Can the Problem of CRT Non-Responder be Overcome?

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## 1/3 of Patients Are Clinical Non-Responders of CRT

<table>
<thead>
<tr>
<th>Study</th>
<th>% Improved Clinical Composite Score</th>
</tr>
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<tbody>
<tr>
<td>MIRACLE I</td>
<td>67%</td>
</tr>
<tr>
<td>MIRACLE II</td>
<td>52%</td>
</tr>
<tr>
<td>MIRACLE ICD</td>
<td>58%</td>
</tr>
<tr>
<td>InSync III Marquis</td>
<td>67%</td>
</tr>
<tr>
<td>PROSPECT</td>
<td>69%</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>67%</td>
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</tbody>
</table>


* AV optimised only
Elements for CRT Response in LBBB

Dyssynchrony

LV Scar
- Non-transmural
- <15% volume

CS Pacing Site
- Delay site
- CS anatomy

Paced CD at Pacing Site

Multi-site Epi vs Endo

Large functional block

Optimization of CRT Delivery after Implant!
Causes of “Non-Responders” to CRT

Cohort of 75 consecutive patients (Mullens et al JACC 2009;53:765)

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
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<tbody>
<tr>
<td>Suboptimal AV/VV timing</td>
<td>47%</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>30%</td>
</tr>
<tr>
<td>Suboptimal LV lead position</td>
<td>20%</td>
</tr>
<tr>
<td>Persistent mechanical dyssynchrony</td>
<td>20%</td>
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</tbody>
</table>
## Indications for CRT (SR)

*ESC Guideline. EHJ 2016;37:2129-2200*

<table>
<thead>
<tr>
<th>Class</th>
<th>Indications</th>
<th>Level</th>
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<tbody>
<tr>
<td><strong>Class I:</strong></td>
<td>OPT (&gt;3 months)</td>
<td>IA if QRS ≥ 150 ms</td>
</tr>
<tr>
<td></td>
<td>NYHC II-IV (ambulatory)</td>
<td>IB if QRS 130-149 ms</td>
</tr>
<tr>
<td></td>
<td>LVEF ≤ 35%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QRS ≥ 130 ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LBBB</td>
<td></td>
</tr>
<tr>
<td><strong>Class II:</strong></td>
<td>Non-LBBB + Above</td>
<td>IIa if QRS ≥ 150 ms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIb if QRS 130 - 149 ms</td>
</tr>
<tr>
<td><strong>Class III:</strong></td>
<td>QRS &lt; 130 ms</td>
<td>--</td>
</tr>
</tbody>
</table>

2013 ACC/AHA/ACCF/HRS focused update: Class I indication only for QRS > 150 ms
## Criteria for Complete LBBB

**Strauss DG et al. AJC 2011;107:927-934 (1)**

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Additional</th>
</tr>
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<tbody>
<tr>
<td>QRS (ms)</td>
<td>≥ 120</td>
<td>Men ≥ 140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Women ≥ 130</td>
</tr>
<tr>
<td>V1</td>
<td>QS rS</td>
<td>QS rS V1 + V2</td>
</tr>
<tr>
<td>I &amp; V6</td>
<td>R NoQ</td>
<td>Mid-QRS notching or slurring in ≥ 2 of leads I, aVL, V1, V2, V5, V6</td>
</tr>
</tbody>
</table>
How to Increase CRT Response

1. **Pre-implantation:**
   - Patient Selection criteria

2. **Implantation:**
   - LV lead site
   - Quadripolar lead

3. **Post implantation management**
The qLV & CRT Response

Gold MR et al. EHJ 2011;32:2516-2524 (1)

qLV is a measure of inter-ventricular delay (electrical dyssynchrony), and long qLV predicts CRT response. (qLV > 95 ms, qLV/QRSd > 70%)
## Quadripolar Electrodes LV Leads

<table>
<thead>
<tr>
<th>Abbott</th>
<th>Biotronik</th>
<th>Boston</th>
<th>Medtronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartet (4 spacings)</td>
<td>Sentus QP (2 spacings)</td>
<td>Acuity x4 (3 spacings)</td>
<td>Attain Performa (3 spacings)</td>
</tr>
</tbody>
</table>

