Heart Failure Update:
A Device Perspective

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April 13th, 2013
What is Heart Failure?
Heart Failure: Defined

- A syndrome of inadequate tissue perfusion (or the requirement for higher cardiac volumes or filling pressures to maintain perfusion)
Heart Failure: Abnormal Mechanics
Heart Failure:

- **Cardinal Manifestations**
  - Dyspnea and fatigue – often limiting exercise
  - Fluid retention – leading to pulmonary and peripheral edema
  - Impaired quality-of-life

- **Progressive disorder**
  - Symptoms eventually at rest or with minimal exertion
  - Deterioration of cardiac structure and function without recurrent injury, “silently”
The Epidemic of Heart Failure
A Growing Medical Challenge

Heart failure management

<table>
<thead>
<tr>
<th></th>
<th>Annual Incidence</th>
<th>Heart Failure Prevalence</th>
<th>Annual Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>U.S.</strong></td>
<td>550,000</td>
<td>6.5 million</td>
<td>350,000</td>
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<tr>
<td><strong>Europe</strong></td>
<td>750,000</td>
<td>6.5 million</td>
<td>600,000</td>
</tr>
</tbody>
</table>

Incidence of Heart Failure by Age

Framingham Results

Average incidence/1000/year

Doubles every decade

Adapted with permission from Kannel WB. *Eur J Clin Pharmacol* 1996;49(suppl 1):S3
Prevalence by severity (NYHA Class)

Class I
- No limitations of physical activity
  - 1.68 M (35%)

Class II
- Slight limitations
  - 240 K (5%)

Class III
- Marked limitations
  - 1.20 M (25%)

Class IV
- Symptoms at rest
  - 1.68 M (35%)

70% of patients have little or no symptoms.

AHA Heart and Stroke Statistical Update 2001
Heart Failure Hospitalizations

CDC/NCHS: Hospital discharges include living patients and in hospital deaths

AHA Heart and Stroke Statistical Update 2001
Causes of Hospital Readmission for Congestive Heart Failure

- Diet Noncompliance: 24%
- Inappropriate Rx: 16%
- Failure to Seek Care: 19%
- Rx Noncompliance: 24%
- Other: 17%

Total HF Costs = $38.1 billion (5.4% of total healthcare costs)

Therapeutic Goals
Treatment Goals for Heart Failure Therapy

Goal: Improve the Quality and Quantity of Life

Objectives

- Relieve symptoms and improve exercise tolerance
- Prevent sudden death, arrhythmias
- Slow progression of the underlying disease
- Decrease ER visits, hospitalizations, and costs
- Prevent complications, such as atrial fibrillation, stroke
Historical Therapy For Heart Failure
Drug Therapy
Enalapril Reduces Mortality in Heart Failure
(SOLVD trial 1991)

ACE inhibitor improves survival in moderate CHF Enalapril, compared to placebo, decreases patient mortality in NYHA class II and III heart failure (p = 0.0036). (Data from The SOLVD Investigators, N Engl J Med 1991; 325:293.)
Metoprolol Reduces Mortality in Heart Failure
(MERIT-HF trial 1999)

34% Reduction at One Year

**Metoprolol reduces mortality in patients with heart failure.** The MERIT-HF trial randomized 3991 patients with NYHA class II to IV heart failure who were treated with digoxin, angiotensin converting enzyme inhibitors, and digoxin to metoprolol CR/XL or placebo. Kaplan-Meier curves show a significant reduction in total mortality at 12 months with metoprolol (7.2 versus 11 percent for placebo, p = 0.006). (Data from The MERIT-HF Study Group, Lancet 1999; 353:2001).
Spironolactone Reduces Mortality in Heart Failure (RALES trial 1999)

Spironolactone reduces mortality in heart failure: Kaplan-Meier analysis of survival among 1663 patients with advanced heart failure in the RALES trial shows that spironolactone reduces mortality by 30 percent (35 versus 46 percent for placebo, p<0.001). (Data from Pitt, B, Zannad, F, Remme, WJ, et al, N Engl J Med 1999; 341:709.)
Results of Heart Failure Therapy

- More than one drug is needed and they work synergistically.
- Optimal drug therapy in combination reduces mortality by about a third.
So How Could Device Therapy Help?
Mechanism of Death in HF

