Indications for and Prediction of Successful Responses of CRT for Patients with Heart Failure

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San Francisco VAMC
October 25, 2008
Presentation Outline

- **Background**
  - Heart failure prognosis
  - Conduction delay and dyssynchrony

- **Clinical trials**

- **Indications and selection of patients to maximize benefits**
Presentation Outline

- Background
  - Heart failure prognosis
  - conduction delay and dyssynchrony
- Clinical trials
- Indications and selection of patients to maximize benefits
CHF Knowledge Base

- 5 million Americans affected in US
- 1 million admissions annually in the US
- Most common admitting diagnosis for patients \( \geq 65 \) years
- Causes or contributes to 250,000 deaths/year in US
- Hospitalization costs $5-15 billion
Epidemiology of Heart Failure in the US

- Causes or contributes to 250,000 deaths/year in US
- 4.7 million symptomatic patients
- Incidence: About 550,000 new cases/year
- Most common admitting diagnosis for age $\geq 65$
- Prevalence is 1% between the ages of 50 and 59, progressively increasing to $>10\%$ over age 80

New York Heart Association Functional Capacity Classification for Patients with Cardiac Disease (1994)

- **Class I**: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

- **Class II**: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

- **Class III**: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

- **Class IV**: Inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
## New Approach to the Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
</table>
| A     | High risk for developing heart failure (HF)  
• Hypertension  
• CAD  
• Diabetes mellitus  
• Family history of cardiomyopathy |
| B     | Asymptomatic LV dysfunction  
• Previous MI  
• LV systolic dysfunction  
• Asymptomatic valvular disease |
| C     | Symptomatic HF  
• Known structural heart disease  
• Shortness of breath and fatigue  
• Reduced exercise tolerance |
| D     | Refractory end-stage HF  
• Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions) |

Remodeling and Reverse Remodeling

Injuries → Therapy

- Acute infarction (hours)
- Infarct expansion (hours to days)
- Global remodeling (days to months)
Clinical Consequences of Cardiac Remodeling

- Increased myocardial oxygen demands
- Arrhythmias (both atrial and ventricular)
- Abnormal pattern of ventricular contraction due to conduction abnormalities
- Systolic dysfunction
- Diastolic dysfunction
- Secondary mitral and tricuspid regurgitation
Ventricular Dyssynchrony

- Abnormal ventricular conduction resulting in a mechanical delay
  - Wide QRS (IVCD); typically LBBB morphology
  - Disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency
  - Regional wall motion abnormalities with increased workload and stress
    - Poor systolic function
    - Impaired diastolic function

![ECG waveform](image-url)
Ventricular Conduction Delays

- **Inter**ventricular conduction delay
  - Time lag between right and left ventricular contraction
  - No “classic pattern” of right before left or vice versa

- **Intra**ventricular conduction delay
  - Inefficient or “segmented” contraction of the left ventricle
  - Blood tends to slosh around instead of getting pumped out

- Both interventricular and intraventricular conduction delays are forms of mechanical dyssynchrony

- Not mutually exclusive (patients can have both forms)
Prevalence of Inter- or Intraventricular Conduction Delay Delay

All heart failure

IVCD 15%

Moderate to severe heart failure

IVCD >30%

Increased 1-year mortality with presence of complete LBBB (QRS > 140 ms)

Risk remains significant even after adjusting for age, underlying cardiac disease, indicators of HF severity, and HF medications

* HR = Hazard Ratio

Wide QRS – Increased Mortality

**Vesnarinone Study (VEST study analysis)**

- NYHA Class II-IV patients
- 3,654 ECGs digitally scanned
- Age, creatinine, LVEF, heart rate, and QRS duration found to be independent predictors of mortality
- Relative risk of widest QRS group 5x greater than narrowest

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Principle of Cardiac Resynchronization

Modification of interventricular, intraventricular, and atrial-ventricular activation sequences with biventricular pacing

[Images of ECG traces]
Cardiac Resynchronization Therapy

CRT with defibrillator: CRT-D
CRT without defibrillator: CRT-P
Principle of Cardiac Resynchronization

Modification of activation sequences improves mechanical performance
Presentation Outline

- Background
  - Heart failure prognosis and conduction and dyssynchrony
- Clinical trials
  - Indications and selection of patients to maximize benefit
CRT Trials – Proof of Concept

- Functional and performance trials:
  - InSync ICD (Europe)  Kuhlkamp V. J Am Coll Cardiol. 2002;39:790-7

