CONGESTIVE HEART FAILURE - LATEST ON MADIT CRT

DR DINESH PUBBI MD FACC ELECTROPHYSIOLOGY
EARLY CRT INTERVENTION REDUCES DEATH AND HEART FAILURE EVENTS:

MADIT-CRT
Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
Acute Exacerbations Contribute to the Progression of the Disease

With each event, hemodynamic alterations/myocardial injury contribute to progressive ventricular dysfunction.

Key Heart Failure Statistics

• Prevalence
  – ~5 million Americans with heart failure
  – >10% of adults in their 70s and 80s
• Incidence
  – 550,000 new cases HF/year
• Morbidity
  – ~1,000,000 HF hospitalizations
• Mortality
  – Causes or contributes to >600,000 deaths/yr
  – >50% of patients die suddenly (SCD)

The Epidemic of Heart Failure
Key Heart Failure Statistics

• **Prevalence**
  - ~5 million Americans with heart failure
  - >10% of adults in their 70s and 80s

• **Incidence**
  - 550,000 new cases HF/year

• **Morbidity**
  - ~1,000,000 HF hospitalizations

• **Mortality**
  - Causes or contributes to >600,000 deaths/yr
  - >50% of patients die suddenly (SCD)

Projected increase in the US population 65 years of Age or Older
Heart Failure: A Public Health Crisis
Hospitalizations Have Tripled in the last 25 Years

Left Ventricular Dysfunction

- Volume Overload
- Pressure Overload
- Loss of Myocardium
- Impaired Contractility

LV Dysfunction
EF < 40%

- Cardiac Output
- Hypoperfusion

- End Systolic Volume
- End Diastolic Volume
- Pulmonary Congestion
Treatment Approach for the Patient with Heart Failure

**Stage A**
At high risk, no structural disease

**Stage B**
Structural heart disease, asymptomatic

**Stage C**
Structural heart disease with prior/current symptoms of HF

**Stage D**
Refractory HF requiring specialized interventions

**Therapy**

- **Stage A**
  - Treat Hypertension
  - Treat lipid disorders
  - Encourage regular exercise
  - Discourage alcohol intake
  - ACE inhibition

- **Stage B**
  - All measures under stage A
  - ACE inhibitors in appropriate patients
  - Beta-blockers in appropriate patients

- **Stage C**
  - All measures under stage A
  - Diuretics
  - ACE inhibitors
  - Beta-blockers
  - Digitalis
  - Dietary salt restriction

- **Stage D**
  - All measures under stages A,B, and C
  - Mechanical assist devices
  - Heart transplantation
  - Continuous (not intermittent) IV inotropic infusions for palliation
  - Hospice care

Hunt, SA, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2001
Diuretics, ACE Inhibitors

Reduce the number of sacks on the wagon.
β-Blockers

Limit the donkey’s speed, thus saving energy
Digitalis Compounds

Like the carrot placed in front of the donkey
Ventricular Dysynchrony

- Abnormal ventricular conduction resulting in a mechanical delay
  - Wide QRS (IVCD); typically LBBB morphology
  - Poor systolic function
  - Impaired diastolic function

ECG depicting interventricular conduction delay
Prevalence of Ventricular Dyssynchrony in Heart Failure

Left Bundle Branch Block More Prevalent with Impaired LV Systolic Function

- Preserved LVSF (1) 8%
- Impaired LVSF (1) 24%
- Moderate/Severe HF (2) 38%

Elements of Cardiac Dyssynchrony

Atrio-ventricular

Intra-ventricular

Inter-ventricular

Cazeau, et al. PACE 2003; 26[Pt. II]: 137–143
Intra-ventricular Dyssynchrony
Septal-Posterior Wall Motion Delay

- Difference in times from peak excursions of the septum and of the posterior wall at the papillary muscle level
- SPWMD $\geq 130$ ms predicted response (LVEDVi) to CRT in study of 25 pts with QRS $\geq 140$ ms\(^1\)
  - From parasternal short-axis view at papillary muscle level

CHF Patients Survival Results\(^1\)


80% of men and 70% of women who have CHF will die within 8 years.\(^2\)

### Chart

- **Men (n = 237)**
- **Women (n = 230)**

- **Probability of survival, %**
- **Time after CHF diagnosis, years**

- 80% of men and 70% of women who have CHF will die within 8 years.\(^2\)
Survival Trends in Heart Failure

Despite favorable trends in survival, heart failure remains highly fatal; among subjects who were given a diagnosis of heart failure in the 1990s, more than 50% were dead in 5 years.¹

Temporal Trends in Age-Adjusted Survival after the Onset of Heart Failure among Men (Panel A) and Women (Panel B).

