Sudden Cardiac Death in Patients with Left Ventricular Dysfunction: Focus on Primary Prevention with ICDs

Andrew E. Epstein, MD
Professor of Medicine
Division of Cardiovascular Disease
The University of Alabama at Birmingham
Birmingham, Alabama
MADIT II: Probability of Survival in ICD vs Conventional Therapy Group

- Trial stopped at 20 months
- Reduction in death rate with ICD Rx: 12% at 1 yr, 28% at 2 yrs, 28% at 3 yrs

Probability of Survival

No. At Risk

<table>
<thead>
<tr>
<th>Year</th>
<th>ICD</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>742</td>
<td>490</td>
</tr>
<tr>
<td>1</td>
<td>502 (0.91)</td>
<td>329 (0.90)</td>
</tr>
<tr>
<td>2</td>
<td>274 (0.84)</td>
<td>170 (0.78)</td>
</tr>
<tr>
<td>3</td>
<td>110 (0.78)</td>
<td>65 (0.69)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.007

Comparison of Medical Therapy, Pacing and Defibrillation Therapies in Heart Failure (COMPANION) Trial

- NYHA Class III or IV
- NSR, QRS \( \geq 120 \text{ ms} \), PR interval >150 ms
- LVEF \( \leq 35\% \), LVEDD \( \geq 60 \text{ mm} \)
- Optimal pharmacological therapy (OPT)
  - \( \beta \)-blocker (for at least 3 months)
  - Diuretic, ACEI/ARB, spironolactone (1 month)
  - Digoxin
- HF hospitalization (or equivalent) in prior 12 months, >1 month prior to enrollment
COMPANION Design

Endpoints
- **Primary**: Combined all-cause mortality and all-cause hospitalization
- **Secondary**: Morbidity and survival
- **Substudy**: QoL

Time Post-Randomization
- <5 Days
- 0
- <2 Working Days
- One Week
- One Month
- Quarterly
COMPANION:
Primary Endpoint: Mortality + Hospitalization

CRT vs OPT: RR=20%, \( P = .008 \) (Critical boundary=.014)
CRT-D vs OPT: RR=20%, \( P = .007 \) (Critical boundary=.022)

12-Month Event Rates
- OPT: 68%
- CRT: 55% (AR=13%)
- CRT-D: 56% (AR=12%)

HFSA Late-Breaking Clinical Trials, September 24, 2003.
COMPANION:
Secondary Endpoint: All-Cause Mortality

CRT vs OPT: RR=24%, \( P=.060 \) (Critical boundary=.014)
CRT-D vs OPT: RR=36%, \( P=.003 \) (Critical boundary=.022)

12-Month Event Rates
OPT: 19%
CRT: 15% (AR=4%)
CRT-D: 12% (AR=7%)

HFSA Late-Breaking Clinical Trials, September 24, 2003.
CRT Improves QoL and NYHA Functional Class

Average Change in QoL Score (MLWHF)

NYHA: Proportion Improving 1 or More Class

* $P<0.05$

Heart Failure Mortality in Meta Analysis of CRT Trials

CONTAK CD (n=490)

InSync ICD (n=554)

MIRACLE (n=532)

MUSTIC (n=58)

Overall

Bradley et al. JAMA 2003; 289: 730
Sudden Cardiac Death in Heart Failure Trial: SCD-HeFT

CAD and DCM
NYHA II and III
LVEF $\leq 0.35$
No prior VT or VF

Randomize

Conventional Rx + Placebo
Conventional Rx + Amiodarone
Conventional Rx + ICD

Double blind

Endpoint: Total Mortality
SCD-HeFT
Mortality by Intention-to-Treat

HR 97.5% CI  P Value
Amiodarone vs Placebo 1.06 0.86, 1.30 0.529
ICD Therapy vs Placebo 0.77 0.62, 0.96 0.007

CARE-HF
Aims

• To assess the effect on morbidity and mortality of adding CRT to optimised pharmacological therapy in patients with moderate and severe HF due to LVSD complicated by cardiac dyssynchrony

