The Implantable Subcutaneous Cardioverter Defibrillator (S-ICD)

Riccardo Cappato, MD

Disclosures

Equity and Intellectual Property Rights: Cameron Health
Consultant to: Boston Scientific; Medtronic; St. Jude; Biosense Webster; ELA Sorin; Boehringer Ingelheim; Bayer Health; Abbott; Pfizer
Speaker’s Bureau: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; Sanofi Aventis; Boehringer Ingelheim; Bayer Health; Abbott
Investigator: Medtronic; Biosense Webster; Sanofi Aventis; Cameron Health, BARD; Bayer Health; Abbott; Pfizer
Grants: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; ELA Sorin
Disclosures

Equity and Intellectual Property Rights: Cameron Health
Consultant to: Boston Scientific; Medtronic; St. Jude; Biosense Webster; ELA Sorin; Boehringer Ingelheim; Bayer Health; Abbott; Pfizer
Speaker’s Bureau: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; Sanofi Aventis; Boehringer Ingelheim; Bayer Health; Abbott
Investigator: Medtronic; Biosense Webster; Sanofi Aventis; Cameron Health, BARD; Bayer Health; Abbott; Pfizer
Grants: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; ELA Sorin

Introduction
Subcutaneous Defibrillator: Clinical Evidence & Current Practice

Aim of technology

• The entirely Subcutaneous (S) - ICD was designed to provide the life-saving benefit of conventional ICDs whilst avoiding the shortcomings of transvenous leads
• By simplifying implant techniques, S-ICDs are also meant for expanding the use of ICDs in clinical practice

S-ICD Technology

Dedicated totally subcutaneous ICD

• 80 joules (delivered)
• Post-shock pacing
• Single electrode
• Reduced complexity
S-ICD Technology

- 3 sense electrodes
- 3 possible bipolar sensing vectors
- Optimal sense vector automatically selected by device
S-ICD Technology
Rhythm Detection

• All detection algorithms work together to identify S-ECG rhythm: heart rate, QRS width and dynamic template matching with learning from previous beats

S-ICD System Components
SQ-Rx Pulse Generator

<table>
<thead>
<tr>
<th>Volume</th>
<th>69 cc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>145 grams</td>
</tr>
<tr>
<td>Thickness</td>
<td>15.7 mm</td>
</tr>
<tr>
<td>Energy</td>
<td>80J (delivered)</td>
</tr>
<tr>
<td>Waveform</td>
<td>Biphasic</td>
</tr>
</tbody>
</table>
Following 2x successful S-ICD shock At 65 J

Subcutaneous Defibrillator: Clinical Evidence & Current Practice

List of Topics

- IDE clinical study
- Effortless registry
- Literature data
IDE Clinical Study

Objective*: 
- Evaluate safety and effectiveness of the S-ICD® System in the treatment of life-threatening ventricular arrhythmias

Design: 
- Prospective, multicenter, single-arm clinical study conducted in the U.S., Europe, and New Zealand.
- Enrollment began Jan 2010 and concluded May 2011
- Follow up: > 1 year for first 100 patients; > 6 month for all patients

Primary Endpoints

1° Efficacy Endpoint: Acute VF Conversion Rate
- 2 consecutive successes out of 4 attempts
- Lower Bound of 2-sided CI $95\% > 88\%$

Sub-Study
VF conversion rate at $\geq 150$ days

1° Safety Endpoint: 180-Day System Complication Free Rate
- Lower Bound of 2-sided CI $95\% > 79\%$

IDE Clinical Study
Study Design

Inclusion Criteria

• Age ≥ 18 years
• Met guidelines for ICD implantation* or replacement of an existing ICD system
• An appropriate pre-operative ECG

Key Exclusion Criteria

• Prior VT reliably terminated with anti-tachycardia pacing
• Existing epicardial patches or subcutaneous array
• Unipolar pacemakers
• Severe renal dysfunction (GFR ≤ 29)


IDE Clinical Study
Patient Enrollment

Patients Enrolled
(N = 330)