### Advantages

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhance stability</td>
<td>Electronic positioning</td>
</tr>
<tr>
<td>Wide bipolar stimulation</td>
<td>Avoid Phrenic nerve stimulation</td>
</tr>
<tr>
<td>Optimize qLV</td>
<td>↓Pacing threshold</td>
</tr>
<tr>
<td>Multi-point pacing</td>
<td>Avoid apical pacing</td>
</tr>
<tr>
<td></td>
<td>- Circumvent pacing at scars</td>
</tr>
</tbody>
</table>
Goals of MultiPoint™ Pacing

- Pacing from two LV sites (& a RV SITE) is designed to capture more tissue and provide additional CRT options to change:
  - Pattern of depolarization
  - Engagement of areas around scar tissue
  - Hemodynamics
  - Resynchronization

MULTIPOINT™ PACING ALLOWS PACING FROM TWO LV SITES THROUGH JUST ONE CRT LEAD.
Ventricular Activation Pattern & Acute Hemodynamics: BiV vs MPP
Menardi E et al. HR 2015;12:1762-1769 (2)
1. 381 pts with CRT-D and quadripolar leads were randomised to BiV or MPP at 3 months

2. Primary safety and efficacy endpoints of non-inferiority were met (safety 93.2%, non-responders 25 - 29.7%)

3. MPP–AS with ≥ 3 cm interelectrode spacing resulted in 87% non-responders at 9 months, and conversion of all 3 month non-responders to responders
MOre REsponse to CRT with MPP (I)
Leclercq C et al. EHJ 2019

1,921 pts received CRT with MPP were studied. Volume non-responders (39.9%) were randomised either to continued BiV (231 pts) or MMP (236 pts) for an additional 6 months. Conversion rate to responders were similar (37.8 vs 31.8%)

Conclusion:
MPP with widely spaced (≥ 3 cm) bipolar MMP-AS may convert more non-responders to responders

[MORE-CRT II, Leclercq C, AHA 2019 : Prospective evaluation of MMP-AS vs BiV]
Post-implantation Management to Maximize Responders

- Pacing Operation issue
- % BiV pacing
- Arrhythmias
  - AT / AF
  - VA
- Optimal resynchronisation
  - AV, VV timing
- Management of current & new medical conditions
AV and VV Optimization in CRT: a Meta-analysis
Auger D et al. AHJ 2013;16:20-29

**Background:** Routine/algorithm based AV/VV optimization was compared to empirical device programming.

<table>
<thead>
<tr>
<th>Study</th>
<th>OPT Outcome Total</th>
<th>Control Outcome Total</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 2006</td>
<td>3 26</td>
<td>4 15</td>
<td>1.9%</td>
<td>0.36 [0.07, 1.89]</td>
</tr>
<tr>
<td>Sawhney 2004</td>
<td>5 20</td>
<td>12 20</td>
<td>2.7%</td>
<td>0.22 [0.06, 0.86]</td>
</tr>
<tr>
<td>Response-HF</td>
<td>9 29</td>
<td>18 36</td>
<td>4.2%</td>
<td>0.45 [0.16, 1.25]</td>
</tr>
<tr>
<td>RYTHM-II</td>
<td>25 78</td>
<td>8 29</td>
<td>4.8%</td>
<td>1.24 [0.48, 3.18]</td>
</tr>
<tr>
<td>Vidal 2007</td>
<td>10 51</td>
<td>13 49</td>
<td>4.8%</td>
<td>0.68 [0.26, 1.73]</td>
</tr>
<tr>
<td>Aldbrecht 2010</td>
<td>73 133</td>
<td>51 72</td>
<td>8.5%</td>
<td>0.50 [0.27, 0.92]</td>
</tr>
<tr>
<td>DECREASE-HF</td>
<td>70 104</td>
<td>59 101</td>
<td>9.2%</td>
<td>1.47 [0.83, 2.59]</td>
</tr>
<tr>
<td>Abraham 2012</td>
<td>30 122</td>
<td>41 116</td>
<td>9.3%</td>
<td>0.60 [0.34, 1.05]</td>
</tr>
<tr>
<td>CLEAR</td>
<td>47 123</td>
<td>54 115</td>
<td>10.1%</td>
<td>0.70 [0.42, 1.17]</td>
</tr>
<tr>
<td>In-Sync III</td>
<td>144 397</td>
<td>71 215</td>
<td>13.6%</td>
<td>1.15 [0.81, 1.64]</td>
</tr>
<tr>
<td>SMART-AV</td>
<td>170 655</td>
<td>69 325</td>
<td>14.3%</td>
<td>1.30 [0.95, 1.79]</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>261 781</td>
<td>248 744</td>
<td>16.7%</td>
<td>1.00 [0.81, 1.23]</td>
</tr>
</tbody>
</table>

