Saving Lives and Preventing Heart Failure: The MADIT Family of Trials

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Update in Electrocardiography & Arrhythmias
UCSF
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DISCLOSURE INFORMATION
Arthur J. Moss, MD

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Scientific</td>
<td>Research Grant</td>
</tr>
</tbody>
</table>

Hold no stock or stock options in any device company. Not a member of any corporate advisory group or speakers’ bureau.
MADIT FAMILY OF Trials

MADIT: 1996 NEJM (n=196; ↓mortality)
MADIT-II: 2002 NEJM (n=1232; ↓mortality)
MADIT-II LTFU: Circulation 2010 (↓mortality)
MADIT-CRT: 2009 NEJM (n=1820; ↓HF)
MADIT-RIT: started 2009, enrolled 1500 pts

MADIT trials have been sponsored by Boston Scientific, but were independently conducted by the MADIT Executive Committee and the Heart Research Follow-up Program of the University of Rochester Medical Center.

MADIT-I

Elig: Hx MI, EF<0.30, NSVT, +EP study
N=196

**MADIT-II**

Risk Factors for Appropriate ICD Rx

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF event*</td>
<td>2.5</td>
<td>0.001</td>
</tr>
<tr>
<td>MI/UA*</td>
<td>1.4</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Elig: Hx MI, EF<30%

N=1232


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**MADIT-II: Survival After First Device Therapy for VT or VF**

![Survival curve for MADIT-II study](image)

Patients at Risk

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Prior to Therapy 720</th>
<th>Post VT Therapy 133</th>
<th>Post VF Therapy 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>420 (0.96)</td>
<td>207 (0.89)</td>
<td>76 (0.80)</td>
</tr>
<tr>
<td>1</td>
<td>51 (0.82)</td>
<td>29 (0.74)</td>
<td>6 (0.74)</td>
</tr>
<tr>
<td>2</td>
<td>15 (0.80)</td>
<td>3 (0.46)</td>
<td>1 (0.32)</td>
</tr>
<tr>
<td>3</td>
<td>6 (0.74)</td>
<td>1 (0.32)</td>
<td></td>
</tr>
</tbody>
</table>
Cause of Death After ICD Therapy

<table>
<thead>
<tr>
<th>First Terminated Arrhythmia</th>
<th>None</th>
<th>VT</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1-year mortality rate)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>6</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Cardiac</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>SCD</td>
<td>2</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>HF</td>
<td>3</td>
<td>8</td>
<td>17</td>
</tr>
</tbody>
</table>

*Adjusted for exposure time.

Interpretation

Life-prolonging ICD therapy transforms a sudden death risk into a later heart failure risk.
MADIT-II: CLINICAL RISK STRATIFICATION APPROACH

- Identified a very high-risk (VHR) group based on BUN >50mg/dl
- Developed a risk score using simple clinical factors in the CONV group
- Evaluated the survival benefit of ICD:CONV therapy

Goldenberg & Moss. JACC 2008;52:288-96

RISK OF ALL-CAUSE MORTALITY IN THE CONVENTIONAL THERAPY GROUP FOR PRESPECIFIED RISK FACTORS

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>HAZARD RATIO</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA &gt;II</td>
<td>1.87</td>
<td>0.004</td>
</tr>
<tr>
<td>ATRIAL FIB</td>
<td>1.87</td>
<td>0.03</td>
</tr>
<tr>
<td>QRS &gt;120ms</td>
<td>1.65</td>
<td>0.02</td>
</tr>
<tr>
<td>AGE &gt;70yr</td>
<td>1.57</td>
<td>0.04</td>
</tr>
<tr>
<td>BUN: 27-50 mg/dl</td>
<td>1.56</td>
<td>0.04</td>
</tr>
</tbody>
</table>
### OUTCOME BY RISK SCORE AND TREATMENT GROUP

<table>
<thead>
<tr>
<th># RISK Factors</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONV. Rx</td>
</tr>
<tr>
<td>0</td>
<td>8%</td>
</tr>
<tr>
<td>&gt;1 risk factor</td>
<td>28%</td>
</tr>
<tr>
<td>VHR Gp (BUN&gt;50mg/dl)</td>
<td>43%</td>
</tr>
</tbody>
</table>

