The Role of ICD Therapy in Cardiac Resynchronization

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CRT CLINICAL TRIALS

MIRACLE 6mo parallel comparison
Contak-CD
InSync ICD
InSync III
MUSTIC 3mo double crossover
PATH-CHF II
COMPANION Prospective mortality study
**SCD in the CRT Population**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants (n)</th>
<th>Deaths/Total (SCD%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE</td>
<td>591</td>
<td>32*/91 (35%)</td>
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<td>InSync III</td>
<td>422</td>
<td>26*/65 (40%)</td>
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*deaths due to VT/VF

Progressive CHF and ventricular arrhythmia-SCD contribute greatly to mortality in the CRT trials.
Endpoints included functional capacity, LV dimensions and performance, QoL and limited assessments of CHF hospitalization.

Duration of follow-up designed to meet US-FDA requirement for device efficacy as CHF therapy.
ICD THERAPY AND MORTALITY

VT/VF with previous MI
EPS in high risk pts
Prophylactic ICD
CRT-ICD

AVID
MUSTT, MADIT
MADIT-II, SCD-HeFT
COMPANION
Survival with VT/VF and LV Dysfunction (AVID)

LVEF <0.20 (Group 1)

LVEF 0.20 - 0.34 (Group 2)

LVEF > 0.34 (Group 3)

NSVT in LV Dysfunction

**LVD and CAD**: ICD and inducible VT at EPS (MUSTT) *Buxton, NEJM 2001*  
(MADIT) *Moss, NEJM*

**LVD without CAD**: ICD provides no benefit over amiodarone to pts with non-ischemic CMP and NSVT (AMIOVERT) *Strickberger, JACC 2002*
ICD therapy vs. conventional medical therapy in patients with NSVT and LV dysfunction not due to CAD or previous MI

ICD reduced overall mortality: $p=0.06$

*Kadish, NEJM 2004*
Prophylactic ICD Implantation

Will Implantation of an ICD in an individual with LV dysfunction (LVD) and CHF reduce all-cause mortality?

MADIT II: LVD due to CAD/MI
COMPANION: CRT-ICD for QRS > 120ms
SCD-HFT: CHF, systolic dysfunction
MADIT II: PREVALENCE OF CHF

- LV dysfunction EF ≤ 0.30 due to MI at risk for SCD:
  - EF 22%
  - 60% > class II CHF
  - 88% > 6mos post MI
  - >70% on β-blockers and ACE-I

- Subgroup with prolong QRSd
MADIT-II: All Cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defibrillator</td>
<td>742 503 273 110 99</td>
</tr>
<tr>
<td>Conventional</td>
<td>490 329 170 65 33</td>
</tr>
</tbody>
</table>

Absolute reduction in overall mortality = 9%

Hazard Ratio = 0.69
P=0.016

Defibrillator Group vs Conventional Group
MADIT-II: Three Year Mortality

CONV (n=490)  ICD (n=742)

K-M survival 0.69  0.78

9% Absolute mortality reduction
Event curves begin to diverge after 1yr

Hazard Ratio (ICD:CONV) 0.69 (95% CI)
(0.51, 0.93)  p = 0.016
MADIT-II: Subgroup QRSd > 150ms

Absolute overall mortality reduction 26%!!!
PRIMARY PREVENTION

Absolute mortality difference demonstrates the incremental benefit of the ICD over conventional therapy

The number of implants needed to save one patient:

\[
\frac{1}{\text{absolute mortality difference}}
\]
MADIT-II: Results

ICD as primary prevention in long QRS:
26% Absolute mortality reduction

Overall MADIT-II (0.09): 11 implants to save 1 life

In pts with QRS >150 (0.26): 4 implants to save 1 life
SCD-HeFT Patient Flow

LVEF \leq 35\%,
NYHA Class II or III CHF
N = 2,500 (expected enrollment)

Randomization

- Conventional CHF Rx & placebo (n = 833)*
- Conventional CHF Rx & amiodarone (double blind) (n = 833)*
- Conventional CHF Rx & ICD (n = 833)*

Bardy NEJM 2005
SCD-HeFT Treatment Group Mortality

*Intention-to-Treat*

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<th>HR</th>
<th>97.5% CI</th>
<th>P-Value</th>
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<tr>
<td>Amiodarone vs. Placebo</td>
<td>1.06</td>
<td>0.86, 1.30</td>
<td>0.529</td>
</tr>
<tr>
<td>ICD Therapy vs. Placebo</td>
<td>0.77</td>
<td>0.62, 0.96</td>
<td>0.007</td>
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Adapted from Bardy, et al. NEJM 2005
SCD-HeFT: RESULTS

Primary therapy with the ICD provided a 7.5% absolute decrease in mortality at 5 years.