Patients Withdrawn PRIOR to Implant
(N = 9)

Implant Attempts
SAFETY COHORT
(N = 321)

Implant Testing Not Completed
(N = 17)

Implant Testing Completed
EFFECTIVENESS COHORT
(N = 304)

Active Patients
(N = 294)

• Not Discharged with System (N=7)
• Exits after Hospital Discharge (N = 12)
• Deaths unrelated to device or procedure (N = 7)
• Death unknown due to limited information from overseas death (N = 1)
# IDE Clinical Study

## Basic Patient Demographics

<table>
<thead>
<tr>
<th>Demographic Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52 ± 16</td>
</tr>
<tr>
<td>Male</td>
<td>74%</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91 ± 25</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>60 ± 7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>65%</td>
</tr>
<tr>
<td>African American</td>
<td>24%</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
</tr>
</tbody>
</table>

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Statistic/Category</th>
<th>N=321</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbidities History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>197 61</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>187 58</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>133 41</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>90  28</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>49  15</td>
<td></td>
</tr>
<tr>
<td>Valve Disease</td>
<td>42  13</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>27  8</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>18  6</td>
<td></td>
</tr>
<tr>
<td>Cardiac Surgical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous Revascularization</td>
<td>92  29</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>48  15</td>
<td></td>
</tr>
<tr>
<td>TV-ICD</td>
<td>43  13</td>
<td></td>
</tr>
<tr>
<td>Valve Surgery</td>
<td>18  6</td>
<td></td>
</tr>
<tr>
<td>Pacemaker</td>
<td>4   1</td>
<td></td>
</tr>
</tbody>
</table>
Patient Age Distribution

40% of patients were lower than 50 years old

Age (years)

% of Patients

18-20 21-30 31-40 41-50 51-60 61-70 71-80 > 80

2% 10% 12% 16% 26% 22% 11% 1%

IDE Clinical Study

Ejection Fraction

Low Ejection Fraction Well Represented

70% of patients with EF < 35%

Ejection fraction
Mean + SD (median): 36 ± 16 (31)

Primary & Secondary Prevention Patient Distribution Similar to NCDR Registry

S-ICD System IDE Study
n = 321 patients

Secondary Prevention 21%
Primary Prevention 79%

NCDR ICD Registry
n = 486,025 patients

Secondary Prevention 22%
Primary Prevention 78%

IDE Study: Broad Range of ICD Indications

- Ischemic (38%)
- Channelopathy (13%)
- Congential (3%)
- Non ischemic CM (10%)
- HCM (13%)
- ARVD (3%)
- Idiopathic VF (20%)
IDE Clinical Study
Primary Effectiveness Endpoint

Primary Effectiveness Endpoint Met:
Acute Defibrillation Efficacy

<table>
<thead>
<tr>
<th>Patients Enrolled</th>
<th>Patients Withdrawn PRIOR to Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 330)</td>
<td>(N = 9)</td>
</tr>
</tbody>
</table>

SAFETY COHORT/Implant Attempts (N = 321)

EFFECTIVENESS COHORT (N = 304)

Primary Effectiveness Met:
• 100% conversion rate of induced arrhythmias in evaluable patients

Acute Induction Testing Not Performed (N = 1)

Acute Induction Testing Non-evaluable (N = 16)

IDE Study

Primary Effectiveness Endpoint Met

• Primary IDE Effectiveness Endpoint
  – Hypothesis: Lower Bound of 2-sided $CI_{95\%} > 88\%$
  – N = 304 patients

<table>
<thead>
<tr>
<th>Induction Testing Not Performed</th>
<th>Non-Evaluable Patients</th>
<th>Evaluable Results</th>
<th>Conversion Rate (%)</th>
<th>95% Lower Bound (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>304</td>
<td>0</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Sensitivity Analysis Exceeds OPC

• **Primary IDE Effectiveness Endpoint**
  – Hypothesis: Lower Bound of 2-sided CI$_{95\%}$ > 88%

