Cardiac Resynchronization Therapy: Current Indications and Future Prospects

Saverio Iacopino, MD, FACC, FESC
CHF Population in Europe

CHF Population

6.5 Million

Incidence = 580’000 (9.0%)
Mortality = 300’000 (4.6%)
Hospital Discharges for CHF

CHF Patients Survival Results

- Women (N = 230)
- Men (N = 237)

HF and/or Decreased LV Function

- About one-half of all deaths in HF patients are characterized as sudden due to arrhythmias.

- The risk of SCD increases as left ventricular function deteriorates (low LVEF).


Incidence of SCD in Specific Populations and Annual SCD Numbers


- General adult population
- Multiple risk subgroups
- Patients with any previous coronary event
- Patients with ejection fraction <35% or CHF
- Cardiac arrest, VT/VF survivors
- High-risk post-MI subgroups

Incidence of Sudden Deaths Per Year (number)

Incidence of Sudden Death (% of group)
Risk of Sudden Death: GISSI-2 Trial

Maggioni AP. Circulation. 1993;87:312-322.

**Patients without LV Dysfunction (LVEF >35%)**

- No PVBs
- 1-10 PVBs/h
- > 10 PVBs/h

**Patients with LV Dysfunction (LVEF ≤ 35%)**

- No PVBs
- 1-10 PVBs/h
- > 10 PVBs/h

---

**Graph A**

- Survival vs. Days
- p log-rank 0.002

**Graph B**

- Survival vs. Days
- p log-rank 0.0001

The greatest opportunity for SCD prevention is in patients that have mild to moderate CHF.
Hospitalization/NYHA Class in HF

- **NYHA CLASS**
  - I
  - II
  - III
  - IV

- **Annual survival (%)**
  - 100
  - 75
  - 50
  - 25
  - 0

- **Hospitalizations/year**
  - Hospitalization/NYHA Class in HF

- **Graph**
  - Survival curve
  - Hospitalization curve
Quality of Life for HF patients

Overall perception of health

- General population: 70
- Depression: 58
- Angina: 56
- AF symptomatic: 52
- Valve disease symptomatic: 48
- Chronic Bronchitis: 48
- Heart Failure NYHA Class II: 55
- Heart Failure NYHA Class III: 45
- Heart Failure NYHA Class IV: 36

SCD in Heart Failure

- 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.
  - ≈ 50% of these premature deaths are SCD (VT/VF)
- The role of device therapy?

---

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,

Reductions in Mortality with ICD Therapy

ICD mortality reductions in primary prevention trials are equal to or greater than those in secondary prevention trials.

4 Moss AJ. Presented before ACC 51st Annual Scientific Sessions, Late Breaking Clinical Trials, March 19, 2002.
7 Connolly S. Circ. 2000;101:1297-1302.
SCD-HeFT Mortality Rate Overall Results

<table>
<thead>
<tr>
<th>Months of Follow-Up</th>
<th>Hazard Ratio (97.5% Cl)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.06 (0.86-1.30)</td>
<td>0.53</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>0.77 (0.62-0.96)</td>
<td>0.007</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone</th>
<th>Placebo</th>
<th>ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>845</td>
<td>847</td>
<td>829</td>
</tr>
<tr>
<td>12</td>
<td>772</td>
<td>797</td>
<td>778</td>
</tr>
<tr>
<td>24</td>
<td>715</td>
<td>724</td>
<td>733</td>
</tr>
<tr>
<td>36</td>
<td>484</td>
<td>505</td>
<td>501</td>
</tr>
<tr>
<td>48</td>
<td>280</td>
<td>304</td>
<td>304</td>
</tr>
<tr>
<td>60</td>
<td>97</td>
<td>89</td>
<td>103</td>
</tr>
</tbody>
</table>

### SCD-HeFT Overall Mortality Results

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (97.5% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs. Placebo</td>
<td>1.06 (0.86-1.30)</td>
<td>0.53</td>
</tr>
<tr>
<td>ICD vs. Placebo</td>
<td>0.77 (0.62-0.96)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ICDs reduce mortality by 23%.