• To investigate the mechanisms underlying the observed effect to identify markers predicting success or failure of CRT

CARE-HF
Primary Endpoint
(All-cause Mortality or Unplanned Hosp. for Major CVS Event)

Event-free Survival

HR 0.63 (95% CI 0.51 to 0.77)
P < .0001

Number at risk
CRT 409 323 273 166 68 7
Medical Therapy 404 292 232 118 48 3

CARE-HF
All-Cause Mortality

Event-free Survival

HR 0.64 (95% CI 0.48 to 0.85)
P = .0019

Number at risk
CRT: 409, 376, 351, 213, 89, 8
Medical Therapy: 404, 365, 321, 192, 71, 5

Recovery of LV Function Post MI

- 261 patients in HEART (ramipril) trial, all with reperfusion therapy
- Day 1, 9/261 had normal LV function (EF ≥0.55, 3.4%)
- 171/261 (66%) had improvement in EF (0.05 ± 0.10). Final EF 0.57 ± 0.96
- Of 252 patients with EF <0.55:
  - 13% complete recovery by day 14
  - 22% complete recovery by day 90
  - Additional 36% had partial recovery by day 90

→ Early dysfunction often improves

Solomon et al.
Ann Intern Med 2001;134:451-8
Reasons for Nonresponse

• Inappropriate patient selection
  • End stage
  • No dyssynchrony
  • No correctable dyssynchrony

• Too strict definition of response
  • Is prevention of disease progression “response”? 

• More attention needs to paid to VV timing and AV delays
Procedural Outcomes and Complications in COMPANION Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>CRT (n=617)</th>
<th>CRT-D (n=595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implant death</td>
<td>1.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Perforation</td>
<td>1.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Any LV lead AE</td>
<td>6.3%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Lead implant failure</td>
<td>13%</td>
<td>9%</td>
</tr>
</tbody>
</table>

## Cardiac Resynchronization Therapy Entry Criteria Randomized Trials

<table>
<thead>
<tr>
<th>Study (n)</th>
<th>NYHA</th>
<th>QRS</th>
<th>EF</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE (524#)</td>
<td>III, IV</td>
<td>≥130</td>
<td>≤ 35%</td>
<td>Published</td>
</tr>
<tr>
<td>MUSTIC SR (58)</td>
<td>III</td>
<td>&gt;150</td>
<td>≤ 35%</td>
<td>Published</td>
</tr>
<tr>
<td>MUSTIC AF (43)</td>
<td>III</td>
<td>&gt;200*</td>
<td>≤ 35%</td>
<td>Published</td>
</tr>
<tr>
<td>PATH CHF (42)</td>
<td>III, IV</td>
<td>≥120</td>
<td>&lt; 35%</td>
<td>Published</td>
</tr>
<tr>
<td>CONTAK CD (581¥)</td>
<td>III-IV</td>
<td>≥120</td>
<td>&lt; 35%</td>
<td>Published</td>
</tr>
<tr>
<td>MIRACLE ICD (362^)</td>
<td>III-IV</td>
<td>≥130</td>
<td>&lt; 35%</td>
<td>Published</td>
</tr>
<tr>
<td>PATH CHF II (89)</td>
<td>III, IV</td>
<td>≥120</td>
<td>&lt; 35%</td>
<td>Published</td>
</tr>
<tr>
<td>COMPANION (1520)</td>
<td>III, IV</td>
<td>≥120</td>
<td>&lt; 35%</td>
<td>Published</td>
</tr>
<tr>
<td>CARE HF (800)</td>
<td>III, IV</td>
<td>≥120</td>
<td>&lt; 35%†</td>
<td>Published</td>
</tr>
<tr>
<td>MIRACLE ICD II (186)</td>
<td>II</td>
<td>≥130</td>
<td>≤ 35%</td>
<td>Presented</td>
</tr>
<tr>
<td>PACMAN (328)</td>
<td>III</td>
<td>≥150</td>
<td>≤ 35%</td>
<td>Enrolled</td>
</tr>
<tr>
<td>VecToR (420)</td>
<td>II-IV</td>
<td>≥140</td>
<td>≤ 35%</td>
<td>Enrolling</td>
</tr>
</tbody>
</table>

**From WT Abraham**

No Randomized Trials Used an Imaging Dyssynchrony Study
Should all Patients with CHF get a CRT Device?

