De Novo CRT in Patients With Conventional Pacemaker Indications Without Heart Failure

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MY CONFLICTS OF INTEREST ARE:
Medtronic, Boston Scientific (consultant); Medtronic (research support); Medtronic (DSMB, Events Committee)
# Indications for Permanent Pacing

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Sinus node disease. Pacing is indicated when symptoms can clearly be attributed to bradycardia.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2) Sinus node disease. Pacing may be indicated when symptoms are likely to be due to bradycardia, even if the evidence is not conclusive.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>3) Sinus node disease. Pacing is not indicated in patients with SB which is asymptomatic or due to reversible causes.</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>4) Acquired AV block. Pacing is indicated in patients with third- or second-degree type 2 AV block irrespective of symptoms.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>5) Acquired AV block. Pacing should be considered in patients with second-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at EPS.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>6) Acquired AV block. Pacing is not indicated in patients with AV block which is due to reversible causes.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
Once pacing indicated, does device selection and programming matter?
Conventional Pacing Lead Positions

• The first-order pacing goal was resolution of bradycardia – atrial leads were added to establish AV synchrony.

• Pacing leads were designed for easy and reliable delivery to the RV apex, RA appendage – where the position was considered convenient and stable after years of clinical practice.
Relationship of Ventricular Pacing to New/Worsened Heart Failure Outcome in SSS PPM Patients (MOST)

Cum%Vp at 30 days and subsequent HFH events

DDDR/Normal QRS

Proportion event-free

Cum%Vp ≤ 40
Cum%Vp > 40

P=0.047

Sweeney et al, Circulation 2003
Risk of HF Relative to Mode/%Pacing (MOST)

The graph shows the risk of HF (Heart Failure) relative to cumulative pacing (%VP) for different modes of pacing: DDDR and VVIR. The x-axis represents cumulative pacing (%VP) grouped into four categories: 0-20, 20-30, 30-40, and >40. The y-axis represents the risk of HF, which is quantified on a scale from 0 to 12.

- In the 0-20% VP category, the risk of HF is higher for VVIR compared to DDDR.
- In the 20-30% VP category, the risk of HF is also higher for VVIR.
- In the 30-40% VP category, the risk of HF remains higher for VVIR.
- In the >40% VP category, the risk of HF is significantly higher for VVIR, indicating a greater risk compared to DDDR.
Death or First Hospitalization for New/Worsened CHF in Diverse ICD Patients (DAVID)

Cumulative Probability

P ~ 0.03

VP = 60%

VP = 3%

N at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Follow-up 0</th>
<th>Follow-up 6</th>
<th>Follow-up 12</th>
<th>Follow-up 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDDR-70</td>
<td>250</td>
<td>159</td>
<td>76</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>VVI-40</td>
<td>256</td>
<td>158</td>
<td>90</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

Wilkoff et al, Cardiac Electrophysiology Review 2003
Relationship of Ventricular Pacing to New/Worsened CHF in Primary Prevention ICD Patients (MADIT II)

Steinberg et al, JCE 2005
Relationship of Ventricular Pacing to ICD Therapy for VT/VF (MADIT II)

Steinberg et al, JCE 2005
Decline in Normal Ventricular Function With RVP?

Nahlawi et al, JACC 2004; Kurshid et al, Heart Rhythm 2014
ECG of Paced QRS Complex
Mechanisms Underlying the Deleterious Effects of RV Apical Pacing

• Intraventricular conduction delay
• LV mechanical and electrical dyssynchrony
• LV remodeling
• Abnormal myocardial histopathology
• LV systolic dysfunction
• Overt congestive heart failure
• Myocardial perfusion defects
• Mitral regurgitation
• Left atrial dilation
• Increased atrial fibrillation
• Promotion of ventricular arrhythmias
• Activation of sympathetic nervous system
Summary of Potential Harm from Chronic RVP

