Implantable Device Endpoints: Implications for Clinical Trial Design

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Disclosures

- Research support
  - VA, NIH
  - Janssen, Medtronic, iRhythm, Gilead Sciences, JT Stroke Shield Foundation
  - Trial enrollment: Janssen, Boehringer Ingelheim

- Advisor/Consultant
  - St Jude Medical, Medtronic, Daiichi Sankyo, Zipline Medical, Precision Health Economics, Cyberheart, thryva, AliveCor, Armetheon, Abbott, Myokardia

- Lecture honoraria
  - Medtronic, St Jude Medical
ICDs ≠ ACLS or resuscitation

What they do

- Pace for bradycardia
- Overdrive pace for fast rhythms
  - Antitachycardic pacing = ATP
- Shock for very fast rhythms
- Arrhythmias are classified by rate, not by mechanism

“The defibrillator’s not working! Quick, everyone scuff your feet on the carpet!”
ICDs ≠ ACLS or resuscitation

What they do
- Pace for bradycardia
- Overdrive pace for fast rhythms
  - Antitachycardic pacing = ATP
- Shock for very fast rhythms
- Arrhythmias are classified by rate, not by mechanism

What they do cannot do
- Assess for hemodynamic stability or perfusion
- Make a bad ventricle pump better

Why they inappropriately shock
- SVT discrimination (rapid AF)
- Oversensing (T-waves)
- Lead noise or fracture

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Department of Medicine
Contemporary ICD programming
Contemporary ICD programming

- 1-3 Zones
- Single Zone: “VF Zone”, defined usually as a rate of > 180-220
Contemporary ICD programming

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- Single Zone: “VF Zone”, defined usually as a rate of > 180-220
- Two Zone
  - “VT Zone” which is usually slower, ATP can be programmed.
  - “VF Zone” which is usually faster, primary therapy is shock.
Contemporary ICD programming

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- Single Zone: “VF Zone”, defined usually as a rate of > 180-220
- Two Zone
  - “VT Zone” which is usually slower, ATP can be programmed.
  - “VF Zone” which is usually faster, primary therapy is shock.
- Three Zone
  - VT1 (slowest) (e.g. 130-160bpm), monitor, ATP, shock
  - VT2 (faster) (e.g. 160-190bpm), ATP, shock
  - VF (fastest) (e.g. bpm), shock
## V. Detection

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Redetect</th>
<th>V. Interval (Rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF</td>
<td>Off</td>
<td>18/24</td>
<td>280 ms (214 bpm)</td>
</tr>
<tr>
<td>FVT</td>
<td>Off</td>
<td>12/16</td>
<td>240 ms (250 bpm)</td>
</tr>
<tr>
<td>VT</td>
<td>Off</td>
<td>16</td>
<td>370 ms (162 bpm)</td>
</tr>
<tr>
<td>Monitor</td>
<td>Off</td>
<td>20</td>
<td>450 ms (133 bpm)</td>
</tr>
</tbody>
</table>

## PR Logic

<table>
<thead>
<tr>
<th>Feature</th>
<th>Setting</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/Afl</td>
<td>On</td>
<td>Stability</td>
</tr>
<tr>
<td>Sinus Tach</td>
<td>On</td>
<td>Onset...</td>
</tr>
<tr>
<td>Other 1:1 SVTs</td>
<td>Off</td>
<td>High Rate Timeout...</td>
</tr>
<tr>
<td>SVT V. Limit</td>
<td>280 ms</td>
<td></td>
</tr>
</tbody>
</table>

## Other Enhancements

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<th>Setting</th>
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<tbody>
<tr>
<td>Atrial</td>
<td>Off</td>
</tr>
<tr>
<td>RV</td>
<td>Off</td>
</tr>
</tbody>
</table>

## Sensitivity

<table>
<thead>
<tr>
<th>Location</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial</td>
<td>0.45 mV</td>
</tr>
<tr>
<td>RV</td>
<td>0.3 mV</td>
</tr>
</tbody>
</table>
AT/AF Detection and Therapies

Detection Zones

AT/AF

350 ms (171 bpm)

Anti-Tachy Pacing (ATP)...