Straight Shot
- LBBB
- QRS > 120ms
- NYHA III, IV
- EF ≤ 35%
- NSR
- Optimal Med Rx

CRT / ICD

Longer Shot
- IVCD / RBBB
- QRS 100-120ms
- NYHA II (I)
- EF 35-40%
- AF
- Optimal Med Rx

ECHO Dyssynchrony
- YES
- No
- ??

Courtesy of Kenneth A. Ellenbogen, MD
Pacemaker and ICD Malfunctions


Pacemakers n=8834
ICDs n=8489
Devices explanted and malfunction confirmed
Over 200,000 ICDs are implanted or replaced annually in patients who are at risk for SD.

In 2005 over 150,000 ICDs were the subject of recalls or safety alerts by their manufacturers.

A recent Food and Drug Administration study suggested that ICD malfunctions are increasing.

The Multicenter Registry is funded entirely by a grant from the Minneapolis Heart Institute Foundation, and is supported by the voluntary efforts of its participants.
Objective

• The aim of the present study was to examine the failure modes and implant times of contemporary ICD pulse generators in those that had failed, or were replaced due to manufacturers' recalls.

• We also evaluated the causes and major adverse clinical events associated with ICD failure and replacement.
Methods

- 9 centers in the U. S. and Canada.

- Failure reports entered via Internet since 4/99:
  - Manufacturer and model
  - Dates of implant and failure
  - Signs of failure and clinical consequence
  - Cause of failure

- A pulse generator failed if it was not performing according to its intended use, or as described in the manufacturer’s published specifications. A normally functioning device that was replaced, removed, or abandoned as the result of a manufacturer’s recall was a failure.
Methods (2)

- Categories of ICD pulse generator failure included:
  - Normal battery depletion (ERI)
  - Premature battery depletion (ERI ≤ 3 yrs)
  - Electronic or housing malfunction
  - Replacement for Recall-Advisory
  - Unknown

- Cause of failure was determined by the reporting center based on clinical and technical evaluations and manufacturers reports.
Causes of ICD Failure

1,355 Pulse Generators

Percent of Pulse Generators

- Normal Battery Depletion: 73%
- Recall Advisory: 10%
- Premature Battery Depletion: 9%
- Electronic Housing Malfunction: 6%
- Unknown: 2%

The Multicenter Registry Investigators
American College of Cardiology, 2006
ICD Types and Manufacturers

N= 1,355
% = 100%

- All
  - Single
    - Guidant: 35%
    - Medtronic: 3%
    - St. Jude: 7%
  - Dual
    - Guidant: 35%
    - Medtronic: 3%
    - St. Jude: 7%
  - Single-R
    - Guidant: 35%
    - Medtronic: 3%
    - St. Jude: 7%
  - Dual-R
    - Guidant: 35%
    - Medtronic: 3%
    - St. Jude: 7%
  - CRT-D
    - Guidant: 35%
    - Medtronic: 3%
    - St. Jude: 7%

The Multicenter Registry Investigators
American College of Cardiology, 2006
Causes of Failure for Each ICD Type

The Multicenter Registry Investigators
American College of Cardiology, 2006
Average Implant Time of Failed ICDs