CHF Population in Europe

CHF Population

- Incidence = 580,000 (9.0%)
- Mortality = 300,000 (4.6%)

NYHA III + IV (30 - 35%)

Wide QRS (10 - 30%)

6.5 Million

1.95 Million

650,000
Prevalence of Inter- or Intraventricular Conduction Delay

General HF Population\textsuperscript{1,2} – IVCD 15%

Moderate to Severe HF Population\textsuperscript{3,4,5} – IVCD >30%

\textsuperscript{1} Havranek E, Masoudi F, Westfall K, et al. Am Heart J 2002;143:412-417
Prevalence and Prognosis of Ventricular Dysynchrony

Ventricular dysynchrony impairs diastolic and systolic function:\n- Reduced LV filling time; Increased mitral regurgitation; Depressed dP/dt

3. Iuliano et al. AHJ 2002;143:1085-91

LBBB More Prevalent with Impaired LV Systolic Function

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preserved LVSF (1)</th>
<th>Impaired LVSF (1)</th>
<th>Mod/Sev HF (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB</td>
<td>8%</td>
<td>24%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Increased All-Cause Mortality with Wide QRS at 45 Months

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

P < 0.001

3. Iuliano et al. AHJ 2002;143:1085-91
Wide QRS – Proportional Mortality Increase

Vesnarinone Study\(^1\) (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

Desincronia Ventricolare

✓ Elettrica: Ritardo di conduzione intraventricolare (BBsn)

✓ Strutturale: disgregazione della matrice di collagene cardiaca che danneggia efficienza meccanica e conduzione elettrica

✓ Meccanica: Anormalità nel movimento delle pareti con incrementato carico di lavoro e sforzo, compromettendo i meccanismi ventricolari

Tavazzi L. Eur Heart J 2000;21:1211-1214
Durrer. Total Excitation of the Isolated Human heart Circulation 1970
Scher: The sequence of Ventricular Excitation Am. J. Cardiol. 1964
Site and Length of the Line-of-Block

QRS Duration

>150 msec

120 - 150 msec

Line of Block

Auricchio et al. Circulation 2004
Electromechanical Decoupling

Electrical disturbance
- wide QRS
- LBBB

Mechanical dysynchrony
- Impaired intra- and inter-ventricular coordination

Hemodynamic Consequences of Ventricular Dysynchrony

Effects of LBBB on LV Contraction and Relaxation (1)

- Reduced LV filling time $^{1,2}$
- Prolonged mitral regurgitation $^{1,2}$
- Impaired systolic function (depressed dP/dt) $^{3,4}$
- Abnormal septal wall motion$^1$
- Mechanical and temporal dysynchrony $^4$

The Cardiac Conduction System and Biventricular Pacing

2006;355:288-294
Proposed Mechanisms of Benefit

Cardiac Resynchronization

- Intraventricular Synchrony
  - ↑ dP/dt, ↑ EF, ↑ CO (↑ Pulse Pressure)
  - ↓ LVESV

- Atrioventricular Synchrony
  - ↓ MR
  - ↓ LA Pressure
  - ↓ LVEDV

- Interventricular Synchrony
  - ↑ LV Diastolic Filling
  - ↑ RV Stroke Volume

Reversed Remodeling

Acute Studies

Systolic Blood pressure

Pulmonary Capillary Wedge Pressure

23 pts mean ± SD

Blanc et al., Circulation 1997
Acute Studies

![Graphs showing LV Pressure vs. LV Volume for different conditions: RV Apex, RV Septum, LV Freewall, Biventricular. The graphs compare Intrinsic (solid red) and Paced (dotted blue) conditions.]
Over 8,000 Patients Studied in Clinical Trials
MUSTIC Trial
CRT Improve Quality of Life (MLHFQ)

S. Cazeau et al. NEJM 2001;344:873-80

[Graph showing quality of life scores across different time points (Baseline, Randomization, CO1, CO2) for active-inactive and inactive-active groups, with a p-value of <0.001 indicating a significant difference between active and inactive groups.]