AT/AF Rx

Ramp(10), Burst+(10), Ramp(10)

Reactive ATP

Rhythm Change

On

Time Interval

Off*

Stop Atrial Rx After

Rx/Lead Suspect... 2 On

Duration to Stop 48 hr

Episode Duration Before Rx Delivery

ATP 1 min

Undo Pending OK

* At 3-month follow-up, ~10% of patients were programmed On (most at the every 7 hrs setting).
Figure 1. Intracardiac electrograms showing recordings of monomorphic ventricular tachycardia (top; MVT), polymorphic ventricular tachycardia (middle; PMVT), and ventricular fibrillation (bottom; VF).
ICD outcomes and intended use

- Initial intended use
  - Termination of malignant arrhythmias
- Indication: Mortality
  - Clinical trials demonstrated survival benefit
  - ICD therapy conflated to survival
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- Initial intended use
  - Termination of malignant arrhythmias
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Are Implantable Cardioverter Defibrillator Shocks a Surrogate for Sudden Cardiac Death in Patients With Nonischemic Cardiomyopathy?

Kenneth A. Ellenbogen, MD; Joseph H. Levine, MD; Ronald D. Berger, MD; James P. Daubert, MD; Stephen L. Winters, MD; Eugene Greenstein, MD; Alaa Shalaby, MD; Andi Schaechter, RN; Haris Subacius, MA; Alan Kadish, MD; for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators

Background—Ventricular tachyarrhythmias long enough to cause implantable cardioverter defibrillator (ICD) shocks are generally thought to progress to cardiac arrest. In previous ICD trials, shocks have been considered an appropriate surrogate for sudden cardiac death (SCD) because the number of shocks has been thought to be equivalent to the mortality excess in patients without ICDs. The practice of equating ICD shocks with mortality is controversial and has not been validated critically.

Methods and Results—The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was a prospective, randomized, multicenter trial of ICD therapy in 458 patients with nonischemic cardiomyopathy. Patients were randomized to receive standard medical therapy (STD) or STD plus an ICD. Shock electrograms were reviewed, and the cause of death was evaluated by a separate blinded events committee. There were 15 SCD or cardiac arrests in the STD group and only 3 in the ICD arm. In contrast, of the 229 patients randomized to an ICD, 33 received 70 appropriate ICD shocks. Patients in the ICD arm were more likely to have an arrhythmic event (ICD shock plus SCD) than patients in the STD arm (hazard ratio 2.12, 95% CI 1.153 to 3.893, \( P < 0.013 \)). The number of arrhythmic events when one includes syncope as a potential arrhythmic event was similar in both groups (hazard ratio 1.20, 95% CI 0.774 to 1.865, \( P = 0.414 \)). Approximately the same number of total events was noted in each arm when we compared syncope plus SCD/cardiac arrest in the STD arm with SCD plus ICD shocks plus syncope in the ICD arm.

Conclusions—Appropriate ICD shocks occur more frequently than SCD in patients with nonischemic cardiomyopathy. This suggests that episodes of nonsustained ventricular tachycardia frequently terminate spontaneously in such patients. (Circulation. 2006;113:776-782.)

Key Words: sudden death/arrhythmia/heart arrest/syncope/defibrillation

Patients with nonischemic dilated cardiomyopathy are at an increased risk for sudden cardiac death (SCD). A number of studies have shown syncope is an indicator of poor prognosis in this patient population. Specifically, patients who experience syncope have an increased risk of SCD. Several small studies examining the role of ICD therapy in these patients have shown an increased rate of appropriate ICD shocks. In some of these studies, appropriate ICD shocks have served as a surrogate for SCD. The underlying assumption in these studies is that episodes of ventricular tachycardia that are long enough to result in an ICD shock are likely to have caused SCD.

Editorial p 764
Clinical Perspective p 782

The DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial was a prospective, randomized trial of ICD therapy in patients with nonischemic cardiomyopathy. This trial demonstrated that ICD therapy produced a decrease in SCD and a trend toward a decrease in all-cause mortality. We sought to determine whether ICD shocks in this patient population could serve as a surrogate for SCD. We reviewed the shock electrograms and the causes of death in this trial to determine whether ICD shocks in this patient population could serve as a surrogate for SCD. We reviewed the shock electrograms and the causes of death in this trial to determine whether ICD shocks in this patient population could serve as a surrogate for SCD.
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- Counterfactual experiment
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- 2x as many patients in ICD-arm had shocks compared to SCD in control-arm
- Increased number of syncope events in control group balanced excess shocks in ICD group
- **Conclusion:** Not all ICD therapies would have led to SCD or death

Should this event be counted?