NYHA class II
No. of deaths
n = 103
SCD 64%
CHF 12%
Other 24%

NYHA class III
No. of deaths
n = 232
SCD 59%
CHF 26%
Other 15%

NYHA class IV
No. of deaths
n = 27
SCD 33%
CHF 56%
Other 11%

Magnitude of SCA in the US

SCA claims more lives each year than these other diseases combined

1. AIDS
   - 450,000 SCA
   - #1 the U.S.

2. Lung Cancer
   - 157,400

3. Breast Cancer
   - 40,600

4. Stroke
   - 167,366

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SCD: Ventricular Fibrillation
The Defibrillator
The Implantable Defibrillator Then

- Initially
  Defibrillation only

- Surgical implant
during CABG

- Evolution to Sub-
  clavicular
ICD Trials Summary

Relative Reduction in All-cause Mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Reduction (3 years)</th>
<th>n=</th>
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<tbody>
<tr>
<td>AVID</td>
<td>31%</td>
<td>1016</td>
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<tr>
<td>CIDS</td>
<td>20%</td>
<td>659</td>
</tr>
<tr>
<td>MADITT</td>
<td>54%</td>
<td>196</td>
</tr>
<tr>
<td>MUSTT</td>
<td>60%</td>
<td>704</td>
</tr>
<tr>
<td>MADITT II</td>
<td>31%</td>
<td>1232</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>23%</td>
<td>2521</td>
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</tbody>
</table>

Years: 3, 2, 2, 2, 5
Results of Heart Failure Therapy

- Optimal drug therapy in combination reduces mortality by about a third
- Defibrillator therapy improves survival an additional 25 to 30%
An interesting Observation
Heart Failure: Assynchronous Mechanics:
Normal Sinus Rhythm
Left Bundle Branch Block
Prevalence and Prognosis of Ventricular Dysynchrony

LBBB More Prevalent with Impaired LV Systolic Function

- Preserved LVSF (1) 8%
- Impaired LVSF (1) 24%
- Mod/Sev HF (2) 38%

Increased All-Cause Mortality with Wide QRS at 45 Months (3)
P < 0.001

- QRS < 120 ms 34%
- QRS > 120 ms 49%

3. Iuliano et al. AHJ 2002;143:1085-91
Abnormal Ventricular Activation
CRT: Three-chamber Pacing
MIRACLE: 2002
Multi-center In Sync Randomized Clinical Evaluation Trial

- Double blinded RCT
- First US trial
- NYHA Class III or IV, on OPT, QRS >130 ms, EF<35%
- Enrollment of 453 patients
Nonresponders: older, ischemic CM, no MR, QRS<150
Responders: had shorter duration on CHF and longer QRS>155
Pivotal Study Phase
CRT Improves NYHA Class

P < 0.001

Chi-square test

Baseline 6-Months
Control (N = 117)

Baseline 6-Months
CRT (N = 124)
Improved Cardiac Mechanics with CRT
Trans-mitral Flow
Could the addition of defibrillator therapy to CRT therapy Help?
COMPANION Study

Comparison of Medical Therapy, Pacing and Defibrillation In Heart Failure
COMPANION: Primary Hypotheses

In Patients with advanced heart failure and QRS widening, when used in conjunction with optimal pharmacologic therapy:

- Bi-ventricular cardiac resynchronization therapy (CRT) alone, or in combination with defibrillation (CRT-D) decreases all-cause mortality and all-cause hospitalization.
COMPANION: Results

Randomized open label 1:2:2

1520 Patients

OPT
308 Patients

OPT/CRT/P
617 patients

OPT/CRT/D
595 patients
COMPANION: All-Cause Deaths

12 month Event-Rate

COMPANION: Reduction in HF Hospitalization with Therapy

Hospitalizations in the first 12 months

133 Admissions

Results of Heart Failure Therapy

- Optimal drug therapy in combination reduces mortality by about a third
- Defibrillator therapy improves survival an additional 25 to 30%
- Cardiac resynchronization therapy in combination with above expands the survival benefit and reduces hospitalizations
The ICD Today: A Cardiac Performance Management System

- Advanced Pacing
- CRT
- Remote wireless Monitoring
- Defibrillation Therapy
Thank You