Aritmie Cardiache.com
MUSTIC Trial

LVESV and LVEDV

MR area

Pacing

No pacing

N = 25

S.Cazeau et al  NEJM 2001;344:873-80
MIRACLE
Time to Death or Worsening HF requiring Hospitalization

P = 0.033
Relative risk = 0.60; 95% CI (0.37, 0.96)

COMPANION Composite of Death or Hospitalization for Any Cause Results

Event-Free Survival (%)

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>308</th>
<th>176</th>
<th>115</th>
<th>72</th>
<th>46</th>
<th>24</th>
<th>16</th>
<th>6</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>617</td>
<td>384</td>
<td>294</td>
<td>228</td>
<td>146</td>
<td>73</td>
<td>36</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>CRT-D</td>
<td>595</td>
<td>385</td>
<td>283</td>
<td>217</td>
<td>128</td>
<td>61</td>
<td>24</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

Days after Randomization

(CRT vs. OPT) \(P = 0.014\)
(CRT-D vs. OPT) \(P = 0.010\)

COMPANION All-Cause Death Results

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>OPT</th>
<th>CRT</th>
<th>CRT-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>308</td>
<td>617</td>
<td>595</td>
</tr>
<tr>
<td>90</td>
<td>284</td>
<td>579</td>
<td>555</td>
</tr>
<tr>
<td>180</td>
<td>255</td>
<td>520</td>
<td>517</td>
</tr>
<tr>
<td>270</td>
<td>217</td>
<td>488</td>
<td>470</td>
</tr>
<tr>
<td>360</td>
<td>186</td>
<td>439</td>
<td>420</td>
</tr>
<tr>
<td>450</td>
<td>141</td>
<td>355</td>
<td>331</td>
</tr>
<tr>
<td>540</td>
<td>94</td>
<td>251</td>
<td>219</td>
</tr>
<tr>
<td>630</td>
<td>57</td>
<td>164</td>
<td>148</td>
</tr>
<tr>
<td>720</td>
<td>45</td>
<td>104</td>
<td>95</td>
</tr>
<tr>
<td>810</td>
<td>25</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>900</td>
<td>4</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>990</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

CARE-HF - Death or Unplanned Hospitalization for CV Event Results

% Patients Free of Death from Any Cause or Unplanned Hospitalization for a Major CV Event

HR 0.63 (95% CI 0.51 to 0.77)
37% Relative Risk Reduction

P < 0.001

No. at Risk
CRT 409 323 273 166 68 7
Medical Therapy 404 292 232 118 48 3

CARE-HF Death from Any Cause Results

HR 0.64 (95% CI 0.48 to 0.85)
36% Relative Risk Reduction

ICD and CRT
Which Patient?

ICD:
✓ Mild to moderate HF – NYHA Class I-III
✓ LV ejection fraction ≤ 35%
✓ Post-MI (≥ 40 days); post-CABG (≥ 3 months)
✓ Optimal medical therapy
✓ Survival > 1 yr

CRT:
✓ Moderate to severe HF (NYHA Class III/IV) patients
✓ Symptomatic despite optimal, medical therapy
✓ QRS ≥ 120 msec
✓ LVEF ≤ 35
✓ Sinus rhythm

CRT plus ICD:
✓ Same as above with ICD indication
CMS ICD Coverage Reference Guide

**History of MI**
- Yes
  - History of inherited conditions with high risk of VT
    - Yes
      - NYHA Class IV
      - Cardiogenic shock or hypotension
      - CABG or PTCA within past 3 months
      - MI within past 40 days
      - Candidate for coronary revascularization
      - Irreversible brain damage from preexisting cerebral disease
      - Other disease with survival < 1 year
    - No
      - Not eligible for defibrillator
  - No
    - History of cardiac arrest due to VF
      - Yes
        - CAD, inducible sustained VT or VF at EPS MADIT
      - No
        - Not eligible for defibrillator
  - No
    - Sustained VT, spontaneous or induced by EPS
      - Yes
        - MADIT
      - No
        - Not eligible for defibrillator