- VT onset
- 1st ATP onset
- 2nd ATP onset
- accelerated VT
- 4.8 J shock
### Three Treatment Arms (abbreviated)*

<table>
<thead>
<tr>
<th>Arm A (Conventional)</th>
<th>Arm B (High-rate)</th>
<th>Arm C (Duration-delay)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zone 1:</strong></td>
<td><strong>Zone 1:</strong></td>
<td><strong>Zone 1:</strong></td>
</tr>
<tr>
<td>&gt;170 bpm, 2.5s delay</td>
<td>170 bpm</td>
<td>≥170 bpm, 60s delay</td>
</tr>
<tr>
<td>Onset/Stability Detection Enhancements ON</td>
<td>Monitor only</td>
<td>Rhythm ID® Detection Enhancements ON</td>
</tr>
<tr>
<td>ATP + Shock</td>
<td>ATP + Shock</td>
<td>ATP + Shock</td>
</tr>
<tr>
<td>SRD 3 min initial</td>
<td>SRD Off</td>
<td>SRD Off</td>
</tr>
<tr>
<td><strong>Zone 2:</strong></td>
<td><strong>Zone 2:</strong></td>
<td><strong>Zone 3 :</strong></td>
</tr>
<tr>
<td>&gt;200 bpm, 1s delay</td>
<td>&gt;200 bpm, 2.5s delay</td>
<td>&gt;250 bpm, 2.5s delay</td>
</tr>
<tr>
<td>Quick Convert™ ATP Shock</td>
<td>Quick Convert™ ATP Shock</td>
<td>Quick Convert™ ATP + Shock</td>
</tr>
</tbody>
</table>

*All programming is within approved labeling. Rhythm ID® and Quick Convert™ are trademarks of Boston Scientific Corporation.

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**Primary prevention**

**Sinus rhythm at enrollment**

**No heart block**

Cumulative Probability of First Inappropriate Therapy by Treatment Group

Slides adapted from those presented by Arthur J Moss, MD at AHA 2012, Los Angeles, CA USA

Cumulative Probability of Death by Treatment Group

![Graph showing the cumulative probability of death by treatment group with time (years) on the x-axis and all-cause mortality (%) on the y-axis. The patients at risk for each treatment group (A: Conventional, B: High Rate, C: Duration Delay) are shown with different markers.}

- Appropriate shocks
- Inappropriate shocks
- Randomization to conventional settings

### Table 3a: Influence of ICD therapy on the risk of mortality

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Deaths/Total</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall inappropriate therapy</td>
<td>10/152</td>
<td>2.61</td>
<td>1.28-5.31</td>
<td>0.008</td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>4/60</td>
<td>2.88</td>
<td>1.02-8.17</td>
<td>0.046</td>
</tr>
<tr>
<td>Inappropriate ATP-only</td>
<td>6/92</td>
<td>3.25</td>
<td>1.33-7.94</td>
<td>0.010</td>
</tr>
<tr>
<td>Overall appropriate therapy</td>
<td>15/186</td>
<td>2.66</td>
<td>1.45-4.88</td>
<td>0.002</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>11/74</td>
<td>6.32</td>
<td>3.13-12.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appropriate ATP only</td>
<td>4/112</td>
<td>1.02</td>
<td>0.36-2.88</td>
<td>0.977</td>
</tr>
</tbody>
</table>

Adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes, ischemic cardiomyopathy, NYHA class III compared to lower NYHA class and implanted device (ICD/CRT-D)

### Table 3b: Influence of ICD therapy by different heart rate ranges on mortality

<table>
<thead>
<tr>
<th>Heart Rate Range</th>
<th>Therapy Type</th>
<th>Deaths/Total</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>170-199 bpm</td>
<td>Inappropriate therapy</td>
<td>9/122</td>
<td>3.16</td>
<td>1.47-6.81</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Appropriate therapy</td>
<td>5/97</td>
<td>0.98</td>
<td>0.37-2.55</td>
<td>0.961</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11/123</td>
<td>3.22</td>
<td>1.59-6.54</td>
<td>0.001</td>
</tr>
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</table>

Adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes, ischemic cardiomyopathy, NYHA class III compared to lower NYHA class and implanted device (ICD/CRT-D)

MADIT-RIT: Factors associated with death

- Appropriate shocks
- Inappropriate shocks
- Randomization to conventional settings

Table 3a: Influence of ICD therapy on the risk of mortality

<table>
<thead>
<tr>
<th>Therapy Range</th>
<th>Deaths/Total patients with the specific ICD therapy</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate therapy 170-199 bpm</td>
<td>9/122</td>
<td>3.16</td>
<td>1.47-6.81</td>
<td>0.003</td>
</tr>
<tr>
<td>Inappropriate therapy ≥ 200 bpm</td>
<td>1/39</td>
<td>0.46</td>
<td>0.06-3.61</td>
<td>0.462</td>
</tr>
<tr>
<td>Appropriate therapy 170-199 bpm</td>
<td>5/97</td>
<td>0.98</td>
<td>0.37-2.55</td>
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Adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes, ischemic cardiomyopathy, NYHA class III compared to lower NYHA class and implanted device (ICD/CRT-D)