James L. Cockrell, Jr., MD
Founding Director, Cardiac Electrophysiology
Washington Adventist Hospital
LifeVest
A Proven Treatment Option
Patients with Low EF Following PCI
WCD Reduces Total Mortality

• Post-PCI low EF (≤35%) patients prescribed the WCD had an 80% lower 90-day mortality (2%) compared to a matched cohort of patients not prescribed the WCD (10%) \(^1\)

• Post-PCI patients prescribed the WCD had a 57% lower risk of death (p<0.0001) over a mean follow-up of over 3 years \(^1\)

• Following the end of WCD use, a continued survival benefit was observed out to 3 years
  – WCD is commonly worn by patients for 90 days following PCI

\(^1\) Zishiri, E et al. Use of the Wearable Cardioverter Defibrillator and Survival After Revascularization in Patients with Left Ventricular Dysfunction. 2011;124:A9816.
Indications: Bridge to ICD

• Post Myocardial Infarction with low EF ($\leq 35\%$)
  < 40 days after MI
  < 90 post CABG
  < 90 post PTCA

• Non-ischemic cardiomyopathy
  < 3 months from diagnosis (90-270 days)

• ICD requires explantation

• Pre transplant, NYHA Class IV
Complications of Heart Failure
When All Else Fails?
Results with LVAD Therapy

- 280 Patients
- 27% in-hospital mortality
- 56% one year survival

Circ 2007;116:497-505
A normal heart pumps blood in a smooth and synchronized way.
Heart Transplantation

- A good solution to the failing heart—get a new heart
- Unfortunately we are limited by supply, not demand
- Approximately 2200 transplants are performed yearly in the US, and this number has been stable for the past 20 years.
Worldwide Heart Transplants

![Graph showing the increase in worldwide heart transplants from 1982 to 2002. The number of transplants increases dramatically from 1990 onwards.](chart)
MEDICAL MIRACLES

But How to Pay the Bill?

Surgeon DeVries With Artificial Heart
The Future of Device Therapy For Heart Failure

- Adaptive CRT
- Refinement of implanted systems from cardiac rhythm management (CRM) to that of cardiac performance management (CPM) systems
The ICD Today

- Defibrillation
- Synchronized Cardioversion
- Anti-tachycardia Pacing (ATP) Therapy
Anti-tachycardia Therapy: Success

Episode duration = 5.3 s

Anti-tachycardia Therapy

Slow VT
Re-entrant VT with CL = 400 ms (150 bpm)

ATP Efficacy = 90-95% \(^1-^3\)

# Heart Failure: Treatment Strategies

<table>
<thead>
<tr>
<th>Clinical Goal</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life (Symptom Relief)</td>
<td>Diuretics Inotropes (acute) Vasodilators</td>
</tr>
<tr>
<td>Prevent Progression</td>
<td>Ace Inhibitors B Blockade</td>
</tr>
<tr>
<td>Survival</td>
<td>Ace Inhibitors B Blockade ICDs</td>
</tr>
<tr>
<td>Reverse Remodeling</td>
<td>Heart Transplant</td>
</tr>
</tbody>
</table>
The Importance of the Sequence of Ventricular Activation

Cardiac Output (l/min): 12

patients with intact AV Conduction

Pacing Mode

VVI

DDD

AAI

Contrasting Mechanics
Issues Associated with Heart Failure

Cardiac resynchronization therapy (CRT)–global synchrony

Baseline

DCM - CRT

Courtesy of C. Stellbrink, MD.
Issues Associated with Heart Failure

Cardiac resynchronization therapy (CRT)–global synchrony

Mitral Valve Function

Diastolic Filling
Issues Associated with Heart Failure

Cardiac resynchronization therapy (CRT)–global synchrony

Mitral Valve Function

Diastolic Filling
Cardiac Resynchronization Therapy

Early Results
MIRACLE Pivotal Phase
CRT Improves 6-Minute Hall Walk Distance

P=0.032
P=0.004
P=0.033
Pivotal Study Phase
CRT Improves NYHA Class

P < 0.001

Baseline 6-Months
Control (N = 117)

Baseline 6-Months
CRT (N = 124)

Chi-square test

Class
I
II
III
IV

93% 90%
64% 52%
27% 13%
0%
MIRACLE: Conclusions

In NYHA Class III and IV systolic heart failure patients with intraventricular conduction delays, CRT