**LVEF ≤ 30% MADIT-II**
- Yes
  - NYHA Class II or III HF
  - SCD-HeFT ischemic
    - Yes
      - Eligible for defibrillator
    - No
      - Not eligible for defibrillator
  - No
    - LVEF ≤ 35%
      - Yes
        - Eligible for defibrillator
      - No
        - Not eligible for defibrillator

**NYHA Class II or III HF SCD-HeFT non-ischemic**
- Yes
  - Eligible for defibrillator
- No
  - Not eligible for defibrillator

**NIDCM > 9 months NYHA Class II or III heart failure and LVEF ≤ 35% SCD-HeFT non-ischemic**
- Yes
  - Eligible for defibrillator
- No
  - Not eligible for defibrillator

**Not eligible for defibrillator**

**CAD, inducible sustained VT or VF at EPS MADIT**
- Yes
  - Eligible for defibrillator
- No
  - Not eligible for defibrillator
Symptomatic HF despite stable, optimal medical therapy

Prolonged QRS and LVEF ≤ 35%

NYHA Class IV heart failure

NYHA Class III heart failure

Meets coverage criteria for the implantation of an ICD

Not eligible for CRT device

Eligible for CRT pacemaker (CRT-P)

Eligible for CRT defibrillator (CRT-D)

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.
## AIAC Guidelines

### ICD - PRIMARY PREVENTION IN CARDIOMYOPATHY

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Description</th>
</tr>
</thead>
</table>
| **CLASS I** | Ischemic Cardiomyopathy, Reduced EF ($\leq 40\%$)  
Non Sustained VT and Sustained Inducible VT  
(Level B) |
|         | Ischemic & Non-Ischemic Cardiomyopathy  
(for Ischemic at least 40 days after AMI)  
Reduced EF ($\leq 30\%$), NYHA II/III, Optimal Medical Treatment  
(Level A) |
| **CLASS II** | Ischemic (at least 40 days after IMA) & Non-Ischemic Cardiomyopathy  
31% $\leq$ EF $\leq$ 35%, NYHA II/III  
Optimal Medical Treatment  
(Level B) |
|         | Ischemic Cardiomyopathy (at least 40 days after IMA)  
Reduced EF ($\leq 30\%$), NYHA I , Optimal Medical Treatment  
(Level B) |
## AIAC Guidelines

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Indications</th>
</tr>
</thead>
</table>
| **CLASS I** | Synus Rhythm, Reduced EF ($\leq 35\%$)  
Ventricular Dyssynchrony (QRS $> 120$ ms)  
NYHA III-IV despite Optimal Medical Therapy |
| **CLASS II** | Pts In Atrial Fibrillation, Reduced EF ($\leq 35\%$)  
Ventricular Dyssynchrony (QRS $> 120$ ms)  
NYHA III-IV despite Optimal Medical Therapy  
Reduced EF ($\leq 35\%$), QRS $\leq 120$ ms  
Ventricular Dyssynchrony (Echo assessment)  
NYHA III-IV despite Optimal Medical Therapy  
Synus Rhythm, Reduced EF ($\leq 35\%$)  
Ventricular Dyssynchrony (QRS $> 120$ms)  
Symptomatic (NYHA II) and with pacing indication or Primary Prevention ICD  
Chronic Right Ventricular Stimulation, Reduced EF ($\leq 35\%$)  
Severe Ventricular Dyssynchrony  
NYHA III-IV despite Optimal Medical Therapy (Upgrade) |

## RECOMMENDATIONS FOR CRT-D USE

The use of ICD in addition of CRT (CRT-D) should be based on recommendations for ICD use in primary or secondary prevention of sudden cardiac death.
Indications of CRT
New Guidelines of ESC

CRT using BIV pacing can be considered in patients with reduced EF and ventricular dyssynchrony (QRS width ≥ 120 msec), who remain symptomatic (NYHA III-IV) despite optimal medical therapy to improve:

✓ Symptoms (Class I, level A)
✓ Hospitalizations (Class I, level A)
✓ Mortality (Class I, level B)
QRS=160 ms

---------Therapy ON---------

---------Therapy OFF---------

QRS=120 ms
Cardiac Resynchronization Therapy: Creating Realistic Patient Expectations

✓ Approximately two-third of patients should experience improvement (responders vs. non-responders)\textsuperscript{1}
  ✓ Some patients may not experience immediate improvement

CRT is adjunctive and is not intended to replace medical therapy. Patients will continue to be followed by HF Specialist and Physician managing implantable devices.