ICD shocks and health care utilization

**Medtronic DWAS Database**
- Contains de-identified device information from Medtronic's CareLink and the implant registration system.
  - Example of available data:
    - Implant information
    - Shock dates
    - Arrhythmia classification
    - Programmed parameters

**Matched Dataset Subjects**
- All device and claims information
  - ✓ Date of Implant
  - ✓ Type of Implant
  - ✓ Patient gender
  - ✓ Patient age at implant
  - ✓ Patient Location (three digit zip code)
  - ✓ Site of Care Location - Implant Service (three digit zip code)

**MarketScan Claims Database**
- Contains de-identified claims information for more than 80 million commercial and Medicare patients.
  - Example of available data:
    - Patient demographics
    - All healthcare utilization
    - Site of service
    - All dx and procedures done
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Example of available data:
• Patient demographics
• All healthcare utilization
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Matched Dataset
Subjects
All device and claims information


In 1873 shock events in 995 patients:
1 in 3 shock events associated with related outpatient/ER care
1 in 7 shock events associated with related inpatient care
Utilization even higher if evaluating any claim, not just related claims

✓ Site of Care Location - Implant Service (three digit zip code)
ICDs trigger a cascade of stuff

<table>
<thead>
<tr>
<th>Any Procedure (primary or secondary)</th>
<th>All Inpatient Visits (N=259)*</th>
<th>Appropriate (N=155)</th>
<th>Inappropriate (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td>221 (85.3%)</td>
<td>144 (92.9%)</td>
<td>58 (72.5%)</td>
</tr>
<tr>
<td>Chest X-Ray</td>
<td>196 (75.7%)</td>
<td>124 (80.0%)</td>
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<td>Cardiac Catheterization</td>
<td>196 (75.7%)</td>
<td>123 (79.4%)</td>
<td>41 (51.3%)</td>
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<td>152 (58.7%)</td>
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<td>Electrophysiology Study / Ablation</td>
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<tr>
<td>Percutaneous Coronary Intervention</td>
<td>17 (6.6%)</td>
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<td>4 (5.0%)</td>
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<td>7 (4.5%)</td>
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<tr>
<td>Heart/pericardium operations</td>
<td>5 (1.9%)</td>
<td>3 (1.9%)</td>
<td>2 (2.5%)</td>
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<tr>
<td>Cardioversion</td>
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<thead>
<tr>
<th>Any Procedure (primary or secondary)</th>
<th>All Inpatient Visits (N=259)*</th>
<th>Appropriate (N=155)</th>
<th>Inappropriate (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiogram</td>
<td>221 (85.3%)</td>
<td>144 (92.9%)</td>
<td>58 (72.5%)</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>196 (75.7%)</td>
<td>124 (80.0%)</td>
<td>54 (67.5%)</td>
</tr>
<tr>
<td>Cardiac Catheterization</td>
<td>196 (75.7%)</td>
<td>123 (79.4%)</td>
<td>41 (51.3%)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>152 (58.7%)</td>
<td>94 (60.6%)</td>
<td>41 (51.3%)</td>
</tr>
<tr>
<td>Emergency Room Visit</td>
<td>103 (39.8%)</td>
<td>67 (43.2%)</td>
<td>28 (35.0%)</td>
</tr>
<tr>
<td>Electrophysiology Study/ Ablation</td>
<td>87 (33.6%)</td>
<td>61 (39.4%)</td>
<td>9 (11.3%)</td>
</tr>
<tr>
<td>Device Interrogation</td>
<td>67 (25.9%)</td>
<td>47 (30.3%)</td>
<td>15 (18.8%)</td>
</tr>
<tr>
<td>Stress Test</td>
<td>42 (16.2%)</td>
<td>29 (18.7%)</td>
<td>7 (8.8%)</td>
</tr>
<tr>
<td>Lead or Device Revision</td>
<td>28 (10.8%)</td>
<td>8 (5.2%)</td>
<td>23 (28.8%)</td>
</tr>
<tr>
<td>Percutaneous Coronary Intervention</td>
<td>17 (6.6%)</td>
<td>10 (6.5%)</td>
<td>4 (5.0%)</td>
</tr>
<tr>
<td>Circulatory Support</td>
<td>9 (3.1%)</td>
<td>7 (4.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Heart/pericardium operation</td>
<td>5 (1.9%)</td>
<td>3 (1.9%)</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>4 (1.5%)</td>
<td>1 (0.6%)</td>
<td>2 (2.5%)</td>
</tr>
</tbody>
</table>

