Primary prevention of SCD with the ICD in Nonischemic Cardiomyopathy

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Disclosures: Consulting and Clinical Trials – Medtronic and Boston Scientific
AVID Mortality

N=1016

- SCD survival – any EF
- Hemodynamic VT; EF ≤ 40%
- If revasc after SCD, EF ≤ 40%
- Excluded if VF/VT within 5 days of MI or CABG/PTCA

- 45% SCD survivors; 55% VT
- Avg. EF 32%
- 81% CAD
- 67% history of MI
- 93% Class I/II

NEJM 1997; 337, 1576
MADIT I - Survival

- Probability of survival

0.0 0.2 0.4 0.6 0.8 1.0

0 1 2 3 4 5

Year

Defibrillator

Conventional therapy

p = .009 at termination
2 yr mortality 39% v 16%
HR - 0.46

MUSTT Randomized Patient Results
Total Mortality

MADIT-II Survival

Probability of Survival

Defibrillator
Conventional

P = 0.007

No. At Risk
Year

Defibrillator 742 502 (0.91) 274 (0.94) 110 (0.78) 9
Conventional 490 329 (0.90) 170 (0.78) 65 (0.69) 3

MADIT II – 8 Year Long Term Follow-up

Number Needed to Treat to save one life (NNT) and Life Years Saved (LYS) for all MADIT II patients (N=1232):

<table>
<thead>
<tr>
<th>@ month</th>
<th>20</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>LYS</td>
<td>0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>↓ Death</td>
<td>31%</td>
<td>37%</td>
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</table>
• 674 Patients s/p Acute MI
• Single lead ICD
• EF ~ 28%
• 70% Q wave MI
• Time to ICD from MI -18 dy
Immediate Risk-Stratification Improves Survival (IRIS) Study

- Randomized comparison of ICDs vs. OMT 5-31 days after MI
- LVEF ≤ 40%, HR > 90 +/- NSVT
- No survival benefit with prophylactic ICD therapy

Primary Prevention ICDs in Nonischemic Cardiomyopathy

• The role of ICDs among patients with ischemic cardiomyopathy was well established, provided that it is not implanted early post-MI.

• Further expansion of ICD indications for patients with nonischemic cardiomyopathy was evaluated in a series of trials.

• This included both narrow and wide QRS patients using conventional ICDs or CRT devices.
**DEFINITE – NIDCM**

- Age 58
- 71% men
- 23% DM
- 25% AF
- QRS 115 ms
- LBBB 20%
- ACE/ARB 97%
- β-blockers 85%

Follow up 29 +/- 14 months

Kadish A et al NEJM 2004;350:2151
**DEFINITE**

Sudden Death Mortality

All-Cause Mortality in NYHA Class III

Kadish A et al NEJM 2004;350:2151
2521 patients with either ischemic or NIDCM
NYHA Class II or III
EF ≤ 35%, QRS 109 msec
Single chamber ICDs – VVI 35/50bpm. Shock only 188 bpm
Amio/placebo drug or ICD/placebo drug
Mortality by Intention-to-treat

N = 2,521

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>97.5% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

Follow-up: 45.5 months
Vital status: 100% known

Bardy, NEJM 2005
Mortality by CHF Etiology

Ischemic Etiology
- ICD Therapy
- Placebo

Non-Ischemic Etiology

HR 97.5% CI
- Ischemic Etiology: HR 0.79, 97.5% CI 0.60, 1.04
- Non-Ischemic Etiology: HR 0.73, 97.5% CI 0.50, 1.07
Mode of Death in SCD-HeFT: ICD - Placebo

Total Deaths:
ICD = 182
Placebo = 244

Adapted from Packer D, et al HRS 2005

*45.5 mo median f/u
Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

Danish NIDCM Trial

- 1116 patients
- Randomized to ICD or “usual clinical care”
- Mean QRS: 146 ms (ICD); 145 ms (control)
- CRT: 58% (ICD); 58% (control)
Outcomes – All-Cause Mortality

Hazard ratio, 0.87 (95% CI, 0.68–1.12)
P = 0.28

<table>
<thead>
<tr>
<th>Years</th>
<th>Control Group</th>
<th>ICD Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>560</td>
<td>556</td>
</tr>
<tr>
<td>1</td>
<td>540</td>
<td>540</td>
</tr>
<tr>
<td>2</td>
<td>517</td>
<td>526</td>
</tr>
<tr>
<td>3</td>
<td>438</td>
<td>451</td>
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<tr>
<td>4</td>
<td>344</td>
<td>358</td>
</tr>
<tr>
<td>5</td>
<td>248</td>
<td>272</td>
</tr>
<tr>
<td>6</td>
<td>169</td>
<td>186</td>
</tr>
<tr>
<td>7</td>
<td>88</td>
<td>107</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>17</td>
</tr>
</tbody>
</table>
Outcomes

Cardiovascular Death

Sudden Cardiac Death

Hazard ratio, 0.77 (95% CI, 0.57–1.05)
P=0.10

Hazard ratio, 0.50 (95% CI, 0.31–0.82)
P=0.005

No. at Risk
Control Group: 560, 540, 517, 438, 344, 248, 169, 88, 12
ICD Group: 556, 540, 526, 451, 358, 272, 186, 107, 17
Comparisons:
DEFINITE, SCD-HeFT, DANISH