- is safe and well tolerated
- improves Quality of Life, functional class, and exercise capacity
- improves cardiac structure and function
- improves heart failure composite response
Cumulative Enrollment in Cardiac Resynchronization Randomized Trials

Results Presented

Cumulative Patients

- PATH CHF
- MUSTIC SR
- MUSTIC AF
- MIRACLE
- PATH CHF II
- CONTAK CD
- MIRACLE ICD
- COMPANION
- MIRACLE ICD II
- CARE HF
PATH-CHF: 1999

Pacing Therapy for Congestive Heart Failure

- This was the **first multicenter trial** and used the standard endocardial RV lead and an **epicardial** LV lead via thoracotomy or thorascopes.
- Single blinded RCT
- 53 centers in **Europe**
- 41 patients
PATH-CHF

Implant

NYHA class III-IV
DCM
QRS > 120 ms
PR > 150

Acute hemodynamic testing

Randomization 1:1

4 weeks
Best single chamber

8 weeks
No CRT

12 weeks
CRT

One year
Best mode

No CRT

Best single chamber
PATH-CHF

- **Primary endpoints**
  - Peak VO2
  - Six-minute walk distance

- **Secondary endpoints**
  - Minnesota Living with Heart Failure score (QOL)
  - NYHA class
  - EF
  - Trend towards decrease in Hospitalizations

- **Acute hemodynamic testing** revealed that the lateral and posterolateral walls were the best target sites.
  - The best responders were those with QRS>150, long PR and dP/dt < 700 mm Hg/s
MUSTIC: 2001
Multicenter Stimulation in CM

- European study with 67 patients
- QRS>150, CHF, EF <35%
- BiVP versus backup VVI pacing at 40 BPM
- Increase in 6 minute walk time, QOL and Peak VO2 with BiVP and persisted for up to 12 months
- 60% decrease in CHF hospitalizations
- First to use endocardial LV leads via the CS
- No significant change in mortality, but a trend towards an improvement.
- Acute hemodynamic studies showed the mid lateral wall to be the best site
Reverse Remodeling with CRT

Changes in LVEF, (%) median +/- 95% CI

- 3 months: P<0.01
- 6 months: P<0.01

OPT (n=151) vs. OPT & CRT (n=172)

St John Sutton et al MIRACLE Trial Circulation, 2003;107:1985-1900
Cardiac Resynchronization Therapy

Myocardial Energetics
An immediate hemodynamic response

Reprinted with permission.

Cardiac Resynchronization Therapy

- A reduction in heart failure symptoms
- Improvement in cardiac performance

- Can such therapy reduce hospitalization and improve survival?
Reduced Mortality in Heart Failure

ACE-I & Beta Blockade Reduce Mortality

1 Year Mortality

- SOLVD-T: Placebo 16.5%, Treatment 12.4%
- MERIT-HF + CIBIS II: Placebo 11.5%, Treatment 7.8%

Further Reduction with CRT + ICD for Higher Risk Patients

Adapted from McMurray JJV; Heart 1999; 82(Suppl IV):IV14-IV22
Conclusions

- Large number of patients studied in RCTs
- Concordant proof that CRT improves quality of life, exercise capacity, functional capacity
  - Improvements persist through 1 year
- CRT reduces the risk of mortality and heart failure due to worsening HF
- CRT + ICD reduces risk of mortality
- CRT improves cardiac function and structure
Heart Failure Device Therapy

Cardiac rhythm management technology
Cardiac Resynchronization Therapy Overview
Cardiac Resynchronization Therapy Effect on LV Size and Function (MIRACLE)

Paired, Median Changes from Baseline

**LVEDV**
- Control (n=151) vs. CRT (n=172)

**LVEF**
- Control (n=151) vs. CRT (n=172)

**MR Jet Area**
- Control (n=151) vs. CRT (n=172)

Effect of β-blocker Therapy

Paired, Median Changes from Baseline at 6 Months

LVEDV

-40 -30 -20 -10 0 10

BB No BB

Absolute %

LVEF

0 2 4 6 8

BB No BB

MR Jet Area

0 1

BB No BB

* p < 0.05, CRT vs. Control within subgroups
† p < 0.05, CRT vs. CRT between subgroups