• Observed in diverse patient device groups
• Dose effect, ie more pacing associated with more harm
• Patients with more baseline LV dysfunction most vulnerable
• Multitude of plausible mechanisms for harm, and individuals may be affected differently
• Clinical manifest harm follows preclinical measures of ventricular dysfunction, ie opportunity for preemption
Principles for Device Selection and Programming

• Almost all PPM patients who are not in permanent AF will receive a dual chamber device (RA/RV)
• If AV conduction is intact, avoid unnecessary RV pacing
  – Longer AV intervals
  – Algorithms to avoid RV pacing
  – Back-up pacing only for ICD patients
• In general, avoid programming to AAI(R) mode and/or extremely long AV intervals
But in many patients, continuous ventricular pacing is unavoidable. How can deleterious effects of RVP be mitigated?
No difference in:
- 6 min hall walk
- SF-36 QoL
- Heart failure hospitalizations

➢ Progressive benefit over time

Yu et al, NEJM 2009; Chan et al, Eur Heart J 2011
Study Purpose and Objectives

**Purpose:** Biventricular pacing is superior to RV apical pacing in patients with AV block and LVEF $\leq 50\%$ who require ventricular pacing

**Endpoints:**

**Primary:** Composite of:

- All-cause mortality,
- HF-related urgent care, defined as
  - HF hospitalization requiring IV therapy, or
  - Any unplanned visit requiring intravenous HF therapy, and
- Increase in left ventricular end systolic volume index (LVESVI) $\geq 15\%$

**Key Secondary:** All-cause mortality,

- All-cause mortality/HF hospitalization,
- HF hospitalization
Acknowledgments

**Steering Committee**
Curtis AB (Principal Investigator), Adamson PB, Chung ES, St. John Sutton MG, Worley SJ

**Echo Core Lab**
St. John Sutton MG, Plappert T

**Adverse Events Advisory Committee**
Boehmer JP, Meyer TE (Chair), Smith AL, De Lurgio DB

**Data Monitoring Committee**
Steinberg JS (Chair), DeMarco T, Elkayam U, Louis TA (Statistician)

**Investigators**
- **Canada:** Rinne C, Thibault B

**Sponsor**
Medtronic Inc.

**Clinical Trials.gov Identifier:** NCT00267098

Caution: Use of CRT devices for AV block and systolic dysfunction patients without ventricular dyssynchrony is not an approved use in the United States.
**Study Design**

- **Implant** (CRT-P/D)
- **Establish OMT** (30-60 days)
- **Randomize** 1:1
- **Control**: RV pacing
- **Treatment**: BiV pacing
- **Double-Blind**
- **Follow-up Every 3 months**

**ELIGIBILITY CRITERIA**

- AV block necessitating pacing
- Left ventricular ejection fraction (LVEF) ≤ 50%
- NYHA functional class I, II or III
- Absence of a Class I indication for resynchronization therapy
- No previous pacemaker or implantable cardioverter defibrillator (ICD)
- Echocardiography performed at Randomization, 6, 12, 18 and 24 months

**OMT**=optimal medical therapy  
**CRT-P**=cardiac resynchronization therapy pacemaker  
**CRT-D**=CRT defibrillator
**Study Flow Diagram**

**Enrollment**
- 918 Assessed for eligibility

**Allocation**
- 691 Randomized 1:1
  - 349 Allocated to Biventricular Pacing
    - 346 Received allocated intervention
    - 3 Did not receive allocated intervention
  - 342 Allocated to Right Ventricular Pacing
    - 342 Received allocated intervention

**Follow-up**
- 52 Exited/lost to follow-up
- 75 Deaths
- 13 Crossed over to Right Ventricular Pacing
  - 3 Met primary endpoint prior to crossover
- 50 Exited/lost to follow-up
- 90 Deaths
- 84 Crossed over to Biventricular Pacing
  - 50 Met primary endpoint prior to crossover