Values were adjusted for age (<55, 55 to 64, 65 to 74, 75 to 84, and 85 years). Estimates are shown for subjects who were 65 to 74 years of age.

Survival Trends: CHD and SCA

Mayo Clinic; Olmsted County, Minnesota¹:
• Analyzed secular trends in CHD deaths and unexpected SCD over a 20-year period (1979-1998)
• In-hospital deaths declined at a greater rate than out-of-hospital:
  – RRR of in-hospital death in 1998: 0.36
  – RRR of out-of-hospital death in 1998: 0.71
• 50% of deaths were unexpected
  – Similar to Framingham results from two decades earlier—even with the intensified secondary and primary prevention efforts

“…these data underscore the increasing importance of primary prevention in sustaining the decline in CHF mortality.”

## Risk of Sudden Death in HF Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>HF Class</th>
<th>Control (n)</th>
<th>Treatment (n)</th>
<th>Total Mortality Reduction w/Treatment</th>
<th>Sudden Death as a % of Total Death in Control Arm</th>
<th>Sudden Death- as a % of Total Death in Treatment Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-HF(^1)</td>
<td>2-4</td>
<td>2001</td>
<td>1990</td>
<td>34%</td>
<td>(60%)</td>
<td>(54%)</td>
</tr>
<tr>
<td>(Metroprolol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>132/217</td>
<td>79/145</td>
</tr>
<tr>
<td>BEST(^2)</td>
<td>3,4</td>
<td>1354</td>
<td>1354</td>
<td>10%</td>
<td>(45%)</td>
<td>(44%)</td>
</tr>
<tr>
<td>(Bucindolol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>203/449</td>
<td>182/411</td>
</tr>
<tr>
<td>CIBIS-II(^3)</td>
<td>3,4</td>
<td>1320</td>
<td>1327</td>
<td>34%</td>
<td>(36%)</td>
<td>(31%)</td>
</tr>
<tr>
<td>(Bisoprolol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83/228</td>
<td>48/156</td>
</tr>
<tr>
<td>CARVEDILOL - (U.S.)(^4)</td>
<td>2-4</td>
<td>398</td>
<td>696</td>
<td>65%</td>
<td>(48%)</td>
<td>(54%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15/31</td>
<td>12/22</td>
</tr>
<tr>
<td>RALES(^5)</td>
<td>3, 4</td>
<td>841</td>
<td>882</td>
<td>30%</td>
<td>(28%)</td>
<td>(29%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>110/386</td>
<td>162/478</td>
</tr>
</tbody>
</table>

References in slide notes.
Residual Risk of SCD in Treatment Arms of CHF-Beta Blocker Trials

- **CIBIS II (1999)**
  - Sudden Deaths: 48
  - Total Deaths: 156
  - Sudden Death % of Total Death: 31%
  - Average Follow Up: 16 months
  - No. Pts in Treatment Arm: n= 1327

- **MERIT-HF (1999)**
  - Sudden Deaths: 79
  - Total Deaths: 145
  - Sudden Death % of Total Death: 54%
  - Average Follow Up: 12 months
  - No. Pts in Treatment Arm: n= 1990

- **U.S. CARVEDILOL (1996)**
  - Sudden Deaths: 12
  - Total Deaths: 22
  - Sudden Death % of Total Death: 54%
  - Average Follow Up: 6.5 months
  - No. Pts in Treatment Arm: n = 696

References:
SCD in Heart Failure \(^1,^2\)

- Despite improvements in medical therapy, symptomatic HF still confers a 20-25% risk of pre-mature death in the first 2.5 yrs after diagnosis.

\[\rightleftharpoons 50\% \text{ of these premature deaths are SCD (VT/VF)}\]

- The role of device therapy?

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\(^1\) Bardy G. The Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) in Woosley RL, Singh S, Arrhythmia Treatment and Therapy, Copyright 2000 by Marcel Dekker, Inc., pp. 323-342.