**Implications**

Frequent shocks could lead to discontinuation of study drug, cointerventions, protocol violations, forced unblinding, downstream procedures, early termination

Remote ICD monitoring and pixie dust

- Relationship of shocks to survival not clear
- Treatment effects similar in shockless devices (PPM)
- Cointervention
  - Effect size attenuation
  - Bias if differential

Varma N, et al. JACC 2015
How do ICD patients die?

- Low energy devices (1994-1999)
- Mostly not primary prevention

Table 2. Patient Characteristics (After ICD Implantation) by Mode of Death

<table>
<thead>
<tr>
<th>Attribute</th>
<th>n</th>
<th>All Deaths</th>
<th>Sudden Deaths</th>
<th>Nonsudden Cardiac Deaths</th>
<th>Noncardiac Deaths</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LED (Js)</td>
<td>306</td>
<td>14.6</td>
<td>16.8</td>
<td>15.1</td>
<td>14.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Follow-up (days)</td>
<td>317</td>
<td>143</td>
<td>133</td>
<td>152</td>
<td>152</td>
<td>128</td>
</tr>
<tr>
<td>OP-MORT (%)</td>
<td>317</td>
<td>17%</td>
<td>18%</td>
<td>16%</td>
<td>17%</td>
<td>NS</td>
</tr>
<tr>
<td>In-hosp (%)</td>
<td>317</td>
<td>70%</td>
<td>29%</td>
<td>88%</td>
<td>80%</td>
<td>74%</td>
</tr>
<tr>
<td>ICD Rx (%)</td>
<td>317</td>
<td>55%</td>
<td>54%</td>
<td>63%</td>
<td>39%</td>
<td>0.005</td>
</tr>
<tr>
<td>ICD ON (%)</td>
<td>317</td>
<td>75%</td>
<td>94%</td>
<td>68%</td>
<td>66%</td>
<td>0.001</td>
</tr>
<tr>
<td>ICD INTERRO (%)</td>
<td>238</td>
<td>44%</td>
<td>54%</td>
<td>42%</td>
<td>32%</td>
<td>0.036</td>
</tr>
<tr>
<td>AA (%)</td>
<td>312</td>
<td>51%</td>
<td>41%</td>
<td>60%</td>
<td>41%</td>
<td>0.005</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>317</td>
<td>16%</td>
<td>20%</td>
<td>13%</td>
<td>17%</td>
<td>NS</td>
</tr>
</tbody>
</table>

AA = antiarrhythmic drug therapy at time of death; Beta-blocker = beta-blocker drug therapy at time of death; ICD = implantable cardioverter defibrillator; ICD ON = ICD active at time of death; ICD Rx = appropriate ICD therapy supplied before terminal event; ICD INTERRO = post-mortem ICD interrogation performed (of those ICDs that were active at time of death); In-hosp = after admission to a hospital or hospice; LED = lowest intra-operative energy of successful defibrillation; n = number of patients with complete data; OP-MORT = percentage of deaths that were in the operative period; p value = statistical significance level by either analysis of variance or contingency table chi-square analysis, as appropriate.

Figure 1. Frequency distribution pie chart for adjudicated mechanisms of SD of 68 consecutive patients with a non-thoracotomy implantable cardioverter defibrillator (ICD) during pre-clinical device evaluation. The portion labeled VT/VF-OTHER includes one each of conversion of supraventricular tachyarrhythmia to ventricular fibrillation (VF), untreated ventricular tachycardia (VT) (as programmed), failure to redetect VT/VF after a shock therapy and trauma from a motor vehicle accident secondary to treated VT/VF. EMD = electromechanical dissociation.

JACC Vol. 39, No. 8, 2002
Potential solutions
Potential solutions

- Standardize programming with ITT + per-protocol
  - Limited data for secondary prevention
  - Unproven or unsafe if recent VT therapies
  - How to handle off-protocol programming changes
  - Increased risk of syncope
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  - Increased risk of syncope

- Stratification: exclude low rate/duration
  - Bias if differential programming over time, even after randomization
Potential solutions

- Standardize programming with ITT + per-protocol
  - Limited data for secondary prevention
  - Unproven or unsafe if recent VT therapies
  - How to handle off-protocol programming changes
  - Increased risk of syncope
- Stratification: exclude low rate/duration
  - Bias if differential programming over time, even after randomization
- Ranked or secondary outcomes
What if we only counted VF?