**Conclusion:** Overall neutral result with resting AV + VV adjustment at rest and/or repeated on follow up assessment. There is significant individual patient response. [Kosmala W, AJC 2014 using a different set of studies suggest a 2.6% ↑ LVEF, but no difference in 6MWD or QOL]. Guideline suggests optimization for non-responders.
Dynamic AV and VV Optimization

Background
1. Different techniques and pt subsets
2. Most are cohort studies
3. ‘Optimal’ AV and VV intervals derived at rest do not account for changes during daily activities, exercise, drugs and LV remodelling.

Dynamic Optimization
1. Medtronic Adaptive CRT
2. Abbott SyncAV (+F0I)
3. Sorin atrial accelerometer sensor (SonR)
4. Biotronik CRT Auto Adapt (EGM based)
Synchronization of LV pacing to spontaneous RV conduction may obviate RVP in CRT.

Acute hemodynamic study on 17 pts with LVEF 30±1% and QRS 135±25 ms with LVP vs BVP.
AdaptivCRT™ Concept

LBBB

AS

RV

S

< 200ms

LVP to fix QRS

AS

LV

V

P

≥ 200ms

AVB and LBBB

AS

RV

S

≥ 200ms

BVP to fix PR and QRS

AS

B

V

P

Medtronic Viva XT CRT-D manual.
aCRT Trial
Martin DO... Lee KL et al. HR 2012;9:1807-14

Pts & Methods: 522 pts with EF ≤ 35%, NYHC III/IV and QRS ≥ 120ms received BVP, and were programmed to either aCRT on vs off (2:1). Control arm had echo-optimisation. CCS and Echo as primary endpoints to assess outcome.

Non-inferiority P < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Unchanged</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdaptivCRT</td>
<td>74%</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Echo control</td>
<td>73%</td>
<td>16%</td>
<td>11%</td>
</tr>
</tbody>
</table>
In AdaptivCRT™, 150 patients had normal AV conduction. Compared to Control Arm with echo-optimized CRT:

**AdaptivCRT:**
- Produced mostly Adaptive LV pacing (73% +/- 25%)
- Resulted in better clinical response at 6 months (81% vs. 69%)
- Reduction in AF

12% improvement in clinical outcomes for patients with Normal AV Conduction*

*Percentage of patients improved in Packer Clinical Composite Score at 6-month follow-up. Clinical Composite Score is a composite measure of mortality, HF hospitalizations, and symptomatic changes.