\(^2\) Sweeney MO PACE 2001;24:871-888.
SCD Prevention by Implantable Device Therapy

1. Post-MI and LV Dysfunction:
   - MADIT / MUSTT / MADIT-II

1. Heart Failure and LV Dysfunction:
   - SCD-HeFT
### MADIT/MUSTT/MADIT-II Study Criteria Comparison

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>MADIT(^1) (196 patients)</th>
<th>MUSTT(^2) (704 patients)</th>
<th>MADIT-II(^3) (1232 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD/Post-MI</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>LV Dysfunction (&lt;35%)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>NSVT</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inducible VT on EPS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Inducible, non-suppressible VT on EPS</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MADIT II: Easier to Qualify for SCD Protection**

<table>
<thead>
<tr>
<th>MADIT II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size: 1218 U.S. patients</td>
</tr>
<tr>
<td>Endpoint: All-cause mortality (patient follow-up = 20 months)</td>
</tr>
<tr>
<td>Published: NEJM 2002</td>
</tr>
</tbody>
</table>

**31%**

*Reduction in the risk of death in heart attack survivors with ICDs, when compared to conventional medical therapy (CMT) alone (p = 0.016).*

**Building to the Next Question:**

ICD therapy in patients with chronic ischemic heart disease improved survival but were the same patients with increased risk of heart failure (HF) events.\(^1\)


SCD-HeFT: Preventing SCD in Heart Failure Patients

Size: 2521 patients in North America and New Zealand
Endpoint: All-cause mortality
Published: NEJM 2005

Reduction in the risk of all-cause mortality when using an ICD, in combination with conventional drug therapy (CDT), when compared to CDT alone ($p = 0.007$)

Building to the Next Question:
ICD therapy saved NYHA Class II/III patients’ lives from tachyarrhythmias – but a major cause of mortality remained: heart failure (31% of deaths, evenly distributed among treatment arms).¹

COMPANION: Providing New Access to CRT

COMPANION

Size: 1520 U.S. patients
Endpoint: All-cause mortality or first hospitalization
Published: NEJM 2004

Reduction in the risk of all-cause mortality or first hospitalization with CRT-D, in combination with OPT, compared to OPT alone (p = 0.011)

Building to the Next Question:

- CRT-Ds save lives in NYHA Class III/IV HF patients, but pump failure was the most common cause of death (44.4%).¹
- 70% of HF patients are in NYHA Class I/II.² There is a need to slow their progression to symptomatic heart failure.

MADIT II

SCD-HeFT

COMPANION

Key Learning

BOTTOM LINE

Ability to save lives from sudden cardiac death…

…heart failure remains an issue
The Next Big Question

Can early intervention with CRT reduce death and heart failure events in patients with mild heart failure (NYHA Class I/II), when compared to ICD-only therapy?
Cardiac Resynchronization Therapy

Increase the donkey’s (heart) efficiency
Achieving Cardiac Resynchronization

Goal: Atrial synchronous biventricular pacing

Transvenous approach for left ventricular lead via coronary sinus

Back-up epicardial approach

Doug Smith:
Achieving Cardiac Resynchronization

- Transvenous Approach
  - Mechanical Goal: Pace Right and Left Ventricles
  - Standard pacing leads in RA and RV
  - Specially designed left heart lead placed in a left ventricular cardiac vein via the coronary sinus

Cardiac Resynchronization System
MADIT-CRT
MULTICENTER AUTOMATIC DEFIBRILLATOR IMPLANTATION TRIAL WITH CARDIAC RESYNCHRONIZATION THERAPY
Introduction

- Heart failure remains a significant health concern; a heart failure event is associated with a five-fold increase in mortality in 5 years.

--Cardiac resynchronization therapy with defibrillation (CRT-D) has been demonstrated to reduce mortality and hospitalizations, improve symptoms, and increase exercise capacity.
Introduction

Prior to MADIT-CRT, CRT-Ds were indicated by FDA for the treatment of patients with the following conditions:

- Moderate to severe heart failure (NYHA Class III/IV) despite optimal pharmacological therapy
- Reduced systolic function (LVEF ≤ 35%)
- Wide QRS (QRS duration ≥ 120 ms)
Rationale for Undertaking MADIT-CRT

– Currently, patients with severe left ventricular systolic dysfunction, a wide QRS complex, and asymptomatic or mildly symptomatic heart failure are indicated for prophylactic ICD therapy without CRT

– Although ICD therapy is effective for the prevention of sudden cardiac arrest, it does not slow the progression of heart failure
  • However, progression of heart failure in these patients is associated with increased mortality and diminished quality of life

Higgins et al, JACC (2001)
Rationale for Undertaking MADIT-CRT

- Retrospective studies of CRT-D in NYHA Class I/II patients reported improvement in echocardiographic variables, suggesting a potential role for CRT-D earlier in the disease process.