• **Sensitivity Analysis**
  – Failure: Patients w/ incomplete testing and ≥ 1 failed shock
  – N = 315 patients

<table>
<thead>
<tr>
<th>Induction Testing Not Performed</th>
<th>Non-Evaluable Patients</th>
<th>Evaluable Results</th>
<th>Conversion Rate (%)</th>
<th>95% Lower Bound (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 16</td>
<td>304 0</td>
<td>100.0</td>
<td>98.8</td>
</tr>
<tr>
<td></td>
<td>1 5</td>
<td>304 11</td>
<td>96.5</td>
<td>93.8</td>
</tr>
</tbody>
</table>

All Analyses Exceed OPC

• **Primary IDE Effectiveness Endpoint**
  – Hypothesis: Lower Bound of 2-sided CI$_{95\%}$ > 88%

• **Sensitivity Analysis**
  – Failure: Patients w/ incomplete testing and ≥ 1 failed shock

• **Worst-Case Sensitivity**
  – All non-evaluable and 1 not tested deemed “Failures”
  – N = 321 patients

<table>
<thead>
<tr>
<th>Induction Testing Not Performed</th>
<th>Non-Evaluable Patients</th>
<th>Evaluable Results</th>
<th>Conversion Rate (%)</th>
<th>95% Lower Bound (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 16</td>
<td>304 0</td>
<td>100.0</td>
<td>98.8</td>
</tr>
<tr>
<td></td>
<td>1 5</td>
<td>304 11</td>
<td>96.5</td>
<td>93.8</td>
</tr>
<tr>
<td></td>
<td>0 0</td>
<td>304 17</td>
<td>94.7</td>
<td>91.7</td>
</tr>
</tbody>
</table>
Chronic Conversion Sub-Study Supports Efficacy

- 77 patients underwent Chronic Conversion testing (≥150 days)
  - 74 patients with evaluable results
  - 3 patients non-evaluable (opposite polarity not tested)

<table>
<thead>
<tr>
<th>Shock Energy (J)</th>
<th>Success</th>
<th>Failure</th>
<th>Non-evaluable</th>
<th>Conversion Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>71</td>
<td>3</td>
<td>3</td>
<td>95.9</td>
</tr>
<tr>
<td>≤ 80</td>
<td>77</td>
<td>0</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

Totality of Spontaneous Episodes

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>VT/VF Episodes</th>
<th>Total</th>
<th>Discrete</th>
<th>Storm</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDE Study</td>
<td></td>
<td>109</td>
<td>28</td>
<td>81 (4 events)</td>
</tr>
<tr>
<td></td>
<td>Episodes</td>
<td>16</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Non-IDE Studies</td>
<td></td>
<td>52</td>
<td>18</td>
<td>34 (4 events)</td>
</tr>
<tr>
<td></td>
<td>Episodes</td>
<td>11</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Commercial Evaluation</td>
<td></td>
<td>51</td>
<td>15</td>
<td>36 (6 events)</td>
</tr>
<tr>
<td></td>
<td>Episodes</td>
<td>12</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
IDE Clinical Study
Safety Results: Analysis Cohort

Patients Enrolled
(N = 330)

SAFETY COHORT/
Implant Attempts
(N = 321)

Patients Withdrawn PRIOR
to Implant Procedure
(N = 9)

IDE Study
IDE Study: Primary Safety Endpoint Met

180-day Type I Complication-Free Rate:
99.0% (97.9% LCL)
Freedom from all Device-, Labeling-, & Procedure-related Complications

180-day Device & Procedure-related Complication-free Rate: 92.1% (88.9% LCL)

IDE Clinical Study
Infections

- All infections requiring explant occurred early in the study before investigators meeting
  - No infections requiring explant occurred in last 214 patients implanted
- No endocarditis or systemic blood stream infections
- 32 out of 33 patients with previous Transvenous-ICD had no reports of infection with the S-ICD® System