What if we only counted VF?

- Monomorphous VT and VF cycle lengths are highly variable
- Factors
  - Antiarrhythmic drugs
  - Sympathetic tone
  - VT location
  - Substrate; prior ablation

---

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All (n = 458)</th>
<th>STD (n = 229)</th>
<th>ICD (n = 229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.3</td>
<td>58.1</td>
<td>58.4</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>326 (71)</td>
<td>160 (70)</td>
<td>166 (72)</td>
</tr>
<tr>
<td>Hx diabetes, n (%)</td>
<td>105 (23)</td>
<td>53 (23)</td>
<td>52 (23)</td>
</tr>
<tr>
<td>Hx AF, n (%)</td>
<td>112 (24)</td>
<td>60 (26)</td>
<td>52 (23)</td>
</tr>
<tr>
<td>Duration of CHF, mean, y</td>
<td>2.83</td>
<td>3.27*</td>
<td>2.39</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>115.1</td>
<td>115.5</td>
<td>114.7</td>
</tr>
<tr>
<td>LBBB, n (%)</td>
<td>90 (20)</td>
<td>45 (20)</td>
<td>45 (20)</td>
</tr>
<tr>
<td>LVEF, median (25th–75 percentile), %</td>
<td>21 (7–35)</td>
<td>22 (10–35)</td>
<td>21 (7–35)</td>
</tr>
<tr>
<td>Qualifying arrhythmia, n (%)</td>
<td>NSVT only 103 (22)</td>
<td>52 (23)</td>
<td>51 (22)</td>
</tr>
<tr>
<td></td>
<td>PVC only</td>
<td>43 (9)</td>
<td>22 (10)</td>
</tr>
<tr>
<td></td>
<td>NSVT and PVC</td>
<td>312 (68)</td>
<td>155 (68)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>99 (22)</td>
<td>41 (18)</td>
<td>58 (25)</td>
</tr>
<tr>
<td>II</td>
<td>263 (57)</td>
<td>139 (61)</td>
<td>124 (54)</td>
</tr>
<tr>
<td>III</td>
<td>96 (21)</td>
<td>49 (21)</td>
<td>47 (21)</td>
</tr>
</tbody>
</table>

Hx indicates history of; AF, atrial fibrillation; CHF, congestive heart failure; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; and NYHA, New York Heart Association.

*P < 0.04 for comparison with ICD group.
Sudden Death in Patients With Cardiac Implantable Electronic Devices

Zian H. Tseng, MD, MAS; Robert M. Hayward, MD; Nina M. Clark, BS; Christopher G. Mulvanny, MS; Benjamin J. Colburn, BA, BS; Philip C. Ursell, MD; Jeffrey E. Olgin, MD; Amy P. Hart, MD; Ellen Moffatt, MD

**IMPORTANCE** Interrogations and autopsies of sudden deaths with cardiac implantable electronic devices (CIEDs) are rarely performed. Therefore, causes of sudden deaths with these devices and the incidence of device failure are unknown.

**OBJECTIVE** To determine causes of death in individuals with CIEDs in a prospective autopsy study of all sudden deaths over 35 months as part of the San Francisco, California, Postmortem Systematic Investigation of Sudden Cardiac Death (POST SCD) study.

**DESIGN, SETTING, AND PARTICIPANTS** Full autopsy, toxicology, histology, and device interrogation were performed on incident sudden cardiac deaths with pacemakers or implantable cardioverter defibrillators (ICDs). The setting was the Office of the Chief Medical Examiner, City and County of San Francisco. Participants included all sudden deaths captured through active surveillance of all deaths reported to the medical examiner and San Francisco residents with an ICD (January 1, 2011, to November 30, 2013).

**RESULTS** Twenty-two of 517 sudden deaths (4.3%) had CIEDs, and autopsy revealed a noncardiac cause of death in 6. Six of 14 pacemaker sudden deaths and 7 of 8 ICD sudden deaths died of ventricular tachycardia or ventricular fibrillation. Device concerns were identified in half (4 pacemakers and 7 ICDs), including 3 hardware failures contributing directly to death (1 rapid battery depletion with a sudden drop in pacing output and 2 lead fractures), 5 ICDs with ventricular fibrillation undersensing, 1 ICD with ventricular tachycardia missed due to programming, 1 improper device selection, and a pacemaker-dependent patient with pneumonia and concern about lead fracture. Of 712 San Francisco residents with an ICD during the study period, 109 died (15.3% cumulative 35-month incidence of death), and the 7 ICD concerns represent 6.4% of all ICD deaths.