**Analysis**
- 349 Analyzed
  - 83 Censored for primary endpoint due to missing LVESVI data
- 342 Analyzed
  - 71 Censored for primary endpoint due to missing LVESVI data

**227 Subjects not randomized:**
- 95 Subjects for whom inclusion criteria not met (e.g., AV conduction testing criteria not met prior to implant)
- 14 Subject withdrawals prior to implant
- 51 Unsuccessful implants
- 67 Implanted subjects not randomized

**BLOCK HF**
# Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>CRT-P (BiV N=243)</th>
<th>CRT-D (BiV N=106)</th>
<th>CRT-P (RV N=241)</th>
<th>CRT-D (RV N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>75%</td>
<td>82%</td>
<td>70%</td>
<td>80%</td>
</tr>
<tr>
<td>Age, years</td>
<td>74 ± 10</td>
<td>72 ± 9</td>
<td>74 ± 11</td>
<td>71 ± 10</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>43 ± 7</td>
<td>33 ± 8</td>
<td>43 ± 7</td>
<td>33 ± 8</td>
</tr>
<tr>
<td>Heart Rate, beats/min</td>
<td>69 ± 23</td>
<td>68 ± 17</td>
<td>69 ± 24</td>
<td>69 ± 17</td>
</tr>
<tr>
<td>QRS Duration, ms</td>
<td>125 ± 33</td>
<td>123 ± 30</td>
<td>125 ± 31</td>
<td>119 ± 30</td>
</tr>
<tr>
<td>NYHA I</td>
<td>14%</td>
<td>10%</td>
<td>20%</td>
<td>16%</td>
</tr>
<tr>
<td>NYHA II</td>
<td>58%</td>
<td>63%</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td>NYHA III</td>
<td>27%</td>
<td>26%</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Left Bundle Branch Block</td>
<td>35%</td>
<td>35%</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>39%</td>
<td>63%</td>
<td>38%</td>
<td>58%</td>
</tr>
<tr>
<td>1st Degree AV Block</td>
<td>17%</td>
<td>27%</td>
<td>15%</td>
<td>31%</td>
</tr>
<tr>
<td>2nd Degree AV Block</td>
<td>33%</td>
<td>33%</td>
<td>29%</td>
<td>38%</td>
</tr>
<tr>
<td>3rd Degree AV Block</td>
<td>49%</td>
<td>40%</td>
<td>56%</td>
<td>32%</td>
</tr>
<tr>
<td>ACE Inhibitor/ARB at Randomization</td>
<td>71%</td>
<td>83%</td>
<td>74%</td>
<td>88%</td>
</tr>
<tr>
<td>Beta Blocker at Randomization</td>
<td>75%</td>
<td>92%</td>
<td>78%</td>
<td>92%</td>
</tr>
<tr>
<td>Diuretics at Randomization</td>
<td>64%</td>
<td>72%</td>
<td>66%</td>
<td>70%</td>
</tr>
</tbody>
</table>
**Primary Endpoint Results:**

**Mortality/HF Urgent Care/LVESVI**

### Table: Estimated HR (95% CI) and Probability HR < 1

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Estimated HR (95% CI)</th>
<th>Probability HR &lt; 1</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Randomized Subjects</td>
<td>0.74 (0.60, 0.90)</td>
<td>0.9978</td>
<td>0.9775</td>
</tr>
<tr>
<td>CRT-P Only</td>
<td>0.73 (0.58, 0.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D Only</td>
<td>0.75 (0.57, 1.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Clinical Components of Primary Endpoint: Mortality/HF Urgent Care Visits**

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</tr>
</thead>
<tbody>
<tr>
<td>All Randomized Subjects</td>
<td>0.73 (0.57, 0.92)</td>
<td>0.997</td>
<td>N/A</td>
</tr>
<tr>
<td>CRT-P Only</td>
<td>0.73 (0.56, 0.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D Only</td>
<td>0.73 (0.53, 1.02)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary Objective Results: HF Hospitalization and Mortality

