Update of Clinical Study and Unresolved Issues in Cardiac Resynchronization Therapy

전북의대 이경석
Relationship of the Implantable Cardioverter Defibrillator and Chronic Resynchronization Therapy: The Perfect Marriage?

David S. Cannom, M.D., and Morton Mower, M.D.
Good Samaritan Hospital Los Angeles, Los Angeles, California
ANE Suppl 2005;10:24

Table 1. Mirowski/Mower Legacy of Pivotal Therapies

<table>
<thead>
<tr>
<th></th>
<th>ICD</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concept</td>
<td>1970</td>
<td>Mid 1970s</td>
</tr>
<tr>
<td>Patent</td>
<td>1971</td>
<td>1990</td>
</tr>
<tr>
<td>First implant</td>
<td>1981</td>
<td>1991</td>
</tr>
<tr>
<td>FDA/CMS approval</td>
<td>1984</td>
<td>2004</td>
</tr>
<tr>
<td>Pivotal trials</td>
<td>MADIT I &amp; II</td>
<td>COMPANION</td>
</tr>
<tr>
<td></td>
<td>SCD-HeFT</td>
<td>CARE-HF</td>
</tr>
<tr>
<td></td>
<td>AVID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CIDS</td>
<td></td>
</tr>
</tbody>
</table>
CRT Studies before COMPANION/CARE-HF

- Short-term studies and “On-therapy” analysis.
- Changes in Functional status:
  * Positive change for some, but not all, measures
  * Inconsistent changes within and across studies.
- All-cause mortality and Total hospitalization:
  * No significant change — MIRACLE, VENTAK CHF/CONTAK CD, or InSync ICD.
  * All studies Underpowered (small sample sizes).
## COMPANION CARE-HF

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III – IV CHF</td>
<td>Class III – IV CHF</td>
</tr>
<tr>
<td>EF $\leq 35%$ (M = 21%)</td>
<td>EF $\leq 35%$ (M = 25%)</td>
</tr>
<tr>
<td>QRS $\geq 120$ ms, NSR</td>
<td>QRS $\geq 120$ ms, NSR</td>
</tr>
<tr>
<td>Ischemic (56%)</td>
<td>Ischemic (38%)</td>
</tr>
<tr>
<td>No. Pts. = 1520</td>
<td>No. Pts. = 813</td>
</tr>
</tbody>
</table>

### Randomization
- OPT vs CRT vs **CRT-D** (1:2:2)
- OPT vs CRT (1:1)
Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure

Michael R. Bristow, M.D., Leslie A. Saxon, M.D., John Boehmer, M.D., Steven Krueger, M.D., David A. Kass, M.D., Teresa De Marco, M.D., Peter Carson, M.D., Lorenzo DiCarlo, M.D., David DeMets, Ph.D., Bill G. White, Ph.D., Dale W. DeVries, B.A., and Arthur M. Feldman, M.D., Ph.D., for the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators*
COMPANION: Endpoints

1. Primary
   * Composite of Death or Hospitalization (both any-cause)
     - Definition of hospitalization: all-cause except elective admission for CRT

2. Secondary
   * All-cause mortality, Cardiac morbidity, Exercise performance (Sub-Study: J Cardiac Fail 2008;14:9)

3. Tertiary
   * Submaximal exercise, QoL...
COMPANION: Total of 1020 primary endpoints were analyzed

* Composite of Death or Any Hospitalization

12-month event rate:

- OPT 68 %
- CRT 56 %
- CRT-D 56%

→ Reductions: ~ 20 %
COMPANION: Secondary Endpoint

* All-Cause Mortality

12 mo Event Rate:
- OPT 19%
- CRT 15%
- CRT-D 12%

→ Reductions:
- CRT = 24% (P=.06)
- CRT-D = 36% (P=.004)

Benefit of CRT on mortality takes time (reverse remodeling), ICD benefit is immediate.
**Mode of Death** in Advanced Heart Failure  
The Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) Trial  
*JACC 2005;46:2329*

**Figure 3.** Kaplan-Meier estimate of the time to first sudden cardiac death. Abbreviation as in Figure 1.
Predictors of Sudden Cardiac Death and Appropriate Shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial *Circulation* 2006;114:2766