LV Reverse Remodeling after CRT

LV End Systolic and Diastolic Volumes

MR area

N = 25

LV Reverse Remodeling after CRT

LV End Systolic and Diastolic Volumes

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1wk</th>
<th>1mo</th>
<th>3mo</th>
<th>off-immed</th>
<th>off-1wk</th>
<th>off-4wk</th>
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<tbody>
<tr>
<td>Left ventricular volume (mL) CRT on</td>
<td>225 ± 10</td>
<td>200 ± 15</td>
<td>175 ± 20</td>
<td>150 ± 25</td>
<td>125 ± 30</td>
<td>100 ± 35</td>
<td>75 ± 40</td>
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<tr>
<td>Left ventricular volume (mL) CRT off</td>
<td>225 ± 10</td>
<td>200 ± 15</td>
<td>175 ± 20</td>
<td>150 ± 25</td>
<td>125 ± 30</td>
<td>100 ± 35</td>
<td>75 ± 40</td>
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</table>

MR area

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1wk</th>
<th>1mo</th>
<th>3mo</th>
<th>off-immed</th>
<th>off-1wk</th>
<th>off-4wk</th>
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</thead>
<tbody>
<tr>
<td>Mitral regurgitation (%) CRT on</td>
<td>10 ± 5</td>
<td>15 ± 7</td>
<td>20 ± 9</td>
<td>25 ± 11</td>
<td>30 ± 13</td>
<td>35 ± 15</td>
<td>40 ± 17</td>
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<tr>
<td>Mitral regurgitation (%) CRT off</td>
<td>10 ± 5</td>
<td>15 ± 7</td>
<td>20 ± 9</td>
<td>25 ± 11</td>
<td>30 ± 13</td>
<td>35 ± 15</td>
<td>40 ± 17</td>
</tr>
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</table>

N = 25

Cardiac Resynchronization Therapy Improves Quality of Life and NYHA Functional Class

Average Change in QoL Score (MLWHF)

<table>
<thead>
<tr>
<th>Study</th>
<th>Average Change</th>
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<tbody>
<tr>
<td>MIRACLE (1)</td>
<td>-20</td>
</tr>
<tr>
<td>MUSTIC SR (2)</td>
<td>-15</td>
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<tr>
<td>MUSTIC AF (3)</td>
<td>-10</td>
</tr>
<tr>
<td>CONTAK CD (4)</td>
<td>-5</td>
</tr>
<tr>
<td>MIRACLE ICD (5)</td>
<td>0</td>
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</table>

NYHA: Proportion Improving 1 or More Class

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion Improving 1 or More Class</th>
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<tbody>
<tr>
<td>MIRACLE (1)</td>
<td>*</td>
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<tr>
<td>CONTAK CD (4)</td>
<td>*</td>
</tr>
<tr>
<td>MIRACLE ICD (5)</td>
<td>*</td>
</tr>
</tbody>
</table>

* P < 0.05

References:
1. NEJM 2002;346:1845-53
2. NEJM 2001;344:873-80
3. Eur Heart J 2002;23:1780-1787

Doug Smith:
Cardiac Resynchronization Therapy Improves Exercise Capacity

Average Change in 6 Minute Walk Distance

- MIRACLE (1)
- MUSTIC SR (2)
- CONTAK CD (3)
- MIRACLE ICD (4)

* P < 0.05

Average Change in Peak VO₂

- MIRACLE (1)
- MUSTIC SR (2)
- CONTAK CD (3)
- MIRACLE ICD (4)

* P < 0.05

1. NEJM 2002;346:1845-53
2. NEJM 2001;344:873-80
4. JAMA 2003; 289:2685-94

Doug Smith:
Benefits Sustained Through 1 Year

Change from baseline in 6 minute walk distance

<table>
<thead>
<tr>
<th>Metrics</th>
<th>MIRACLE (1)</th>
<th>InSync (2)</th>
<th>MUSTIC (3)</th>
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<tr>
<td>Meters</td>
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<td>40</td>
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<td>60</td>
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<tr>
<td>80</td>
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Change from baseline in NYHA Class

<table>
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<th>MIRACLE (1)</th>
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<tbody>
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<td>Improvement score</td>
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<td>-0.5</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>-1.5</td>
<td></td>
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Change from baseline in QoL (MLWHF) Score