- Mortality benefit trials
<table>
<thead>
<tr>
<th>Trial</th>
<th>QoL</th>
<th>NYHA</th>
<th>6 min walk</th>
<th>Peak VO$_2$</th>
<th>Exercise time</th>
<th>LVEF</th>
<th>MR</th>
<th>Others</th>
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<tbody>
<tr>
<td>PATH-CHF (n=41)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+ LVEDP + LV dp/dt$_{\text{max}}$</td>
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<tr>
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<tr>
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<td></td>
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<td>+ Filling time</td>
</tr>
<tr>
<td>MUSTIC (n=67)</td>
<td>+</td>
<td></td>
<td>+</td>
<td>↔</td>
<td>↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔↔leftrightarrow</td>
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<td>+</td>
<td>+</td>
<td>+ LVEDV + LVESV</td>
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<td>+</td>
<td>+</td>
<td>↔leftrightarrow</td>
<td>+</td>
<td>+ LVEDV + LVESV</td>
</tr>
<tr>
<td>COMPANION (1212)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↔leftrightarrow</td>
<td>+</td>
<td></td>
<td>30 and 40% ↓ All deaths/hosp (1°) 24 and 36% ↓ All deaths (2°)</td>
<td></td>
</tr>
<tr>
<td>CARE-HF (n=813)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
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<td>37% ↓ All deaths/hosp (1°) 36% ↓ All deaths (2°)</td>
<td></td>
</tr>
</tbody>
</table>

+ Statistically significant improvement with CRT ($p \leq 0.05$)
leftrightarrow Not statistically significant or No statistical analysis performed on data
Blank Indicates test neither performed nor reported
### Summary of Patient Selection

<table>
<thead>
<tr>
<th></th>
<th>NYHA</th>
<th>QRS duration (ms)</th>
<th>LVEF (%)</th>
<th>IVCD/LBBB</th>
<th>Ischemic DCM</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>CRT/D</td>
<td>Control</td>
<td>CRT/D</td>
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<tr>
<td><strong>PATH-CHF</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>III: 82%</td>
<td></td>
<td>178±34</td>
<td>20±7</td>
<td>100% (LBBB)</td>
<td>6%</td>
</tr>
<tr>
<td>IV: 18%</td>
<td></td>
<td>174±30</td>
<td>21±6</td>
<td>87% (LBBB)</td>
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<tr>
<td><strong>InSync</strong></td>
<td></td>
<td>178±28</td>
<td>22±6</td>
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<td>47%</td>
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<tr>
<td>III: 68%</td>
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<tr>
<td>IV: 32%</td>
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<tr>
<td><strong>InSync ICD</strong></td>
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<td>170±30</td>
<td>25±7</td>
<td>57%</td>
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<tr>
<td>II: 32%</td>
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<tr>
<td>III: 59%</td>
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<tr>
<td>IV: 21%</td>
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<tr>
<td><strong>MUSTIC</strong></td>
<td></td>
<td>167±19</td>
<td>22±8</td>
<td>87% (LBBB)</td>
<td>37%</td>
</tr>
<tr>
<td>III: 100%</td>
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<tr>
<td><strong>MIRACLE</strong></td>
<td></td>
<td>165±20</td>
<td>22±6</td>
<td>58%</td>
<td>50%</td>
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<tr>
<td>III: 91%</td>
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<tr>
<td>IV: 9%</td>
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<td>167±21</td>
<td>22±6</td>
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<tr>
<td><strong>MIRACLE ICD</strong></td>
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<td>162±22</td>
<td>24±6</td>
<td>87%</td>
<td>76%</td>
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<td>III: 90%</td>
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<tr>
<td>IV: 10%</td>
<td></td>
<td>165±22</td>
<td>24±7</td>
<td>87%</td>
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<tr>
<td><strong>COMPANION</strong></td>
<td></td>
<td>158</td>
<td>22</td>
<td>76% / 9% (L / RBBB)</td>
<td>59%</td>
</tr>
<tr>
<td>III: 82%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV: 18%</td>
<td></td>
<td>160</td>
<td>21</td>
<td>71% / 11% (L / RBBB)</td>
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<tr>
<td><strong>CARE-HF</strong></td>
<td></td>
<td>160</td>
<td>25</td>
<td>---</td>
<td>36%</td>
</tr>
<tr>
<td>III: 93%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>IV: 7%</td>
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<td>160</td>
<td>25</td>
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Presentation Outline

- **Background**
  - Heart failure prognosis
  - Conduction delay and dyssynchrony

- **Clinical trials**
  - Indications and selection of patients to maximize benefits
ACC/AHA/HRS 2008 Guidelines for CRT and CRT-D Therapy

Available at
http://content.onlinejacc.org/cgi/content/short/j.jacc.2008.02.033 and
http://circ.ahajournals.org/cgi/reprint/CIRCUALTIONAHA.108.189742

The full-text guidelines are also available on the following Web sites:
ACC (www.acc.org),
AHA (www.americanheart.org), and
HRS (www.hrsonline.org)
Applying Classification of Recommendations and Level of Evidence

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class IIa</th>
<th>Class IIb</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Benefit ≥ Risk</td>
<td>Risk ≥ Benefit</td>
</tr>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
<td>Additional studies with broad objectives needed; Additional registry data would be helpful</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
</tbody>
</table>

Level of Evidence

<table>
<thead>
<tr>
<th>Level A:</th>
<th>Level B:</th>
<th>Level C:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses Multiple populations evaluated;</td>
<td>Data derived from a single randomized trial or nonrandomized studies Limited populations evaluated</td>
<td>Only consensus of experts opinion, case studies, or standard of care Very limited populations evaluated</td>
</tr>
</tbody>
</table>
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

1. LVEF ≤ 35%, and
2. QRS duration ≥ to 0.12 seconds, sinus rhythm, and
3. NYHA Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy.