<table>
<thead>
<tr>
<th>Type</th>
<th>Years</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual</td>
<td>5.1</td>
<td>35</td>
<td>3%</td>
</tr>
<tr>
<td>Single</td>
<td>4.8</td>
<td>791</td>
<td>58%</td>
</tr>
<tr>
<td>Dual-R</td>
<td>3.4</td>
<td>388</td>
<td>29%</td>
</tr>
<tr>
<td>Single-R</td>
<td>2.5</td>
<td>93</td>
<td>7%</td>
</tr>
<tr>
<td>CRT-D</td>
<td>1.9</td>
<td>48</td>
<td>4%</td>
</tr>
<tr>
<td>All</td>
<td>4.1</td>
<td>1,355</td>
<td>100%</td>
</tr>
</tbody>
</table>

*p < 0.001

The Multicenter Registry Investigators
American College of Cardiology, 2006
Average Implant Time of Failed ICDs According to Cause of Failure

According to Cause of Failure

- Normal Battery Depletion
- Recall
- Premature Battery Depletion
- Electronic Housing

The Multicenter Registry Investigators
American College of Cardiology, 2006
ICDs with and w/o Rate Response

The Multicenter Registry Investigators
American College of Cardiology, 2006
Proportion of Failed ICDs That Were Functioning 3, 4, & 5 Years After Implant

The Multicenter Registry Investigators
American College of Cardiology, 2006
Major Adverse Clinical Events

- 20 patients had a major adverse clinical event.
- 1 patient died due to short-circuiting during shock delivery.
- 1 patient died of a stroke following replacement of a normally functioning recalled device.
- 4 patients were rescued when their devices failed to treat VT/VF during device testing.
- 3 patients experienced syncope due to battery depletion (2) and electronic component failure.
- 11 patients received inappropriate shocks caused by electronic and housing defects.

The Multicenter Registry Investigators
American College of Cardiology, 2006
Limitations

- Average implant time may significantly underestimate device longevity when compared to actuarial survival data.

- The longevity of an ICD pulse generator is the result of a complex interplay between multiple hardware components, the ICD lead, and the individual patient’s needs for therapy, energy requirements for pacing and defibrillation, and diagnostic information including electrograms. We did not evaluate all these variables.
Conclusions

• Based on this analysis of failed ICDs, the performance of ICDs, particularly those offering advanced pacing capabilities, has been adversely affected by early battery depletion, electronic or housing failure and recalls.

• A comprehensive, independent national registry is needed to accurately estimate ICD longevity and determine the incidence of unexpected failure modes and adverse clinical events.
Complications Associated with ICD Replacement in Response to Advisories:
Canadian Heart Rhythm Society Working Group on Device Advisories

- 17 Centers, 2915 recalled devices
  - 533 (18.3%) replaced
    - 66% primary prevention

- Complications in 43 pts (8.1%)
  - Major requiring reoperation: 31 pts (5.8%)
  - Death: 2 pts
  - Minor complications: 12 pts (2.3%)
  - Of explanted devices, 3 (0.1%) had malfunction (early battery depletion), none with clinical consequence.

Indications for ICD Therapy

Class I

• Cardiac arrest due to VF or VT not due to a transient or reversible cause

• Spontaneous sustained VT in association with structural heart disease

• Syncope of undetermined origin with clinically relevant, hemodynamically significant, sustained VT or VF induced at EP study when drug therapy is ineffective, not tolerated, or not preferred

• Nonsustained VT in patients with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at EP study that is not suppressible by a Class I antiarrhythmic drug.

Class II

• Patients with LVEF ≤ .30, at least 1 month post MI and at least 3 months post coronary revascularization surgery

Indications for Resynchronization Therapy

Class II

- Medically refractory, NYHA Class III or IV heart failure despite optimal medical therapy
- Ischemic or nonischemic cardiomyopathy with
  - QRS ≥130 ms
  - LVEF ≤0.35

Summary

• Multiple RCTs have shown that CRT:
  • Is safe and well tolerated improves quality of life, functional status, and exercise capacity.
  • Improves cardiac structure and function.
  • Reduces hospitalization and mortality with or without ICD backup.

• Studies needed to risk stratify, identify likely responders, and new groups who may benefit from CRT.

• Reliability/advisory issues recognized and need guidelines for management.