<table>
<thead>
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<th>MIRACLE</th>
<th>InSync</th>
<th>MUSTIC</th>
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<tbody>
<tr>
<td>Improvement score</td>
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<td></td>
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</tr>
<tr>
<td>-5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10</td>
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<td>-15</td>
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<td></td>
</tr>
<tr>
<td>-25</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

1. World Congress of Cardiology 2002 (MIRACLE)
2. Eur J Heart Fail 2002;4:311-20 (InSync Europe & Canada)
3. JACC 2002;4:111-8 (MUSTIC)
Cardiac Resynchronization Therapy: An Adjunct to Optimal Medical Therapy

1 NEJM 1993;329:1-7 (RADIANCE)
2 Circulation 1996;94:2793-2799 (PRECISE)
3 JAMA 1988;259:539-544
4 Am J Cardiol 1993;71:1106-1107 (SOLVD Treatment)
5 J Cardiac Failure 1997;3:173-179
6 NEJM 2002;346:1845-53 (MIRACLE)
### Who Responds to Cardiac Resynchronization?

<table>
<thead>
<tr>
<th>Responder Parameter(s)</th>
<th>Finding</th>
<th>Limitation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA III/IV, QRS $\geq$ 130 ms, EF $\leq$ 35%, LVEDD $\geq$ 55 mm</td>
<td>Confirmed in RCTs of over 2,500 patients</td>
<td>□~ 70% respond favorably</td>
</tr>
<tr>
<td>QRS $\geq$ 150/155 and/or $dP/dt \leq$ 700 mm Hg/s</td>
<td>Correlated with improved $dP/dt$ (^1,2)</td>
<td>□Small studies, &lt; 30 pts; □No clinical endpoint □not confirmed by MIRACLE</td>
</tr>
<tr>
<td>Difference in time to peak systolic contraction</td>
<td>Correlated with ↓ volumes (^3,4,5)</td>
<td>□Small studies, ≤ 30 pts; □Varying techniques □No clinical endpoint</td>
</tr>
<tr>
<td>No MI, significant mitral regurgitation</td>
<td>Correlated with improved NYHA(^6)</td>
<td>□Observational study; □not confirmed by MIRACLE</td>
</tr>
</tbody>
</table>

Improved Cardiac Function Without Oxidative Stress


Cardiac Resynchronization Therapy Does Not Promote Ventricular Arrhythmias

- Analyzed 1,044 patients with ICDs from 2 trials:
  - CONTAK CD
  - MIRACLE ICD

- Odds ratio (CI): 0.92 (0.67 – 1.27)

Relative Cost of CRT

Cost per patient
- Dialysis
- CABG
- PTCA
- Hip/ knee replace
- CRT
- CRT+ICD

Total Annual Expenditures

Doug Smith:
MADIT-II
Multicenter Automatic Defibrillator Implantation Trial - II

MADIT-II Hypothesis

ICD therapy is able to reduce overall mortality assuming:

- Mortality in control = 19%
- Mortality in ICD = 11.8%
- 38% reduction in mortality at 2 years

MADIT-II Inclusion Criteria

- Q-wave MI ≥ 4 weeks
- LVEF ≤ 0.30
- ≥ 21 years of age; no upper age limitation
- No requirement for NSVT or EPS
MADIT-II Exclusion Criteria

- Indication for ICD approved by FDA
- NYHA Class IV at enrollment
- CABG < 3 months
- Q-wave MI < 4 weeks
- Advanced cerebrovascular disease
- High likelihood of death during trial
MADIT-II Endpoints

**Primary:**
- All cause mortality (intention-to-treat analysis)

**Secondary:**
- Predictability of ICD discharge based on VT inducibility at EPS
- Usefulness of SAECG, HRV, TWA in predicting mortality or ICD discharge
- Cost-effectiveness
- Quality of life