1.3% Explant Rate for Infections

IDE Clinical Study
Inappropriate shocks

Rate of inappropriate therapy is consistent with current transvenous ICDs*

- 38 patients experienced shock due to non-VT/VF event
  - 15 patients (4.6%) – SVT> Discrimination zone
  - 24 patients (7.4%) – Oversensing

Reduction of Inappropriate Shocks Associated with Dual Zone Programming

- No patients experienced a shock due to discrimination error in Conditional Shock (dual) zone
- Study demonstrated that dual zone programming is important tool for reducing inappropriate shock rate

<table>
<thead>
<tr>
<th>Oversensing</th>
<th>Rate &gt; Shock Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate Shocks (%)</td>
<td>Single Zone</td>
</tr>
<tr>
<td>13.9</td>
<td>6.1</td>
</tr>
</tbody>
</table>

**EFFORTLESS** Registry

EFFORTLESS Registry

European Registry Designed to Capture Clinical Outcome and Cost Effectiveness Data of S-ICD® System

Objective:
To demonstrate the early, mid-term, and long-term clinical outcome and cost effectiveness of the S-ICD System

Outcome measures:
• Perioperative (30 days post implant) S-ICD System Complication Free rate
• 360 day S-ICD System Complication Free Rate
• Percentage of Inappropriate Shocks for AF/SVT
• Prospective Quality of Life

Preliminary Results of the EFFORTLESS S-ICD System Registry as of April 27, 2012*
• 210 Active Patients
• 98.5% effective conversion of induced VT/VF within 1 procedure
• No inappropriate shocks have been recorded for AF/SVT within a programmed conditional shock zone
• Annual inappropriate shock rate of 7% with some of these patients receiving shocks due to Rate > Shock Zone

* Heart Rhythm - May 2012; Vol 9 (S1-S3), AR07-2.

Site Participation in 9 Geographies
Subcutaneous Defibrillator: Clinical Evidence & Current Practice

Conclusions

• S-ICD represents a novel approach for the prevention of VT/VF induced sudden death
• S-ICDs avoid procedural difficulties and complications associated with transvenous leads
• Primary and secondary prevention unless antibrady and/or anti-tachy pacing required

Clinical Experience With the Subcutaneous Defibrillator

Conclusions

• Selection of S-ICD as a substitute of TV-ICD therapy must be made based on
  – physician’s clinical judgment and comfort with new technology
  – growing volume of data available on new therapy clinical impact
  – upcoming comparative data on S-ICD vs TV-ICD therapy efficacy and safety outcomes
Advantages and Limits of S-ICD Therapy

What is the real clinical utility of ATP?

- 6% of SCD-HeFT patients had >1 shock/year
- 3% of SCD-HeFT patients had >1 episode MMVT/year
- PainFree Rx ll indicated ATP success rate of 72%
- Accordingly ATP likely to be clinically beneficial in ~2% of these primary prevention patients
Usefulness of ATP for Fast VT

PainFREE RxII

• Shock vs. ATP for VT 188-250 bpm
• 634 patients, 11±3 months follow up
• 1,837 analyzed “VT” events, 431 FVT, (134 VF)
• **Shock limb;** 147 events in 51 patients
  – 110 shocks delivered (if arrhythmia HR > 188 bpm!)
  – 34% spontaneous conversions in ICD arm
• **ATP limb;** 284 events in 47 patients
  – 2 pts accounted for 131 (46%) of episodes
  – 72% success with ATP, 229/284 episodes
  – 62 shocks delivered
  – no spontaneous conversions in ATP arm
• QOL; Some scores better with ATP, (FVT event patients)

**Mortality;** Shock 7%, ATP 10%, p=0.22

Wathen et al, 2004

The S-ICD: For All Primary Prevention Pts?