**% LV Only Pacing:**
- AdaptivCRT with Normal AV intervals (n=150) - 81%
- Echo-optimized with Normal AV intervals (n=91) - 69%
SYNC AV™ CRT ALGORITHM

INTRINSIC-AVI ADAPTIVE DYNAMIC AV DELAY

DeltaAV Nominal = -50 ms. Optimising 0 or -10 to -120 ms, VV ± 30ms

SyncAV™ CRT technology adjusts the AV delay for the next 256 cycles using the following equation:

\[
AV_{\text{Delay}} = (\text{Intrinsic Conduction Time}) - (\text{SyncAV CRT Delta})
\]

Adaptive AVI based on iAVI

Intrinsic Conduction Time = 184 ms
SyncAV™ CRT Delta = -50 ms

AV\_Delay w/SyncAV™ CRT = (184 - 50) = 134 ms
BVP with Fusion
Vatasescu R et al, Europace 2009;11:1675-1682

CARTO mapping in 15pts with DCM + LBBB, EF 25±5% with BVP. RV fusion occurred in 8/15 pts who had shorter AVI (164±24 vs 234±55 ms, p=0.0006)

Results & Conclusion:
6 months responder rate was higher (100 vs 28.5%) as was the degree of LVESV reduction (39±17 vs 1.0±14%)
Fusion – Optimized Interval (FOI) for Manual /VV BV CRT Synchronization: Acute Effect


FOI optimises AVI, and at the AVI narrowest QRS, further optimized VV interval.
Fusion – Optimized Interval (FOI) for Manual AV/VV BV CRT Synchronization: Acute Effect

Dp/dt was improved from $102 \pm 71$ to $127 \pm 95$ mmHg/s compared with normalised CRT in 31 pts, with QRS
# Adaptive CRT vs SyncAV

<table>
<thead>
<tr>
<th></th>
<th>Adaptive CRT</th>
<th>FOI + SyncAV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Principle</strong></td>
<td>LV pacing fusion with intrinsic RB</td>
<td>Minimize QRS</td>
</tr>
<tr>
<td><strong>Maximum PR</strong></td>
<td>&lt; 200 ms</td>
<td>&lt; 300 ms</td>
</tr>
<tr>
<td><strong>Adaptation</strong></td>
<td>Once/min</td>
<td>Once after 256 beats</td>
</tr>
<tr>
<td><strong>Acute Response</strong></td>
<td>Improved RV function</td>
<td>Maximum QRSd reduction</td>
</tr>
<tr>
<td><strong>compared to BV</strong></td>
<td>Similar LV hemodynamics</td>
<td>Improved hemodynamic</td>
</tr>
<tr>
<td><strong>Long term</strong></td>
<td>• Non-inferior to echo-AVI</td>
<td>• Fixed FOI or SyncAV</td>
</tr>
<tr>
<td></td>
<td>• In those with normal PR interval, improved clinical outcome</td>
<td>improved remodelling but not clinical outcome</td>
</tr>
<tr>
<td></td>
<td>• AF improved in those with BiV over LV</td>
<td>(combined FOI + SyncAV prospective trial underway)</td>
</tr>
</tbody>
</table>

**FOI + SyncAV**

- Non-inferior to echo-AVI
- Improved RV function
- Improved hemodynamic
- Maximum QRSd reduction

**Adaptive CRT**

- LV pacing fusion with intrinsic RB
- Minimize QRS
- < 200 ms
- Once/min
- Improved RV function
- Similar LV hemodynamics
- Fixed FOI or SyncAV improved remodelling but not clinical outcome
MPP

FOI

SyncAV
Role of Further Medication Optimization after CRT
Schmidt S et al. EHJ 2014;35:1051-60

Pts & Background: Improvement in LVEF after CRT may allow higher doses of ACEI/ARB and BB, but lower doses of diuretics. Retrospective review of meds changes after CRT in 185 pts (with initial OPT) and a mean FU of 44.6m

Conclusion: Higher doses of ACEI/ARB and BB, and ↓ diuretics improve HF death + hospitalization after CRT
Real World Action in Non-responders after CRT

1. **Clinical assessment:**
   OMT, intercurrent illnesses (e.g. anemia, ↑ T₄, infection, arrhythmia, ischemia)

2. **Device data**
   - % BVP
   - Fluid index + Activity score + HRV
   - AF burden
   - VPC

3. **Confirm LVP/Phrenic nerve stimulation**

4. **Treatment of arrhythmias**

5. **Optimization of AV/VV intervals**
   Include selection of pacing configurations in MPP

6. **Consider alternative LV stimulation sites**