<table>
<thead>
<tr>
<th></th>
<th>DEFINITE</th>
<th>SCD-HeFT</th>
<th>DANISH</th>
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</thead>
<tbody>
<tr>
<td>ACE/ARB</td>
<td>97%</td>
<td>89%</td>
<td>97%</td>
</tr>
<tr>
<td>(\beta)-blockers</td>
<td>85%</td>
<td>78%</td>
<td>92%</td>
</tr>
<tr>
<td>Mineralocorticoid</td>
<td>?</td>
<td>30%</td>
<td>58%</td>
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</table>
Mortality: DEFINITE - DANISH

A. Death from Any Cause

Cumulative Event Rate

Hazard ratio, 0.87 (95% CI, 0.68–1.12)
P=0.28

Control Group

ICD Group

DEFINITE CONTROL

DEFINITE ICD

Years
Mortality Comparisons

A. Death from Any Cause

Cumulative Event Rate

Hazard ratio, 0.87 (95% CI, 0.68–1.12)
P=0.28

Control Group

ICD Group

SCD-HeFT CONTROL

SCD-HeFT ICD
COMPARISON OF REPORTED SCD RATES

**DANISH**: Unusually low SCD rate: 1.5% per year, only 35% of all deaths were sudden.
DANISH Trial-
Why was this a negative study?

• Selection Bias: Enrolled unusually low risk NIDCM patients
  — were the more ill already offered ICDs?
• Well – treated on GDMT
• Underpowered
• Outcome adulterated by CRT in control group
  — Much higher % of CRT eligible patients enrolled than found in usual US outpatient clinics (30% v 60% in DANISH)
CARE-HF

Hazard Ratio 0.60
(95% CI 0.47 to 0.77; P<0.0001)

Survival

0.00 0.25 0.50 0.75 1.00

Time (days)

0 400 800 1200 1600

Number at risk

CRT 409 383 358 338 209 85 9
Medical therapy 404 372 331 298 178 63 6
Hazard ratio = 0.32 (95% c.i. 0.17-0.63)
p = 0.0004

Gold et al
Heart Rhythm
2015
Predictors of Reverse Remodeling with CRT

- Nonischemic Cardiomyopathy
- LBBB
- Female Gender
- QRS duration
COMPANION: All-Cause Mortality

CRT vs. OPT: RR = 24%, p=0.060 (Critical boundary=0.014)
CRT-D vs. OPT: RR = 36%, p=0.003 (Critical boundary=0.022)

12-month Event Rates
OPT: 19%
CRT: 15% (AR=4%)
CRT-D: 12% (AR=7%)
REVERSE CRT ON Mortality Rate: CRT-P vs. CRT-D

P = 0.18
HR = 1.53 (0.82-2.85)

Multivariate Analysis
HR = 2.74, p = 0.009

Gold et al. 2013
CeRtiTuDe — Overall Mortality

Among the 1,611 patients with complete follow-up, 286 deaths

CRT-D: 6.2 %/year
CRT-P: 12.2 %/year

p-value log-rank < 0.0001
Effect of CHF Etiology on CRT-P Vs CRT-D

**Ischemic Cardiomyopathy**

- CRT-D
- CRT-P

**Non-Ischemic Dilated Cardiomyopathy**

- CRT-D
- CRT-P

Cumulative Survival

Follow-Up (Months)

<table>
<thead>
<tr>
<th>Follow-Up (Months)</th>
<th>CRT-D</th>
<th>CRT-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1820</td>
<td>655</td>
</tr>
<tr>
<td>12</td>
<td>1685</td>
<td>492</td>
</tr>
<tr>
<td>24</td>
<td>1295</td>
<td>420</td>
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<tr>
<td>36</td>
<td>970</td>
<td>195</td>
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<tr>
<td>48</td>
<td>677</td>
<td>143</td>
</tr>
<tr>
<td>60</td>
<td>476</td>
<td>96</td>
</tr>
</tbody>
</table>

**Non-Ischemic Dilated Cardiomyopathy**

- CRT-D
- CRT-P

Cumulative Survival

Follow-Up (Months)

<table>
<thead>
<tr>
<th>Follow-Up (Months)</th>
<th>CRT-D</th>
<th>CRT-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1943</td>
<td>682</td>
</tr>
<tr>
<td>12</td>
<td>1570</td>
<td>601</td>
</tr>
<tr>
<td>24</td>
<td>1239</td>
<td>535</td>
</tr>
<tr>
<td>36</td>
<td>902</td>
<td>270</td>
</tr>
<tr>
<td>48</td>
<td>632</td>
<td>187</td>
</tr>
<tr>
<td>60</td>
<td>458</td>
<td>132</td>
</tr>
</tbody>
</table>

HR 0.76, 95% CI 0.62-0.92, p=0.005

HR 0.92, 95% CI 0.73-1.16, p=0.49

All-cause Mortality in NICM Patients with Primary Prevention ICD or CRT

From: Golwala H et al. Circulation 2017; 135: 201-203
SUMMARY

- SCD remains a major cause of mortality among patients with cardiomyopathy regardless of the etiology.
- The Danish Study was an important and well-executed study, but the population enrolled was atypical.
- The cause of the neutral result remains unclear (CRT use/medical therapy/low SCD population).
- Patients with DCM need device therapy, although there is equipoise whether CRT candidates likely to remodel (women/LBBB/wide QRS) should get CRT-D or CRT-P.