- Accordingly, MADIT-CRT was undertaken to determine if early intervention with CRT-D in patients with asymptomatic or mild heart failure could reduce death and heart failure events.
MADIT-CRT Primary & Secondary Effectiveness Hypotheses

- **Primary:**
  It was hypothesized that CRT-D would reduce the risk of the combined endpoint of all-cause mortality or heart failure event, whichever came first, when compared with ICD in patients with asymptomatic or mildly symptomatic heart failure with left ventricular dysfunction & wide QRS
MADIT-CRT Primary & Secondary Effectiveness Hypotheses

- **A heart failure event** was defined as a patient having signs and symptoms of heart failure, with either:
  - Intravenous decongestive therapy in an outpatient setting, or
  - Augmented intravenous or oral decongestive therapy during in-hospital stay

- **Secondary:** Evaluate the effects of CRT-D, relative to ICD, on the patient-specific rates of recurrent heart failure events over the full study period
MADIT-CRT Methods

Scope:
MADIT-CRT was led by Dr. Arthur J. Moss at the University of Rochester, in Rochester NY. MADIT-CRT is the largest randomized NYHA Class I / II CRT-D trial to date, with 1820 patients enrolled at 110 centers in 14 countries. Average follow-up was 34.3 months. Boston Scientific commercially available product was used.

Baseline Evaluation
To document inclusion / exclusion criteria and establish baseline heart status

Randomization (3:2 CRT-D: ICD)
Stratified by center and ischemic status

Clinic Follow-up Visits
1 month post enrollment / randomization, 3 months post randomization, and quarterly thereafter to a common study closure date

**Baselines evaluation includes history and physical exam, electrocardiogram and echocardiogram. Patients are randomized and then baseline testing is completed including BNP (US only), quality-of-life assessment, 6 minute walk test, and Holter monitor recording (CRT-D patients only).**

**The 12 month follow-up visit includes echocardiogram, BNP (US only), 6 minute walk test, Holter monitor recording (CRT-D patients only) and device interrogation. Other follow-up visits include history and physical exam, clinical events, and device interrogation. Quality-of-life assessments were conducted at 6 month intervals.**
MADIT-CRT met its endpoint in June, 2009 and results were published in the September 2009 NEJM online addition.

Results showed that CRT-D was associated with a 34% reduction in the risk of the primary endpoint.

Primary effectiveness endpoint achieved.

The FDA requested to see additional 6 months of data analyzed (through December 2009)

It was subsequently discovered and validated that in the LBBB subgroup, patients received substantial benefit from CRT-D. Non-LBBB patients did not show evidence of benefit. The LBBB sub-group made up approximately 70% of the total MADIT-CRT population.