Patient Selection for CRT Reasons for Low (or no) Response to CRT

- Inappropriate patient selection
- Inappropriate lead positioning
- Inappropriate AV delay tuning
- Inappropriate CRT delivery (PM functioning)
- Inappropriate drug treatment
- Spontaneous or PM mediated arrhythmias
Definition of Responder/Non Responder

**RESPONDER**

- Survival + at least 1 NYHA class down + 10% increase in peak VO2, for at least 6 months. *Alonso. AJC 1999*
- Improvement ≥ 1 NYHA class. *Oguz. Eur J H Fail 2002*
- LVESV decreased by > 15%. *Stellbrink. J ACC 2001*
- Persistent decrease of ≥ 1 NYHA class, irrespective of the changes of others parameters.

**NON RESPONDER:**

- No decrease in NYHA class + no decrease in the QOL score. *Reuter. AJC 2002*
- Therapy considered as neutral or not beneficial (same NYHA class or decline of status; need for heart transplant; death due to progressive, drug-refractory pump failure). *Lunati. J CE 2002*
Reasons for low (or no) response to CRT
1. Inappropriate patient selection

- No Ventricular asynchrony +++
  - CRT may create ventricular asynchrony !!
- End stage cardiomyopathy
  - Severe RV dysfunction, High pulmonary hypertension
- Additional indications for Heart Surgery
  - Valve replacement, CABG
Reasons for low (or no) response to CRT
2. Inappropriate lead positioning

- LV lead placed in the Great Cardiac Vein
- RV lead close to the apex
- High lat RA lead in inter atrial conduction block
  - Short AVD: good BiV capture + poor LA contraction
  - Long AVD: poor BiV capture + good LA contraction
Possible Venous Tributaries of the CS

CS venous anatomy allowing LV lead tip should usually be positioned in a basal/mid-basal lateral (region C) or basal/mid-basal postero-lateral (region D) location.
Varying Patient Anatomy
Reasons for low (or no) response to CRT

3. Inappropriate setting of AV delay

- Long AV Delay
  160 ms: Opt A

- Short AV Delay
  50 ms: opt E

- Optimized AV Delay
  100 ms: opt E + A

Importance of AV delay optimization
Reasons for low (or no) response to CRT

4. Inappropriate CRT delivery: Up to 20%!
Reasons for low (or no) response to CRT
5. Inappropriate drug treatment

- ACE inhibitors:
  - increase in dosage, re-introduction
- Diuretics:
  - decrease in dosage +++
- Beta-Blockers:
  - Introduction
  - increase in dosage
- Combination: Amiodarone and beta-blockers
### CRT Procedure and Device Related Risks

#### Procedure Related Complications in 571 Patients Attempted; Proportion (n)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Proportion (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsuccessful implant</td>
<td>7.5%</td>
<td>43</td>
</tr>
<tr>
<td>CS Dissection or Perforation</td>
<td>6%</td>
<td>35</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.3%</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>0.3%</td>
<td>2</td>
</tr>
</tbody>
</table>

#### Device Related Complications in 6 months in 528 Patients Successfully Implanted; Proportion (n)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Proportion (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV Lead Revision</td>
<td>5.7%</td>
<td>30</td>
</tr>
<tr>
<td>PM Pocket/ RV Lead Infection</td>
<td>1.3%</td>
<td>7</td>
</tr>
</tbody>
</table>

Reduced Procedure Time with Increased Experience

![Graph showing reduced procedure time with increased experience](image)

**Reduced Procedure Time with Increased Experience**

- **P < 0.001**

CS dissection
When to Consider Epicardial Approach for LV Pacing

- Failure to implant LV lead: 0 to 10%
- LV lead in mid or great cardiac vein: 0 to 10%
- Interest of endocardial versus epicardial pacing