Event curves do not diverge until 18mo after ICD.

Amiodarone did not improve survival in heart failure pts.
ICD THERAPY FOR SCD

ICD: The most effective therapy to reduce SCD in the overall LV dysfunction and CHF population

The impact of ICD therapy appears greatest in the prolonged QRS population

Annual mortality in overall CHF population at 7.2%
MADIT and SCD-HeFT RESULTS

ICD as primary prevention for SCD:

MADIT-II (0.09): 11 implants to save 1 life

MADIT-II QRS >150 (0.26): 4 implants to save 1 life

SCD-HeFT: 14 implants to save 1 life
MORTALITY AND DYSSYNCHRONY

LV dysfunction, CHF, and prolonged QRSd each individually increase the risk of death.

The CRT population differs from the general LV dysfunction population due to prolonged QRS.
SCD in the CRT Population

Mechanism of death at 2yrs in the non-ICD CRT Trials:

<table>
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<th>Trial</th>
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<th>Deaths/VF</th>
<th>Mortality (%)</th>
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Meta-analysis of CRT trials shows that CRT significantly reduces CHF mortality, but only a trend in reducing all-cause mortality. 

Bradley JAMA 2003
ICD in CRT: COMPANION

Comparison of CRT-P, CRT-D, and no device
EF < 0.35, NYHA Class III-IV, QRSd > 120ms:

Endpoints: Overall mortality and hospitalization
Overall mortality
Statistical power: CRT-D vs. optimal med. Rx
CRT-P vs. optimal med. Rx
COMPANION: Secondary Endpoint of All-Cause Mortality

Bristow NEJM 2003

Any Death

12 month event rate reductions:
CRT = 23.9%
CRT-D = 43.4%
p = .002, CRT-D vs. OPT
p = .12, CRT vs. OPT

12 month OPT Event Rate (1-y) = 19.0%
COMPANION: Mortality

Population enrolled similar to other CRT trials and to CHF trials except for prolonged QRSd:

19% 1yr mortality in COMPANION control group
7.2% annual mortality in SCD-HeFT control group

CRT-D & control event curves separate immediately

CRT-ICD reduced mortality by 8% at 1yr
The effect of ICD therapy in the MADIT-II prolonged QRS group closely resembles the impact of CRT-D in COMPANION
COMPANION MORTALITY BENEFIT

What was the relative contribution of CRT vs ICD to the mortality reduction in COMPANION?

CRT-P produced no statistically significant impact on mortality (over the 1yr follow-up period)

CRT-D impact much earlier than ICD alone in the other trials
MORTALITY: CRT-D vs ICD

MADIT-II: 9% reduction at 3 yrs

MADIT-II QRS >150 (0.26): 26% reduction at 3 yrs

SCD-HeFT: 7.5% reduction at 5 yrs

COMPANION: 8% reduction at 1 yr
US CRT TRIALS: LIMITATIONS

Relatively short follow-up period to assess the potential effects on remodeling and mortality

No direct comparison of CRT-P and CRT-D

No US clinical trial assessed the isolated impact of CRT on mortality. CRT vs. ICD benefit unknown
CARE-HF: CRT-P

What is the isolated effect of CRT on mortality, LV function and hospitalization?

NYHA Class III-IV, QRSd > 120ms, EF < 0.35
CRT-P vs optimal medical therapy, NO ICD

Cleland, NEJM, 2005
CARE HF: Patient Flow

Enrolled n=813, mean follow up 29mo

OPT
Death or Hosp  n = 224 (0.55)
Death         n =  120 (0.30)

CRT
Death          n= 159 (0.39)  HR 0.63 [.51-.77]
              p < 0.001
Death          n =  82 (0.20)  HR 0.64 [.48-.85]
              p < 0.002

Echocardiographic endpoints: MR, IVMD, LVESI  p < 0.01
Symptom and Quality of Life score  p < 0.01

Cleland, NEJM 2005(352)
CONCLUSIONS

1. CRT Improves functional status, LV performance and decreases hospitalization
2. CRT-D improves overall mortality over control
3. CRT-P improves overall mortality over control
4. The incremental benefit of CRT-D over CRT-P has not been tested