HEART FAILURE
SPECIALIST’S PERSPECTIVE:
EP DEVICES-WHO, WHEN
AND WHAT?

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HEART FAILURE SPECIALIST’S PERSPECTIVE –EP DEVICES
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I will discuss off label use and/or investigational use in my presentation.

I have financial relationships to disclose:
Employee of: university of florida
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A remodeled ventricle from any cause exhibits dys-synchrony at an interventricular, intraventricular and atrio-ventricular level.

The single most robust indicator of good outcomes to CRT is the presence of a QRS duration of > 149 msecs with LBBB.
CRT

- What have we learned about the QRS
- Untreated QRS most reliable predictor of prognosis and CRT need
- Change in QRS with CRT not predictive of response
- The non specificity of the QRS hides a highly variable phenotype of dys-synchrony and LBBB-best predictor of outcome
The phenotype of dys-synchrony is highly variable.

Resting measures of mechanical dys-synchrony are not useful as predictors of outcome with CRT.
CRT

• CRT in appropriate patients with HF reverses the structural phenotype, improves LV performance, reduces MR, decreases symptoms, and improves quality of life and decreases progressive pump failure and SCD

• Women with HF and LBBB receiving CRT seem to respond better than men
CRT

- There is no single echocardiographic predictor for a successful response to CRT before or after implant
- Women and non ischemic cardiomyopathy patients have the greatest likelihood for a “super response” with EF improving > 15%
- Echo optimization remains unproven
- CRT only devices reduce SCD
813 patients with advanced heart failure (LVEF ≤ 35%, NYHA class III or IV), and cardiac dyssynchrony despite standard pharmacological therapy. Randomized

Control
Continued optimal pharmacological therapy  
\( n=404 \)

Cardiac Resynchronization Therapy (CRT)
Pharmacological therapy with CRT  
\( n=409 \)

Endpoints (mean 29.4 months):
Time to first event for the composite of hospitalization for a major cardiovascular event or all-cause mortality

Presented at ACC Scientific Sessions 2005
Baseline clinical characteristics were similar between the treatment groups, with 46% of patients having dilated cardiomyopathy and 38% with ischemic heart disease.

Mean LV ejection fraction was 25%.

Of the 409 patients randomized to the CRT device, 95% had a successful implantation.

The primary endpoint of all-cause mortality or hospitalization for a major cardiovascular event occurred less frequently in the CRT group than the medical therapy alone group (hazard ratio [HR] 0.63, 95% CI 0.51-0.77).

The major secondary endpoint of all-cause mortality was also lower in the CRT group (HR 0.64, 95% CI 0.48-0.85).

*Presented at ACC Scientific Sessions 2005*
The composite of death or hospitalization for worsening heart failure was also lower in the CRT group (HR 0.54, p<0.001).

Patients in the CRT group had a lower NYHA class and a higher Euro Quality of Life score at 90 days.

Mean left ventricular ejection fraction was higher on average in the CRT group compared with the medical therapy alone group.
Among patients with advanced heart failure despite standard pharmacological therapy, treatment with cardiac resynchronization therapy was associated with a reduction in the primary endpoint of all-cause mortality and hospitalization for major cardiovascular events compared with standard pharmacological therapy.

Similar results were observed in the COMPANION trial, which showed a reduction in the composite endpoint of death or hospitalization through a mean 16 month follow-up in patients treated with CRT with or without an implantable defibrillator, but the reduction in mortality did not reach statistical significance (p=0.06).
CRT

- Outcome is directly related to the % of time paced and the presence or absence of atrial fibrillation.
- Small increases of % paced yield survival benefits: >99.6% better than 98.5-99.6%, is better than 98.5-95, is better than < 95%. Atrial fibrillation negates these small advantages.
CRT

- Decide up front as to whether CRT beneficial- QRS < 149 msec, large LA volumes
- CRT devices are cost effective
- Battery life is short so many patients will require a second generator
Background

CLINICAL IMPORTANCE

• Over 1 million people world-wide and 819,000 people in the US have atrioventricular (AV) block
  • Currently treated with standard pacemaker (i.e. right ventricular (RV pacing)) therapy

• Approximately 6 million in the US are currently diagnosed with heart failure (HF) and approximately 670,000 new cases confirmed each year
  • According to AHA 2012 statistics, this costs the US approximately $20 to $56 billion annually

• DAVID and MOST Trial results have shown that RV pacing may have long-term deleterious effects

• Can biventricular (BiV) pacing prevent progression of heart failure and its clinical and economic consequences in AV block?
Study Design

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 Purpose and Objectives**

**Purpose:** Biventricular pacing is superior to RV apical pacing in patients with AV block and LVEF <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) >15%

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

- All-cause mortality/HF hospitalization,
- HF hospitalization
Primary Endpoint Results: Mortality/HF Urgent Care/LVESVI

<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>
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</tr>
</tbody>
</table>
**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
- 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


Benefit for NYHA class I and II patients has been shown in CRT-D trials, and while patients may not experience immediate symptomatic benefit, late remodeling may be avoided along with long-term HF consequences. There are no trials that support CRT-pacing (without ICD) in NYHA class I and II patients. Thus, it is anticipated these patients would receive CRT-D unless clinical reasons or personal wishes make CRT-pacing more appropriate. In patients who are NYHA class III and ambulatory class IV, CRT-D may be chosen but clinical reasons and personal wishes may make CRT-pacing appropriate to improve symptoms and quality of life when an ICD is not expected to produce meaningful benefit in survival.
CRT-CLINICAL GOALS FOR “RESPONSE”