MADIT-II Protocol

Inclusion criteria

ICD implant n=742

EPS after implant

No-ICD implant n=490

Conventional Post-MI drug Rx

20 months mean follow-up

- Avoid AAD
- Optimize: BB, ACE-I, Diuretics

## MADIT-II

### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Conventional Rx</th>
<th>ICD Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 490 )</td>
<td>( n = 742 )</td>
</tr>
<tr>
<td>LVEF (mean)</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>AMI &gt; 6 mos</td>
<td>87%</td>
<td>88%</td>
</tr>
<tr>
<td>AGE (mean)</td>
<td>64 yr</td>
<td>65 yr</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>56%</td>
<td>58%</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>42%</td>
<td>45%</td>
</tr>
</tbody>
</table>

# MADIT-II Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Conventional Rx n=490</th>
<th>ICD Rx n=742</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class I</td>
<td>39%</td>
<td>35%</td>
</tr>
<tr>
<td>II</td>
<td>34%</td>
<td>35%</td>
</tr>
<tr>
<td>III</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td>IV</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>QRS interval ≥ 0.12 sec</td>
<td>50%</td>
<td>51%</td>
</tr>
</tbody>
</table>

### MADIT-II Patient Characteristics

<table>
<thead>
<tr>
<th>Medications at Last Contact</th>
<th>Conventional Rx n = 490</th>
<th>ICD Rx n = 742</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE I</td>
<td>72%</td>
<td>68%</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>Lipid Lowering Statins</td>
<td>64%</td>
<td>67%</td>
</tr>
<tr>
<td>Digitalis</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Class I AA</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

## MADIT-II Results

<table>
<thead>
<tr>
<th></th>
<th>Conventional Rx</th>
<th>ICD Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n =490</td>
<td>n=742</td>
</tr>
<tr>
<td>Lead Problems</td>
<td>-</td>
<td>1.8%</td>
</tr>
<tr>
<td>Non-fatal Infections</td>
<td>-</td>
<td>0.7%</td>
</tr>
<tr>
<td>Heart Failure Hospitalization</td>
<td>14.9%</td>
<td>19.9%</td>
</tr>
</tbody>
</table>

MADIT-II Conclusions

For post-MI patients with LVEF ≤ 30%:

- ICD therapy significantly reduced the incidence of overall mortality by 31%.
- ICD therapy provided significant benefit among patients who were on optimal drug therapies.

# MADIT-II Survival Results


<table>
<thead>
<tr>
<th>Year</th>
<th>No. At Risk</th>
<th>Defibrillator</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>742</td>
<td>502 (0.91)</td>
<td>329 (0.90)</td>
</tr>
<tr>
<td>1</td>
<td>502</td>
<td>274 (0.94)</td>
<td>170 (0.78)</td>
</tr>
<tr>
<td>2</td>
<td>274</td>
<td>110 (0.78)</td>
<td>65 (0.69)</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>65 (0.69)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.007
MADIT-II Statistical Analysis
Triangular Sequential Design

Log-Rank Statistic

Variance

Sequential Monitoring in the Triangular Design

11/13/01 – Reached efficacy boundary (P = 0.027)

01/16/02 – Closeout (P = 0.016)

Efficacy boundary for defibrillator

Inefficacy boundary for defibrillator

Boundary indicating no difference between groups

Mortality rate by type of therapy

MADITT-II, mean follow-up 20 months

- Non-ICD group (n=490): 19.8% mortality rate (p=0.016)
- ICD group (n=742): 14.2% mortality rate

MADIT-II: Survival Results

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NO. OF PATIENTS</th>
<th>HAZARD RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yr</td>
<td>370</td>
<td></td>
</tr>
<tr>
<td>60–69 yr</td>
<td>426</td>
<td></td>
</tr>
<tr>
<td>≥70 yr</td>
<td>436</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1040</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.25</td>
<td>831</td>
<td></td>
</tr>
<tr>
<td>&gt;0.25</td>
<td>401</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>461</td>
<td></td>
</tr>
<tr>
<td>≥II</td>
<td>771</td>
<td></td>
</tr>
<tr>
<td>QRS interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.12 sec</td>
<td>618</td>
<td></td>
</tr>
<tr>
<td>0.12–0.15 sec</td>
<td>352</td>
<td></td>
</tr>
<tr>
<td>&gt;0.15 sec</td>
<td>262</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1232</td>
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Hospitalizations for heart failure by type of therapy

MADITT-II, mean follow-up 20 months

Hospitalization rate (%)

- Non-ICD group (n= 490) - 14.9%
- ICD group (n= 742) - 19.9%

(p=0.09)