Mean 15.7 mo F/U
83 SD / 1519 pts

<table>
<thead>
<tr>
<th></th>
<th>OPT</th>
<th>CRT</th>
<th>CRT-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 15.7 mo F/U</td>
<td>5.8%</td>
<td>7.8%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

**TABLE 2. Risk of Sudden Cardiac Death**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>P Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-D</td>
<td>0.47</td>
<td>0.02</td>
<td>(0.24 to 0.91)</td>
</tr>
<tr>
<td>CRT</td>
<td>1.21</td>
<td>0.48</td>
<td>(0.71 to 2.09)</td>
</tr>
<tr>
<td>LVEF &gt;20%</td>
<td>0.55</td>
<td>0.01</td>
<td>(0.35 to 0.87)</td>
</tr>
<tr>
<td>QRS &gt;160 ms</td>
<td>0.63</td>
<td>0.05</td>
<td>(0.40 to 0.997)</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.47</td>
<td>&lt;0.01</td>
<td>(0.27 to 0.82)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>2.62</td>
<td>&lt;0.01</td>
<td>(1.61 to 4.26)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>1.69</td>
<td>0.03</td>
<td>(1.06 to 2.69)</td>
</tr>
</tbody>
</table>
Impact of Cardiac Resynchronization Therapy on Exercise Performance, Functional Capacity, and Quality of Life in Systolic Heart Failure With QRS Prolongation: COMPANION Trial Sub-Study J Cardiac Fail 2008;14:9

1° End point: Δ peak VO$_2$

Data missing: 31% at 6mo
→ No difference between Tx groups.

Within Tx groups
CRT ↑ (P < .05)
Δ: 1.13ml/kg/min at 3mo, 1.26 at 6 mo

OPT: no significant ↑

Predictor of Clinical Outcome
peak VO$_2$ < 12.5ml/kg/min
→ mortality (↑3x) in CRT cohort
COMPANION:
Summary of Major Outcomes

• Reduction in the Combined Endpoints of Death + all cause Hospitalization was due to CRT

• Therapy with an ICD in addition to CRT substantially increased the mortality reduction, attributable to reduction in SCD (HR 0.64)

• Follow up only 12 months
The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure

John G.F. Cleland, M.D., Jean-Claude Daubert, M.D., Erland Erdmann, M.D., Nick Freemantle, Ph.D., Daniel Gras, M.D., Lukas Kappenberger, M.D., and Luigi Tavazzi, M.D., for the Cardiac Resynchronization — Heart Failure (CARE-HF) Study Investigators*
CARE-HF

1. Primary endpoint
   : composite of Death from any cause or Hospitalization for a major cardiovascular event.

2. Secondary endpoint
   : Death from any cause classified according to endpoint.
Kaplan-Meier Estimates of the Time to the **Primary End Point** and the Principal **Secondary Outcome**

29.4 months

**1° End point**

<table>
<thead>
<tr>
<th>Risk Reduction</th>
<th>37% (P&lt; .001)</th>
</tr>
</thead>
</table>

**2° End point**

<table>
<thead>
<tr>
<th>Risk Reduction</th>
<th>36% (P&lt; .002)</th>
</tr>
</thead>
</table>

Deaths 82 (20%), SCD 29 (35%)

Deaths 120 (30%), SCD 38 (32%)

HR=0.64

HR=0.63
Quality of Life Data from CARE-HF Study Outcomes in Analyses Stratified According to NYHA Class

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>OPT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>39</td>
<td>&lt; 105</td>
</tr>
<tr>
<td>II</td>
<td>112</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>III ~ IV</td>
<td>152</td>
<td>&gt; 80</td>
</tr>
</tbody>
</table>

### Continuous outcome

<table>
<thead>
<tr>
<th></th>
<th>Medical Therapy Alone (N=404)</th>
<th>Medical Therapy plus Cardiac Resynchronization (N=409)</th>
<th>Difference in Means (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class</td>
<td>2.7±0.9</td>
<td>2.1±1.0</td>
<td>0.6 (0.4 to 0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure score§</td>
<td>40±22</td>
<td>31±22</td>
<td>-10 (-8 to -12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EuroQoL EQ-5D score¶</td>
<td>0.63±0.29</td>
<td>0.70±0.28</td>
<td>0.08 (0.04 to 0.12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Conclusion of CARE-HF