**CONCLUSIONS AND RELEVANCE** Systematic interrogation and autopsy of sudden deaths in one city identified concerns about CIED function that might otherwise not have been observed. Current passive surveillance efforts may underestimate device malfunction. These methods can provide unbiased data regarding causes of sudden death in individuals with CIEDs and improve surveillance for CIED problems.
## Cause of death in 8 ICD SCDs in San Francisco

- **7 of 8 ICDs with device failure, mostly VF undersensing**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Device</th>
<th>Cause of SCD</th>
<th>VF Status</th>
<th>Subarachnoid Hemorrhage</th>
<th>Hardware Issue</th>
<th>Device Issue</th>
<th>VF Algorithm Issue</th>
<th>Arrhythmic</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>78♂</td>
<td>with Dilated CM</td>
<td>DC ICD</td>
<td>Massive subarachnoid hemorrhage, cardiomegaly (heart 760g)</td>
<td>VF documented at time of death (likely secondary to subarachnoid hemorrhage). See eFigure 6.</td>
<td>VF</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>76♂</td>
<td>with Ischemic CM, AF, CAD</td>
<td>DC ICD</td>
<td>Scar from remote MI and CM but no acute MI or other COD</td>
<td>Episodes of VF during EMS rescue were not recorded by device and required external shocks for rescue. Delay to shock due to ATP programming in the VF zone. See Figure 2.</td>
<td>VF</td>
<td>Arrhythmic</td>
<td>Yes (VF episodes missed; Programming and Device algorithm issue)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>70♂</td>
<td>with Ischemic CM, CHF</td>
<td>CRT-D</td>
<td>CM without acute MI or other COD</td>
<td>VF undersensed with device interpreting return to sinus rhythm (no shock delivered). See Figure 3.</td>
<td>VF</td>
<td>Arrhythmic</td>
<td>Yes (VF undersensing; Device algorithm issue)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>74♂</td>
<td>with CAD s/p MI, ischemic CM, AF, VT</td>
<td>DC ICD</td>
<td>Scar from remote MI and 99% LAD stenosis but no acute MI</td>
<td>VF with undersensing. 40 VF and 2 VT episodes identified and 17/42 shocks aborted due to undersensing. The second event showed significant undersensing with a significant delay in therapy. See eFigure 7.</td>
<td>VF</td>
<td>Arrhythmic</td>
<td>Yes (VF undersensing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>54♀</td>
<td>with dilated CM, ESRD on HD</td>
<td>DC ICD</td>
<td>N/A</td>
<td>VT that was undersensed. This was treated with ATP but wavered VT cycle length resulted in a delayed shock. VT degraded into fine VF that was undersensed. Patient left in VF/VF and device stopped recording and was unable to detect after that point. See eFigure 8.</td>
<td>VF</td>
<td>Arrhythmic</td>
<td>Yes (VT undersensing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>71♀</td>
<td>with AF, CAD, ischemic CM</td>
<td>SC ICD</td>
<td>Acute RCA thrombus. Cardiomegaly, cirrhosis, COPD</td>
<td>Extended VF with undersensing leading to a delay in interval counts that delayed therapy. See eFigure 9.</td>
<td>VF</td>
<td>Arrhythmic</td>
<td>Yes (VF undersensing, Programming and Device algorithm issue)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>80♀</td>
<td>with ischemic CM, CAD, CHF</td>
<td>CRT-D</td>
<td>N/A</td>
<td>VF storm with 4 shocks and multiple rounds of ATP. Final event shows VT but device did not rescue due to programming of tachycardia zone. See eFigure 10.</td>
<td>VT</td>
<td>Arrhythmic</td>
<td>Yes (VT slower than VT zone; Programming)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>80♀</td>
<td>with Ischemic CM, AF</td>
<td>DC ICD</td>
<td>Hypertensive heart disease, COPD</td>
<td>VF with successful defibrillation x 3 followed by RV lead noise and increase in lead impedance with 4th shock suggesting lead fracture. See Figure 4.</td>
<td>VF</td>
<td>Arrhythmic</td>
<td>Yes (Lead fracture; Hardware failure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF - atrial fibrillation, CAD - coronary artery disease, CHB - complete heart block, CHF - congestive heart failure, CM - cardiomyopathy, COD - cause of death, CRT-D - cardiac resynchronization therapy pacemaker, CRT-P - cardiac resynchronization therapy defibrillator, DC - dual chamber, MI - myocardial infarction, PEA - pulseless electrical activity, PPM - permanent pacemaker, RV - right ventricle, RVR - rapid ventricular response, SC - single chamber, VF - ventricular fibrillation, VT - ventricular tachycardia
Summary