Comment: QRS interval can be as short as 120 ms

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

1. LVEF ≤ 35%, and
2. QRS duration ≥ to 0.12 seconds, atrial fibrillation, and
3. NYHA Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy

Comment: QRS interval can be as short as 120 ms and presence of AF

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

1. LVEF less than or equal to 35%, and

2. NYHA functional Class III or ambulatory Class IV symptoms who are receiving optimal recommended medical therapy, and

3. Frequent dependence on ventricular pacing, CRT is reasonable.

Comment: QRS interval not a criterion

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

1. LVEF less than or equal to 35%, and
2. NYHA functional Class I or II who are receiving optimal recommended medical therapy, and
3. Undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent dependence on ventricular pacing

Comment: NYHA Class I and II patients

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
Cardiac Resynchronization Therapy* in Patients With Severe Systolic Heart Failure

CRT is not indicated for asymptomatic patients with reduced LVEF in the absence of other indications for pacing.

CRT is not indicated for patients whose functional status and life expectancy are limited predominantly by chronic non-cardiac conditions.

*All primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.
RethinQ Study
The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS Study

**Background:** Some studies suggested that QRS duration has little or no predictive value for chronic improvement Mechanical dyssynchrony by analysis of wall motion with echo-Doppler methods – A better predictor of responders

**Question:** Do HF patients with narrow QRS complexes but echo evidence of LV mechanical dyssynchrony benefit from CRT?

**Definition of mechanical dyssynchrony:** An opposing-wall delay of 65 msec or more on tissue Doppler imaging or a mechanical dyssynchrony in the septal-to-posterior wall of 130 msec or more on M-mode echocardiography
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td><strong>QRS interval (ms)</strong></td>
<td>106±13 (29%: 120-130 ms)</td>
<td>107±12 (24%: 120-130 ms)</td>
</tr>
<tr>
<td><strong>NYHA III</strong></td>
<td>99%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Ischemic cardiomyopathy</strong></td>
<td>51%</td>
<td>54%</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td>26±6</td>
<td>25±5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak VO2 (1° end point)</strong></td>
<td></td>
<td>p=0.3</td>
</tr>
<tr>
<td><strong>QoL (2°)</strong></td>
<td></td>
<td>P=0.91</td>
</tr>
<tr>
<td><strong>NYHA (2°)</strong></td>
<td></td>
<td>P=0.006</td>
</tr>
<tr>
<td><strong>6 min walk</strong></td>
<td></td>
<td>P=0.23</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td>p=0.83</td>
</tr>
</tbody>
</table>
Patients with heart failure and narrow QRS intervals may not benefit from CRT, even in the presence of mechanical dyssynchrony. CRT resulted in NYHA class improvement, a subjective secondary end point. A sub-group with QRS between 120 to 130 ms showed improvement with CRT.
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<td>III: 88% IV: 12%</td>
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<td>174± 30</td>
<td>20±7</td>
</tr>
<tr>
<td>InSync</td>
<td>III: 68% IV: 32%</td>
<td></td>
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<td>22±6</td>
</tr>
<tr>
<td>InSync ICD</td>
<td>II: 32%, III: 59%, IV: 21%</td>
<td></td>
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<td>MIRACLE ICD</td>
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<td>162± 22</td>
<td>165±22</td>
<td>24± 6</td>
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<td>160</td>
<td>22</td>
</tr>
<tr>
<td>CARE-HF</td>
<td>III: 93% IV: 7%</td>
<td>III: 94% IV: 6%</td>
<td>160</td>
<td>160</td>
<td>25</td>
</tr>
</tbody>
</table>
Typical Patient Profile in Clinical Trial
Best Responder?

- LVEF < 30%
- NYHA functional class III
- QRS duration ≥ 160 ms with LBBB
- Optimal medical therapy – beta-blocker
Can CMS Make Better Patient Selection?

CMS CRT/CRT-D Coverage Reference Guide

**Symptomatic heart failure despite stable, optimal medical therapy**

- Yes:
  - QRS duration ≥ 120 ms and LVEF ≤ 35% (NYHA Class IV heart failure)
  - Yes:
    - NYHA Class IV heart failure
    - Yes: Meets coverage criteria for the implantation of an ICD
    - Yes:
      - Eligible for CRT defibrillator (CRT-D)
      - Eligible for CRT pacemaker (CRT-P)
      - Not eligible for CRT device

Reference CMS Local Coverage Decision and Bulletins for any specific coverage requirements specific to your region or state. Some local policies require a QRS duration ≥ 130 ms.