• CRT alone reduces total mortality by 36% (HR 0.64, P<.002)

• Effect continued over 18 months

• BNP level decreased at 3 mo, further↓ at 18 months (1,122 pg/ml)

• However a significant number of SCDs (35%) occurred in the CRT arm some of which could be prevented
COMPANION somewhat higher risk population than CARE-HF

<table>
<thead>
<tr>
<th></th>
<th>CARE-HF (n=813)</th>
<th>COMPANION (n=1520)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OPT</td>
<td>CRT-P</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66</td>
<td>66.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73</td>
<td>73.5</td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>7</td>
<td>6.5</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>EF (%)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>35</td>
<td>38</td>
</tr>
</tbody>
</table>

1-year Control Group Mortality:
COMPANION 19 % > CARE-HF 12.6 %
Strikingly Similar

### Table 1. Mode of Death Overall, and Within Each Treatment Group

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>OPT</th>
<th>CRT</th>
<th>CRT-D</th>
<th>CARE-HF n (%)</th>
<th>OPT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[%†]</td>
<td>[%†]</td>
<td>[%†]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>308</td>
<td>617</td>
<td>595</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>54 (18.8) [75.3]</td>
<td>109 (17.1) [83.2]</td>
<td>76 (12.8) [72.4]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCD</td>
<td>18 (5.8) [23.4]</td>
<td>48 (7.8) [36.6]</td>
<td>17 (2.9) [16.2]</td>
<td>38 (32)</td>
<td>29 (35)</td>
<td></td>
</tr>
<tr>
<td>Pump failure</td>
<td>34 (11.0) [44.2]</td>
<td>53 (8.6) [40.5]</td>
<td>52 (8.7) [49.5]</td>
<td>56 (47)</td>
<td>33 (40)</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>4 (1.3) [5.2]</td>
<td>2 (0.3) [1.5]</td>
<td>4 (0.7) [3.8]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac procedure</td>
<td>2 (0.6) [2.6]</td>
<td>6 (1.0) [4.6]</td>
<td>2 (0.3) [1.9]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0 (0) [0]</td>
<td>0 (0) [0]</td>
<td>1 (0.2) [1.0]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>0 (0) [0]</td>
<td>5 (0.8) [3.8]</td>
<td>3 (0.5) [2.8]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>11 (3.6) [14.3]</td>
<td>14 (2.3) [10.7]</td>
<td>21 (3.5) [20.0]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (2.6) [10.4]</td>
<td>3 (0.5) [2.3]</td>
<td>5 (0.8) [4.8]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>77 (25.0)</td>
<td>131 (21.2)</td>
<td>105 (17.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*% of deaths by randomized patients within each group. †% of deaths within each treatment group.*
Early and Late Hemodynamic and Electrophysiologic Effects of CRT

- Proarrhythmia & Long Term Sustained Benefit
Effect of Epicardial or Biventricular Pacing to **Prolong QT Interval and Increase Transmural Dispersion of Repolarization**. *Does Resynchronization Therapy Pose a Risk for Patients Predisposed to Long QT or Torsade de Pointes?* *Circulation* 2003;107:740

Comparison of the QT interval and JT interval among baseline rhythm, RV Endocardial, biventricular, and LV epicardial pacing in 29 pts.

→ **Early Effect**
Effect of Epicardial or Biventricular Pacing to **Prolong QT Interval** and **Increase Transmural Dispersion of Repolarization**. Does Resynchronization Therapy Pose a Risk for Patients Predisposed to Long QT or Torsade de Pointes? *Circulation* 2003;107:740

**Incessant R-on-T VPCs and TDP post BiV**
Effect of Epicardial or Biventricular Pacing to Prolong QT Interval and Increase Transmural Dispersion of Repolarization

Pacing site-dependent Changes in QT Interval and TDR in an Arterially-perfused Rabbit LV Wedge Preparation

Early Effect
Impact of Upgrade to Cardiac Resynchronization Therapy on Ventricular Arrhythmia Frequency in Patients With Implantable Cardioverter-defibrillators

JACC 2005;46:2258

• Positive Effect of CRT
  ↓ Wall stress
  ↓ Ischemia
  ↑ Cardiac Output

  → Late Effects

• Negative Effect of CRT
  Altered direction & duration of LV repolarization

• ? Effect
  → Cancel each other
Rates of therapies in major CRT-D trials

Frequency and Causes of ICD Therapies: **Is Device Therapy Proarrhythmic?**
Joseph J. Germano, DO, Matthew Reynolds, MD, MSc, Vidal Essebag, MD, PhD, and Mark E. Josephson, MD*,†
*AJC 2006;97:1255
BiV pacing: Is It Proarrhythmic?