- ICDs treat based on rate, not mechanism
- SCD, aborted SCD, ATP, and shock are not interchangeable events
  - Surrogacy is challenging
- What to count may depend on goal of the trial
  - Endpoints with VF should include all-cause mortality
  - ATP further complicates things
  - Should all polymorphic VT be included, even if nonsustained?
  - ICD programming should be protocled to reflect current standard of care
  - VT suppression can be a reasonable target in some cases
Flecainide Therapy Reduces Exercise-Induced Ventricular Arrhythmias in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia

Christian van der Werf, MD,* Prince J. Kannankeril, MD, MSCI,‡ Frederic Sacher, MD,|| Andrew D. Krahn, MD,¶ Sami Viskin, MD,# Antoine Leenhardt, MD,** Wataru Shimizu, MD, PhD,†† Naokata Sumitomo, MD,‡‡ Frank A. Fish, MD,‡ Zahurul A. Bhuiyan, MD, PhD,† Albert R. Willems, MD, PhD,* Maurits J. van der Veen, MD, PhD,§§ Hiroshi Watanabe, MD, PhD,¶¶ Julien Laborde, MD,¶¶ Michel Haïssaguerre, MD,¶ Björn C. Knollmann, MD, PhD,§ Arthur A. M. Wilde, MD, PhD*

Amsterdam and Ede, the Netherlands; Nashville, Tennessee; Bordeaux, Paris, and Bayonne, France; London, Ontario, Canada; Tel Aviv, Israel; and Suita, Tokyo, and Niigata, Japan

van der Werf C, et al. JACC, 2011
van der Werf C, et al. JACC, 2011

The dual action of flecainide's Na\(^+\)/H\(^+\) channel blockade further reduces the rate of triggered beats (23, 24). This dual action could explain why flecainide is so effective in severe CPVT and provides a rationale for combination therapy with \(\beta\)-blockers.

RyR2-mediated sarcoplasmic reticulum Ca\(^{2+}\) release importantly regulates the beating rate of sinoatrial nodal cells (31), especially in response to catecholamines (32), and flecainide reduces the rate of spontaneous sarcoplasmic...
The rationale for combination therapy with flecainide is so effective in severe CPVT and provides a trigger for beats. Standard therapy exercise tests were performed on patients receiving the same treatment as flecainide, and it was found that those receiving flecainide were at the same stable flecainide dose in combination with an unchanged or lower dose of another drug. The ventricular arrhythmia score per patient on the baseline exercise test and on the previous exercise test at the same standard therapy dose is shown. The figure shows the reproducibility of ventricular arrhythmia score on exercise testing. The figure indicates the number of patients, and a dotted line represents 1 patient. The median time interval between the 2 tests is shown. The number of patients in each ventricular arrhythmia category and change of ventricular arrhythmia category on the last exercise test at the flecainide starting dose (96 mg; range 50 to 150 mg) and on the first exercise test at the final (stable) flecainide dose (178 mg; range 100 to 300 mg) is shown. The sinus rates at maximal exercise on the first exercise test are higher compared with baseline exercise testing (increase of 32 and 19 beats/min, respectively). This dual action could explain why the reduction in sinus rate during exercise may further contribute to flecainide’s efficacy in CPVT. The reduction in sinus rate during exercise may further contribute to flecainide’s efficacy in CPVT. The use of Ca-channel blockers has been reported to decrease ventricular ectopy in CPVT patients with ischemia and impaired left ventricular function (24–27,35,36). Other pharmacological agents, including beta-blockers after failure of standard therapy, have been tested in small cohorts (19–22). The use of Ca-channel blockers, amiodarone, and magnesium, lack of antiarrhythmic agents, and lack of follow-up (36). Other pharmacological agents, including beta-blockers, are considered potentially harmful effect in CPVT patients (17,18). Yet, ICDs have a limited efficacy in CPVT patients who were survivors of cardiac arrest or syncope or sustained VT persisted despite ICD implantation can lead to significant complications (17,18). Conversely, the high fatality rate of untreated CPVT patients (22–25) van der Werf et al. JACC, 2011. May 31, 2011: 2245.}

van der Werf C, et al. JACC, 2011
Thank you!

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