**MADIT-II:**
Extended 8-year Follow-up
MADIT-II: 8-year Follow-up

ICD is effective chronic therapy for saving lives

$82,000 per LYS at 8 years

Need to Rx 7 pts. to save 1 life in 8 yrs

HR = 0.63
P <0.001


Post-Trial Analysis:*
Benefit by Device-Type

<table>
<thead>
<tr>
<th>ICD-Type</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-Chamber vs. Non-ICD</td>
<td>0.70</td>
<td>0.009</td>
</tr>
<tr>
<td>Dual-Chamber vs. Non-ICD</td>
<td>0.88</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, BUN, EF, QRS duration, HF status at trial closure
MADIT-II: LTFU CONCLUSIONS

• Short-term ICD benefit sustained at 8-yr F-U
  – 37% reduction in mortality
  – Need to Rx 7 patients to save 1 life in 8 yrs.

• Long-term benefit
  – 0-4 yrs: 41% reduction in mortality
  – >4 yrs: 29% reduction in mortality
  – Better with single- than dual-chamber pacing
Cardiac Resynchronization Therapy (CRT)

CRT reverses the remodeling of the heart in cardiac patients with severe heart failure (NYHA class III-IV) and wide QRS resulting in reduced heart failure and death.

PATH-CHF: JACC 2001
MUSTIC: NEJM 2001
MIRACLE: NEJM 2002
CONTAK-CD: JACC 2003
COMPANION: NEJM 2004
CARE-HF: NEJM 2005
2005 ACC/AHA/ESC CRT Guidelines

CRT indicated for patients with:
- sinus rhythm
- widened QRS interval (≥ 120 ms)
- severe LV dysfunction (EF ≤ 0.35)
- severe HF (NYHA class III/IV) despite optimal medical therapy

MADIT-CRT (2005-2009)

**Primary Hypothesis:** in minimally symptomatic cardiac pts. (NYHA I/II) with ischemic or nonischemic cardiomyopathy, decreased EF, and wide QRS, CRT-D will reduce mortality or HF event (whichever comes first) when compared to ICD-only therapy.
DYSFUNCTIONAL REMODELING

Early
EF = 0.30
NYHA I-II
ECG QRS = 0.12s

Late
EF = 0.20
NYHA III-IV
ECG QRS = 0.16s

Can CRT prevent this?

MADIT-CRT (2005-2009)

Eligibility:
EF ≤ 0.30
QRS ≥ 0.13s
Ischemic heart disease NYHA I or II
Non-ischemic heart disease NYHA II

Exclusion:
NYHA III/IV
CABG, PTCA, or MI past 3 mo.
Chronic AF
Implanted ICD, CRT, or CRT device
**MADIT-III: MADIT-CRT**

Elig: IHD or NIHD, NYHAI/II, EF<0.30, QRS>130ms

- **N = 1820**
- **Hazard Ratio = 0.66**
- **P = 0.001**

### CRT-D:ICD Hazard Ratios for Prespecified Subgroups

**Variable** | **Hazard Ratio**
--- | ---
Age | <65 yr | ≥65 yr
Sex* | Male | Female
NYHA Class | Ischemic I | Ischemic II | Nonischemic II
QRS* | <150ms | ≥150ms
LVEF | ≤0.25 | >0.25
LVEDV | <240ml | ≥240ml
LVESV | ≤170 | >170
All patients

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**Significant Sex-Rx Interaction**

**Significant QRS-Rx Interaction**
MADIT-CRT: Reduction in Death with CRT-D in Women

P=0.02
Adjusted Hazard Ratio = 0.28

Mean Changes in Echo LV Volumes and EF from Baseline to 1-year by Treatment Group

CRT-D therapy is associated with significant reduction in heart size and improvement in heart function.
MADIT-CRT: Changes in Dyssynchrony (Regional Strain) from Baseline to 12 Months with CRT-D

Is CRT Antiarrhythmic or Proarrhythmic?
MADIT-CRT: Reduction in VT/VF with CRT-D

Wang P, et al. AHA Abstract 2010

Probability of VT/VF by ECHO Response

Barsheshet A, et al. JACC 2011
MADIT-CRT: Lead Position and Outcome

We analyzed the impact of left ventricular lead position on clinical outcome in patients randomized to CRT-D in the MADIT-CRT study


METHODS

LV Lead Core-Lab

• Venograms
  – RAO 20-30
  – LAO 20-40

• Chest X-rays
  – AP and Lateral Chest X-rays

• LV lead Classification
  – Short-axis
  – Long-axis
Classification Methodology

Adapted from ESC guidelines, EHJ 2007

LV Lead Position & Clinical Outcome

Death &/or Heart Failure

- No difference among Anterior, Posterior and Lateral lead positions
- Apical lead positions associated with a significantly worse clinical outcome
QRS Morphology in MADIT-CRT

![Pie chart showing QRS duration with IVCD, RBBB, and LBBB categories.]