2. COGNIS CRT-D System Guide
Consistent Results with LBBB across Subgroups

- All LBBB: Favor CRT-D (0.43, 0.33, 0.56), Favor ICD (0.45, 0.31, 0.64)
- Age < 65: Favor CRT-D (0.55, 0.38, 0.80), Favor ICD (0.47, 0.32, 0.65)
- Age ≥ 65: Favor CRT-D (0.40, 0.29, 0.54), Favor ICD (0.40, 0.14, 0.76)
- Male: Favor CRT-D (0.58, 0.44, 0.76), Favor ICD (0.23, 0.14, 0.38)
- Female: Favor CRT-D (0.40, 0.30, 0.53), Favor ICD (0.40, 0.30, 0.53)
- NYHA I: Favor CRT-D (0.45, 0.23, 0.88), Favor ICD (0.45, 0.31, 0.64)
- NYHA II - Ischemic: Favor CRT-D (0.46, 0.32, 0.65), Favor ICD (0.45, 0.31, 0.64)
- NYHA II - Non-ischemic: Favor CRT-D (0.45, 0.31, 0.64), Favor ICD (0.45, 0.31, 0.64)
- QRS < 150: Favor CRT-D (0.58, 0.38, 0.89), Favor ICD (0.36, 0.14, 0.76)
- QRS ≥ 150: Favor CRT-D (0.40, 0.30, 0.53), Favor ICD (0.40, 0.30, 0.53)
- LVEF < 25: Favor CRT-D (0.48, 0.36, 0.63), Favor ICD (0.45, 0.31, 0.64)
- LVEF ≥ 25: Favor CRT-D (0.44, 0.28, 0.69), Favor ICD (0.45, 0.31, 0.64)
- LVESV ≤ 170: Favor CRT-D (0.40, 0.28, 0.57), Favor ICD (0.45, 0.31, 0.64)
- LVESV > 170: Favor CRT-D (0.51, 0.37, 0.70), Favor ICD (0.45, 0.31, 0.64)
- LVEDV ≤ 240: Favor CRT-D (0.43, 0.30, 0.60), Favor ICD (0.45, 0.31, 0.64)
- LVEDV > 240: Favor CRT-D (0.49, 0.35, 0.68), Favor ICD (0.45, 0.31, 0.64)
- BUN ≤ 25: Favor CRT-D (0.45, 0.34, 0.60), Favor ICD (0.53, 0.34, 0.81)
- BUN > 25: Favor CRT-D (0.45, 0.34, 0.81), Favor ICD (0.53, 0.34, 0.81)
- US Centers: Favor CRT-D (0.43, 0.32, 0.58), Favor ICD (0.49, 0.32, 0.74)
- Non-US Centers: Favor CRT-D (0.43, 0.32, 0.58), Favor ICD (0.49, 0.32, 0.74)
- Small Centers: Favor CRT-D (0.41, 0.25, 0.68), Favor ICD (0.46, 0.35, 0.60)
- Large Centers: Favor CRT-D (0.46, 0.35, 0.60), Favor ICD (0.46, 0.35, 0.60)
### LBBB Sub-population Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ICD (n=520)</th>
<th>CRT-D (n=761)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>64±11</td>
<td>64±11</td>
<td>0.59</td>
</tr>
<tr>
<td>Gender (% Male)</td>
<td>70</td>
<td>69</td>
<td>0.54</td>
</tr>
<tr>
<td>QRS Width (ms)</td>
<td>164±20</td>
<td>162±18</td>
<td>0.06</td>
</tr>
<tr>
<td>Left Bundle Branch (%)</td>
<td>100</td>
<td>100</td>
<td>---</td>
</tr>
<tr>
<td>NYHA Class I (Ischemic)</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>NYHA Class II (Ischemic)</td>
<td>33</td>
<td>33</td>
<td>0.93</td>
</tr>
<tr>
<td>NYHA Class II (Non-Ischemic)</td>
<td>55</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>23±5</td>
<td>24±5</td>
<td>0.13</td>
</tr>
<tr>
<td>LVEDV (mL)</td>
<td>254±69</td>
<td>249±63</td>
<td>0.14</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>183±56</td>
<td>178±51</td>
<td>0.13</td>
</tr>
<tr>
<td>Hx of AF (%)</td>
<td>13</td>
<td>9</td>
<td>0.03</td>
</tr>
</tbody>
</table>
CRT therapy was ON during echocardiographic measurements and may have influenced the results.
Results

• In asymptomatic or mild heart failure patients with wide QRS, LV dysfunction, and LBBB on stable optimal heart failure pharmacologic therapy, CRT-D, as compared to ICD, was significantly associated with:

  – An acceptable safety profile
  – **Primary Endpoint Showed**: Reduction of 57% ($p < 0.001$) in the risk of a composite of all-cause mortality or heart failure events. This was driven by:
    • Reduction of 35% ($p = 0.048$) in the risk of death
    • Reduction of 63% ($p < 0.001$) in the risk of heart failure events

  – **Secondary Endpoint Showed**: Reduction of 43% ($p = 0.001$) in the risk of recurrent heart failure events
New CRT-D Indication

Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with heart failure who receive optimal pharmacologic therapy (OPT) for heart failure and who meet any one of the following classifications:

- Moderate to severe heart failure (NYHA Class III/IV) with EF ≤ 35% and QRS duration ≥ 120 ms
- Left bundle branch block with QRS ≥ 130 ms, EF ≤ 30% and mild (NYHA Class II) ischemic or nonischemic heart failure or asymptomatic (NYHA Class I) ischemic heart failure
Questions?

THANK YOU
How to Stop a Heart Attack Before It Happens

Amazingly detailed new heart scans help doctors spot trouble without surgery. How technology could save your life
“You got a better idea? The paddles are BROKEN. Just turn the key.”
Example of a Bullet Point Slide

• Bullet Point
• Bullet Point
  – Sub Bullet
Example of a chart

![Bar chart with four quarters (1st Qtr, 2nd Qtr, 3rd Qtr, 4th Qtr) and four directions (East, West, North, South). The chart shows data with peaks in the 3rd Qtr for South and East, followed by West and North.]
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