![Graph showing success rates for various devices]

- InSync: 88%
- InSync It: 90%
- Mustic: 92%
- Miracle: 93%
- Med OTW: 96%
LV pacing using epicardial approach
Incremental Cost-Effectiveness Cardiovascular Interventions

- Economically Unattractive
- Expensive
- Borderline Cost-Effective
- Cost-Effective
- Highly Cost-Effective

Incremental Cost per Life-Year Saved

- PTCA (chronic CAD, severe angina 1 VD): $8,461
- CABG (chronic CAD, mild angina, 3 VD): $17,701
- Hypertension Therapy (diastolic 95-104 mmHg): $40,750
- End Stage Renal Disease Treatment: $67,000
- Exercise SPECT (atypical angina who can walk on treadmill): $120,000
- Lovastatin (chol. = 290 mg/dL, 50 yrs old, male, no risk factors): $135,000
- Carotid Disease Screening (65 yrs old, male, no symptoms): $150,000
- Routine Coronary Angiography (35-84 yrs old, low risk MI, has CHF): $1,000,000

Sources:
Incremental Cost-Effectiveness
ICD, CRT, and CRT-D Therapies

Incremental Cost per Life-Year Saved

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost per Life-Year Saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPANION CRT</td>
<td>$28,000</td>
</tr>
<tr>
<td>SCD-HeFT ICD</td>
<td>$33,000</td>
</tr>
<tr>
<td>COMPANION CRT-D</td>
<td>$38,200</td>
</tr>
<tr>
<td>MADIT-II ICD</td>
<td>$50,000</td>
</tr>
<tr>
<td>AVID ICD</td>
<td>$67,000</td>
</tr>
</tbody>
</table>

- COMPANION CRT: Cost-Effective
- SCD-HeFT ICD: Expensive
- COMPANION CRT-D: Borderline Cost-Effective
- MADIT-II ICD: Highly Cost-Effective
- AVID ICD: Economically Unattractive

Actual Key Questions

✓ QRS<120ms or QTc dispersion?
✓ Which implication in patients with unstable haemodinamic profile?
✓ CRT in Right Bundle Branch Block?
✓ “Up-grading” in RVA pacing?
✓ CRT in chronic Atrial Fibrillation?
Over 8,000 Patients Studied in Clinical Trials

Prevalence of AF in moderate-to-severe CHF varies between 25% and 50%
The interaction between AF and HF means that neither can be treated optimally without treating both.
Does early intervention with CRT-D slow the progression of HF in high-risk patients with mild HF (NYHA I – II) when compared to ICD only therapy?

MADIT-CRT Question
MADIT-CRT

Hypothesis: in minimally symptomatic high-risk pts with IHD (NYHA I or II) or NIHD (NYHA II), wide QRS ($\geq .13s$), and low EF ($\leq .30$), CRT will slow or prevent the development of heart failure

- CRT-D vs ICD-only
- 1820 pts: 110 enrolling centers in US & Europe
- Endpoint: HF or death, whichever comes first
- Enrollment complete, in f/up phase
Kaplan-Meyer Curves for Death and for HF/Death – Both Rx Arms

(CRT-D vs. ICD)

Note: Of 1820 enrolled patients, 300 have experienced a 1st end-point event.
LV Sequential Pacing

LAO
Triple-site biventricular pacing
Multi-site Pacing

Improvement in PV Loop Parameters with MPP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Best Single Site</th>
<th>Best Multi Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV dP/dt_{Max}</td>
<td>11.2%</td>
<td>13.7%</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Stroke Work</td>
<td>14.0%</td>
<td>16.3%</td>
</tr>
<tr>
<td>p = 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Stroke Volume</td>
<td>0.3%</td>
<td>5.5%</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV Ejection Fraction</td>
<td>2.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 Month Results with MPP

- 100% of patients had ≥1 NYHA functional class improvement compared to 71% in the PROSPECT trial
- 71% of patients had >15% reduction in ESV compared to 56% in the PROSPECT trial
- 71% of patients had >5 percentage point increase in EF compared to 51% in the PROSPECT trial