- **IVCD, 306, 17%**
- **RBBB, 228, 13%**
- **LBBB, 1281, 70%**

**QRS Duration, ms**
- IVCD: 142±14
- RBBB: 153±15
- LBBB: 163±19

MADIT-CRT: Outcome by LBBB & Non-LBBB

![Graphs showing survival free of HF event over time for LBBB and non-LBBB.]

- **LBBB**
  - CRT-D (n=761)
  - ICD (n=520)
  - HR=0.45 P=0.001

- **non-LBBB**
  - CRT-D (n=328)
  - ICD (n=209)
  - HR=1.25 P=0.25
MADIT-CRT: Outcomes in LBBB & Non-LBBB

**Background**

Overview

Effectiveness

Safety

Conclusions

Add'l Outcomes

**FDA Approval**

FDA approved MADIT-CRT indication for cardiac resynchronization therapy on Sept 16, 2010 for patients with:

- NYHA I/II,
- QRS>130ms,
- EF<0.30, and
- LBBB
Other Randomized CRT Trials Involving Pts. with Minimal HF

- REVERSE: JACC 2008 (n=600); composite end point
- RAFT: NEJM Dec 2010; (n=1798); heart failure or death end point

REVERSE Trial (n=610; JACC 2008)

1° End Point (Composite Heart Failure)
Compare the proportion of “Improved” or “Unchanged” subjects between the CRT-ON and CRT-OFF groups at 12 months; EF<35%, QRS>120ms

- Composite includes: mortality, HF hospitalizations, chronic worsening of HF to NYHA Class III or IV requiring crossover of study assignment, NYHA and the patient global assessment
- P=0.10 for primary end point

2° End Point (LV Volumes & EF)
Compare the change in LV volumes and EF at 12 months between the CRT-ON and CRT-OFF groups
**REVERSE Trial**

**JACC 2008**

<table>
<thead>
<tr>
<th>LVESVI (ml/m²)</th>
<th>LVEDVI (ml/m²)</th>
<th>LVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P</em>&lt;0.0001</td>
<td><em>P</em>&lt;0.0001</td>
<td><em>P</em>&lt;0.0001</td>
</tr>
</tbody>
</table>

- CRT-off
- CRT-on

![Graph showing LVESVI, LVEDVI, and LVEF comparisons between CRT-off and CRT-on conditions.](image)

**RAFT**

Death or Hospitalization for Heart Failure

- ICD-CRT
- ICD

Hazard ratio, 0.75 (95% CI, 0.64–0.87)

*P*<0.001

<table>
<thead>
<tr>
<th>Years of Follow-up</th>
<th>No. at Risk ICD-CRT</th>
<th>No. at Risk ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>894</td>
<td>904</td>
</tr>
<tr>
<td>1</td>
<td>790</td>
<td>770</td>
</tr>
<tr>
<td>2</td>
<td>615</td>
<td>572</td>
</tr>
<tr>
<td>3</td>
<td>429</td>
<td>384</td>
</tr>
<tr>
<td>4</td>
<td>278</td>
<td>214</td>
</tr>
<tr>
<td>5</td>
<td>130</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>19</td>
</tr>
</tbody>
</table>

MADIT-CRT: CONCLUSIONS

• CRT reduces the risk of heart failure/death in NYHA class I/II pts. with low EF and wide QRS

• Women obtain a significantly greater benefit from CRT-D than men

• Improvement in cardiac substrate with CRT-D associated with reduction in VT/VF

• LV pacing: more effective from basal- or mid-LV site than from apical LV site

• Patients with LBBB obtain the best benefit from CRT-D with marked reduction in heart failure and death during 30 months of follow-up

THANK YOU