- Ventak CHF: Decrease in ATP for VT after BiVP (JACC 2000;36:824)
- Compare BiVP with LVepi. QTc dispersion ↑ during LVepi, Unaffected during BiVP (JCE 2006;17:151)
- Large scale clinical BiVP trials do Not report Proarrhythmia
- Continued Reports of Early Incessant VT after BiVP (JCE 2008 Mar 20 Epub)

→ In Recently Underwent CRT, Small in Number though, Proarrhythmic Potential of LV Epicardial Pacing Should be Considered.
Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the Cardiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]  

 Mean F/U: 36.4 mo

1° outcome: All cause mortality 40%↓

2° outcome: Mode of Death

Heart failure death 45%↓

Sudden death 46%↓
Long-Term Survival of Patients With Heart Failure and Ventricular Conduction Delay Treated With Cardiac Resynchronization Therapy

- Multicenter Longitudinal Observational Study (MILOS) - AJC2007;99:232

4 European Centers, Enroll 1,303 for 8 years → Analyze 1060 (82%)

NYHA II, III, IV (5, 80, 15%), CRT : CRT-D = 454:606, 1° End point: Death+TPL+LVAD

1yr = 92%
5yr = 56%

HFD = 25.1%
SCD = 9.5%

→ Favorable long-term outcome, Reproducible at Different Centers
→ Leading cause of death = HF,
→ Total mortality ↓~20%, SD ↓96% (HR 0.04, P<.002) in ICD back-up than CRT alone

- DB-Random, 3-arm study
- 306 pt (III~IV), ≤ 35%, ≥150ms
- 3 mo, 6 mo F/U Echo
  ➔ ↓LVESV & EDV
  : greatest in simultaneous BiV
  ➔ all showed EF↑
  : more modest in LV alone

* Optimal VV delay = -0.333 x (RV-LV electrical delay) - 20ms

on-going “B-LEFT HF study”.
CRT in Chronic Afib
AF and Heart Failure

• Twin modern epidemics, often present concomitantly and directly predispose to each other.

• **Prevalence** of AF according to the NYHA Classes:
  - 5% in I
  - 10~25% in II-III
  - ~50% in IV

• **Incidence** of AF in HF: up to 5% / yr

• Most of the CRT Trials → Excluded AF

• Several relatively small studies reports benefit of CRT in AF
  
  PAVE (Post AVN ablation Evaluation, II~III (45%)) : BiV. vs. RVP 6 mo → 6min walk↑, < ↓ EF in BiV.

- 162 AF / 673 HF (≤35%, ≥120ms, ≥ II)
- Biv. pacing % at 2 mo.
  - > 85% ➔ continue rate control (48)
  - ≤ 85% ➔ AVJ ablation (114)
  
  Rate control ➔ Biv. pacing 88.2 ± 3.1%
  (Resting HR=76.4 ± 5.1bpm)

- Large and Sustained Long-term (~4 year) ↑ of EF and FC, Similar to SR, only in AVJ ablation group.

➔ Even relatively high % Biv. capture may be Inadequate. (Regularity~Pseudofusion)
Unresolved Issues In CRT

• CRT in NYHA I ~ II Heart Failure: REVERSE(+) → MADIT-CRT, RAFT: ongoing
• CRT in Narrow QRS: Positive small studies(+) → RethinQ: Lack of benefit
• Should CRT be combined with ICD back-up?
  = Incremental benefit of CRT-D over CRT alone?
  → No Ongoing Randomized Controlled Trials
  (cf. CRT-D vs. ICD in HF I ~ II: MADIT-CRT: ongoing)
• Economic considerations on CRT → recently, positive reports(+)
• **Predictors of Response to CRT:**
  PROSPECT: Dysynchrony → additive effect (+)…….
수고 하셨습니다.