• Clinical functional improvement (+ 30 M 6MWT)
• Improvement in cardiac structure and function
  • 20% de cr LVEDV, 5% incr EF, 3mm de cr LVEDD
• Improved MR jet area > 2 cm2
• Improved neurohormones
• < 50% de cr NT Pro BNP 1 month post
CRT

- Why is CRT not effective in certain patients
  - Patient selection
  - Patient selection
  - Patient selection
Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex

Frank Ruschitzka, M.D., William T. Abraham, M.D., Jagmeet P. Singh, M.D., Ph.D., Jeroen J. Bax, M.D., Ph.D., Jeffrey S. Borer, M.D., Josep Brugada, M.D., Ph.D., Kenneth Dickstein, M.D., Ph.D., Ian Ford, M.D., Ph.D., John Gorcsan, III, M.D., Daniel Gras, M.D., Henry Krum, M.B., B.S., Ph.D., Peter Sogaard, M.D., D.M.Sc., Johannes Holzmeister, M.D., for the EchoCRT Study Group

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Study Overview

• In a randomized trial, patients with heart failure and a QRS duration of less than 130 msec were assigned to cardiac-resynchronization therapy (CRT) or no CRT.

• There were no significant differences in rates of death from any cause or hospitalization for heart failure.
Study Enrollment, Randomization, and Follow-up.

Kaplan–Meier Estimates for Primary-Outcome Events.

Characteristics of the Patients at Baseline.

### Table 2. Protocol-Specified Cardiovascular Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control Group (N = 405)</th>
<th>CRT Group (N = 404)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause or hospitalization for heart failure</td>
<td>102 (25.2)</td>
<td>116 (28.7)</td>
<td>1.20 (0.92–1.57)</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Components of primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>90 (22.2)</td>
<td>99 (24.5)</td>
<td>1.16 (0.87–1.55)</td>
<td>0.25</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>26 (6.4)</td>
<td>45 (11.1)</td>
<td>1.81 (1.11–2.93)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Other cardiovascular outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization for cardiovascular event</td>
<td>137 (33.8)</td>
<td>147 (36.4)</td>
<td>1.11 (0.88–1.40)</td>
<td>0.36</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>17 (4.2)</td>
<td>37 (9.2)</td>
<td>2.26 (1.27–4.01)</td>
<td>0.004</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10 (2.5)</td>
<td>17 (4.2)</td>
<td>1.74 (0.80–3.81)</td>
<td>0.15</td>
</tr>
<tr>
<td>Follow-up data censored</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Owing to LVAD implantation</td>
<td>10 (2.5)</td>
<td>7 (1.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Owing to heart transplantation</td>
<td>5 (1.2)</td>
<td>3 (0.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Death after data were censored owing to LVAD implantation or heart transplantation†</td>
<td>4 (1.0)</td>
<td>1 (0.2)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated by means of the Cox model with adjustment for country, and P values were calculated by the stratified log-rank test. LVAD denotes left ventricular assist device.
† Because these deaths occurred after LVAD implantation or heart transplantation, they were not included in the analysis of mortality.
Serious Adverse Events after Implantation, According to Study Group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Control Group (N = 405)</th>
<th>CRT Group (N = 404)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events</td>
<td>no. of patients with event (%)</td>
</tr>
<tr>
<td>All events</td>
<td>732</td>
<td>221 (54.6)</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>423</td>
<td>160 (39.5)</td>
</tr>
<tr>
<td>Worsening heart failure</td>
<td>181</td>
<td>93 (23.0)</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>35</td>
<td>25 (6.2)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>29</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>26</td>
<td>21 (5.2)</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>17 (4.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11</td>
<td>10 (2.5)</td>
</tr>
<tr>
<td>Noncardiovascular event</td>
<td>259</td>
<td>121 (29.9)</td>
</tr>
<tr>
<td>Infection</td>
<td>54</td>
<td>45 (11.1)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>41</td>
<td>28 (6.9)</td>
</tr>
<tr>
<td>Other</td>
<td>55</td>
<td>36 (8.9)</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>38</td>
<td>22 (5.4)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>19</td>
<td>16 (4.0)</td>
</tr>
<tr>
<td>Musculoskeletal disorder</td>
<td>18</td>
<td>15 (3.7)</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>5</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>CRT-D–system related</td>
<td>32</td>
<td>29 (7.2)</td>
</tr>
<tr>
<td>ICD lead</td>
<td>13</td>
<td>13 (3.2)</td>
</tr>
<tr>
<td>Lead for right atrial pacing</td>
<td>5</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Lead for left ventricular pacing</td>
<td>4</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Implantation related</td>
<td>18</td>
<td>16 (4.0)</td>
</tr>
</tbody>
</table>

* Data for subcategories with an incidence of less than 3.0% are not shown. Patients could have more than one event. CRT-D denotes cardiac-resynchronization device with defibrillator, and ICD implantable cardioverter–defibrillator.

Conclusions

• In patients with systolic heart failure and a QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality.
CRT

• Why is CRT not effective in certain patients
  • Technical and procedural issues
  • Epicardial lead
  • Arrhythmias-PVCs and atrial fibrillation
CRT-AREAS OF UNCERTAINTY

• Atrial fibrillation
• RBBB or non LBBB
• Scar and positioning
• Qualitative aspects of dys-synchrony