<table>
<thead>
<tr>
<th>Cohort</th>
<th>HF Hospitalization</th>
<th>Mortality</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated HR (95% CI)</td>
<td>Probability HR &lt; 1</td>
<td>Estimated HR (95% CI)</td>
</tr>
<tr>
<td>All Randomized Subjects</td>
<td>0.70 (0.52, 0.93)</td>
<td>0.9922</td>
<td>0.83 (0.61, 1.14)</td>
</tr>
</tbody>
</table>

**Event-Free Rate (%)**

<table>
<thead>
<tr>
<th>Number of Months</th>
<th>Number at Risk</th>
<th>BiV Arm</th>
<th>RV Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>349</td>
<td>290</td>
<td>250</td>
</tr>
<tr>
<td>20</td>
<td>270</td>
<td>228</td>
<td>200</td>
</tr>
<tr>
<td>40</td>
<td>198</td>
<td>193</td>
<td>168</td>
</tr>
<tr>
<td>60</td>
<td>137</td>
<td>128</td>
<td>132</td>
</tr>
<tr>
<td>80</td>
<td>93</td>
<td>94</td>
<td>111</td>
</tr>
<tr>
<td>100</td>
<td>54</td>
<td>55</td>
<td>68</td>
</tr>
</tbody>
</table>

**Number of Months**

<table>
<thead>
<tr>
<th>Number at Risk</th>
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<td>111</td>
</tr>
<tr>
<td>100</td>
<td>55</td>
<td>68</td>
</tr>
</tbody>
</table>
Strengths and Limitations

**STRENGTHS:**
- Prospective, randomized, double-blind control design
- Largest, longest follow-up trial to date
- First to show difference in outcomes in AV block and LV systolic dysfunction patients with BiV vs. RV pacing

**LIMITATIONS:**
- Long enrollment duration
- All patients received CRT systems
- Censoring due to missing LVESVI in primary objective
- Crossover imbalance between arms:
  - 24.6% crossed over from RV to BiV
  - 4.6% crossed over from BiV to RV
Conclusions

• In patients with AV block and LV systolic dysfunction (LVEF ≤ 50%), BiV pacing compared to RV pacing leads to a significant 26% reduction in the combined endpoint of mortality, heart-failure related urgent care, and increase in LVESVI.

• Furthermore, there is a 27% relative risk reduction in the composite endpoint of heart-failure urgent care and all-cause mortality.
Packer Clinical Composite Score

- **PP=0.999**
  - BIV: 53% Improved, 39% Unchanged, 24% Worsened
  - RV: 46% Improved, 34% Unchanged, 28% Worsened

- **PP>0.999**
  - BIV: 42% Improved, 32% Unchanged, 21% Worsened
  - RV: 38% Improved, 30% Unchanged, 23% Worsened

- **PP=0.998**
  - BIV: 37% Improved, 47% Unchanged, 39% Worsened
  - RV: 39% Improved, 51% Unchanged, 38% Worsened

**BLOCK HF**

N=691

N=686

N=648

N=622
# Packer Clinical Composite Score at 6 Months

<table>
<thead>
<tr>
<th>Episode Type</th>
<th>Number(%) of Subjects</th>
<th>BIV Arm (N=349)</th>
<th>RV Arm (N=342)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worsened</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>10 (2.9%)</td>
<td>16 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>HF Hospitalization</td>
<td>18 (5.2%)</td>
<td>32 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Therapy Discontinuation for Worsening HF</td>
<td>0 (0%)</td>
<td>12 (3.5%)</td>
<td></td>
</tr>
<tr>
<td>Worsened NYHA</td>
<td>50 (14.3%)</td>
<td>34 (9.9%)</td>
<td></td>
</tr>
<tr>
<td>Moderately/Markedly Worse Global Assessment</td>
<td>4 (1.1%)</td>
<td>2 (0.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unchanged</strong></td>
<td>83 (23.8%)</td>
<td>113 (33.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Improved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Assessment &amp; NYHA</td>
<td>184 (52.7%)</td>
<td>133 (38.9%)</td>
<td></td>
</tr>
<tr>
<td>Global Assessment Only</td>
<td>37 (10.6%)</td>
<td>26 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>NYHA Only</td>
<td>126 (36.1%)</td>
<td>91 (26.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 (6%)</td>
<td>16 (4.7%)</td>
<td></td>
</tr>
</tbody>
</table>

