</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td></td>
<td>30 (0.28)</td>
<td>80 (0.12)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
REVERSE LV REMODELING AND SUBSEQUENT VENTRICULAR TACHYARRHYTHMIAS; Barsehshet/Goldenberg et al. JACC 2011
RECURRENT VENTRICULAR TACHYARRHYTHMIAS;
Oullet/Goldenberg et al. JACC 2012
### RECURRENT VENTRICULAR TACHYARRHYTHMIAS; Oullet/Goldenberg et al. JACC 2012

<table>
<thead>
<tr>
<th>Endpoint†</th>
<th>All Patients</th>
<th>LBBB Patients</th>
<th>Non-LBBB Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>First VTE (CRT-D vs. ICD)</td>
<td>0.71 (0.57–0.89)</td>
<td>0.003</td>
<td>0.58 (0.44–0.77)</td>
</tr>
<tr>
<td>Subsequent VTEs (CRT-D vs. ICD)</td>
<td>1.58 (0.99–2.53)</td>
<td>0.05</td>
<td>0.98 (0.61–1.60)</td>
</tr>
</tbody>
</table>

#### Treatment Effect

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D responder* vs. ICD</td>
<td>0.54</td>
<td>0.42–0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRT-D nonresponder† vs. ICD</td>
<td>1.45</td>
<td>1.17–1.80</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
REVERSE LA REMODELING AND SUBSEQUENT ATRIAL TACHYARRHYTHMIAS; Brenyo/Goldenberg et al. JACC 2011

A

N = 626

ICD

N = 752

CRT-D

P < 0.001

% Reduction in Left Atrial Volume

-30

-25

-20

-15

-10

-5

0

B

N = 621

ICD

CRT-D: Low Responders

N = 170

N = 581

CRT-D: High Responders

% Reduction in Left Atrial Volume

-30

-25

-20

-15

-10

-5

0

P < 0.001 for the overall difference

R = 0.63

P < 0.001

Percent Change in LAV

Percent Change in LVESV

-75

-50

-25

0

25

50
REVERSE LA REMODELING AND SUBSEQUENT ATRIAL TACHYARRHYTHMIAS; Brenyo/Goldenberg et al. JACC 2011

**A**

Unadjusted P=0.03

Unadjusted P=0.03

CRT-D <20% reduction

ICD Only

CRT-D >=20% reduction

Patients at Risk
ICD Only 621 (598 (0.02)) 513 (0.03) 392 (0.06) 275 (0.07) 185 (0.07)
CRT-D <20% 170 (164 (0.02)) 147 (0.04) 127 (0.06) 98 (0.06) 58 (0.05)
CRT-D >=20% 581 (565 (0.02)) 484 (0.02) 319 (0.03) 175 (0.03) 66 (0.03)

**B**

Unadjusted P=0.001

Unadjusted P=0.001

CRT-D <20% reduction

ICD Only

CRT-D >=20% reduction

Patients at Risk
ICD Only 621 (598 (0.04)) 513 (0.06) 392 (0.09) 275 (0.11) 185 (0.11)
CRT-D <20% 170 (164 (0.04)) 147 (0.07) 127 (0.09) 98 (0.14) 58 (0.14)
CRT-D >=20% 581 (565 (0.02)) 484 (0.03) 319 (0.05) 175 (0.06) 66 (0.06)
TAKE HOME MESSAGES:
CRT IN MILD HF PTS

- Clinical benefit directly related to reverse remodeling of LV/LA
- No evidence for clinical benefit in non-LBBB pts
- No evidence for difference in efficacy within LBBB pts by QRS width
- Combined assessment can be used to identify enhanced responders
- Data regarding apical lead position require further validation
TAKE HOME MESSAGES: CRT IN MILD HF PTS

- Reverse remodeling effects on LV are directly related to reduced risk for ventricular tachyarrhythmias.

- Reverse remodeling effects on LA are directly related to reduced risk for atrial tachyarrhythmias.

- CRT may increase recurrent VA risk in non-LBBB patients (NYHA I/II).