- RV arm had 18% incidence of x-over to BIV
Change in NYHA Class from Baseline

BIV arm had significantly better improvement at 12 months.
Improvement in Quality of Life from Baseline

Significant difference seen at 6 and 12 months (PP > 0.95)
For patients with AV block and systolic dysfunction, BIV pacing not only reduces the risk of mortality/morbidity, but also leads to better clinical outcomes and improved patient quality of life and HF status.
What About Patients With Preexisting RV Pacemakers? An Opportunity for Intervention at Generator Change?

- 50 patients with RV PPM and >80% RVP at time of generator replacement
- LVEF < 50% but no CHF
- Randomized to CRT-P upgrade vs simple generator change
- CRT-P patients had better exercise capacity and QoL, lower BNP and fewer hospitalization days
- But required longer procedure and fluoroscopy times

Gierula et al, Europace 2013
Based on BLOCK HF and proposed indications, panel voted:

- 6-1 that CRT-P device is safe
- 7-0 that CRT-P device is effective
- But 3-3-1 that benefits outweigh risks
- Tiebreaker by chairman brought final vote to 4-3-1
- Panel stipulated that indications should be changed to eliminate patients without AVB and that there be “verifiable confidence that ventricular pacing is needed in this patient most of the time”
### What Do the Guidelines Say?

#### Table 3. Indications for CRT in Patients with Right Ventricular Pacing for Brady Indications

<table>
<thead>
<tr>
<th>Guidelines, Year</th>
<th>Indication (Excluding Classic CRT Indications for Native QRS &gt; 120 ms)</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 ACCF/AHA guideline for the management of heart failure and 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities</td>
<td>1. CRT can be useful in patients with atrial fibrillation and LVEF ≤ 35% on recommended medical therapy if • the patient requires ventricular pacing or otherwise meets CRT criteria; and • AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT. 2. CRT can be useful for patients on recommended medical therapy who have LVEF ≤ 35%, and are undergoing placement of a new or replacement device with anticipated requirement for significant (&gt;40%) ventricular pacing</td>
<td>IIA</td>
</tr>
<tr>
<td>2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy</td>
<td>1. CRT is indicated in patients with LVEF &lt;35% and high percentage of RV pacing, who remain in NYHA III or ambulatory NYHA IV despite optimal medical therapy (upgrade). 2. CRT should be considered in HF patients with reduced LVEF, and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF (de novo implant).</td>
<td>IIA</td>
</tr>
<tr>
<td>2012 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure</td>
<td>CRT is indicated in patients with an indication for conventional pacing and no other indication for CRT if: • NYHA III or IV with LVEF ≤ 35% irrespective of QRS duration, to reduce the risk of HF worsening • NYHA II with LVEF ≤ 35% irrespective of QRS duration, to reduce the risk of HF worsening</td>
<td>IIA</td>
</tr>
</tbody>
</table>

Guglin and Barold, ANE 2015
Implications

1. Consider primary CRT-P in patients
   - Who have clinical indication for permanent pacemaker
   - With projected dominant ventricular pacing
   - LVEF < 50%

2. Consider upgrade to CRT-P in patients
   - At time of generator replacement
   - When LV function has significantly declined
   - When no other cause for LV dysfunction is likely
   - Particularly if very wide QRS and HF symptoms

3. In all predominantly paced patients
   - Perform regular assessment of LV function, HF status and QRS duration
Thank you!