Clinically relevant questions

• Can pts with hemodynamically well tolerated VT access to ER and get medically assisted ATP or controlled ECV rather than ICD shock therapy?
  – impact of shocks on natural course of LV dysfunction
ICD Shocks Associated with Higher Risk of Death in SCD-HeFT

Hazard Ratios for the Association of ICD Shock with the Risk of Death, According to Shock Type

<table>
<thead>
<tr>
<th>Shock Type</th>
<th>Hazard Ratio for Death (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 App vs. no App</td>
<td>5.68 (1.97–8.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥1 Inapp vs. no Inapp</td>
<td>1.98 (1.29–3.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Both shock types vs. no shock</td>
<td>11.27 (6.70–18.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Appropriate and Inappropriate Shocks were associated with a Higher Risk of Death

Poole et al. NEJM 2008;359:1009

Defibrillation Voltage Gradients TV-ICD

- Transvenous ICD, Dual Coil, Active Can
- Modelled by Matthew Jolley

Myocardial Voltage Gradients @ DFT
Defibrillation Voltage Gradients

TV-ICD

- Transvenous ICD, Dual Coil, Active Can
- Modelled by Matthew Jolley

50 v/cm

Myocardial Voltage Gradients @ DFT

Defibrillation Voltage Gradients

S-ICD

- Jolley M…Triedman J.
- Computer Modelling, ICD systems
- Subcutaneous ICD, abdominal-right posterior @ DFT

Voltage Metrics @ DFT 42.5 J

Myocardial Voltage Gradients

Jolley et al Heart Rhythm 2008;5:565
Defibrillation Voltage Gradients

S-ICD

- Jolley M…Triedman J.
- Computer Modelling, ICD systems
- Subcutaneous ICD, abdominal-right posterior @ DFT

20 V/cm

Voltage Metrics @ DFT 42.5 J

Myocardial Voltage Gradients

Jolley et al Heart Rhythm 2008;5:565

High Defibrillation Shock Strengths Cause Myocardial Damage

Walcott & Ideker
Resuscitation 2003;59:59

Myocardial Voltage Gradients

- Defibrillation 5 V/cm
- Electroporation >30 V/cm (Leaky myocyte membranes)
  - Decreased contractility
- Ventricular stunning >50 V/cm
  - Ventricular proarrhythmia

Jones et al Circ Res 1980
Weaver et al NEJM 1988
Bardy et al Circ 1995
Xie et al Circ 1997
Strickberger et al JCEP 1998/9
The PRAETORIAN trial
A Prospective, Randomized comparison of subcutaneous & transvenous Implantable cardioverter-defibrillator therapy

Study Design The PRAETORIAN trial is an investigator-initiated, randomized, controlled, multicenter, prospective 2-arm trial that outlines the advantages and disadvantages of the subcutaneous ICD. Patients with a class I or IIa indication for ICD therapy without an indication for bradycardia or tachycardia are included. A total of 700 patients are randomized to either the subcutaneous or transvenous ICD (1:1). The study is powered to claim noninferiority of the subcutaneous ICD with respect to the composite primary endpoint of inappropriate shocks and ICD-related complications. After noninferiority is established, statistical analysis is done for potential superiority. Secondary endpoint comparisons of shock efficacy and patient mortality are also made.

Conclusion The PRAETORIAN trial is a randomized trial that aims to gain scientific evidence for the use of the subcutaneous ICD compared with the transvenous ICD in a population of patients with conventional ICD with respect to major ICD-related adverse events. This trial is registered at ClinicalTrials.gov with trial ID NCT01296022. (Am Heart J 2012; 163:753-760.e2)

S-ICD® System Clinical Studies
Implant Duration (Cumulative)
Mean Implant Months: 19.2 ± 10.8
Maximum: 49.7 Months
(Data as of 18 Sept 2012)

Recent Developments in S-ICD Technology
CE Trial - 55 Patients

Europe/New Zealand
• Enrollment: 12 Dec 2008 → 13 Feb 2009

Detection of VF
• 137/137 episodes: Sensitivity 100%
• Time-to-therapy: 14 ± 2 seconds

Conversion of VF @ 65J (2 inductions per pt)
• 52/53 (>98%) pts met the primary conversion endpoint

Example of Detection and Conversion of Ventricular Fibrillation

Bardy et al, 2010

Köbe et al 2012
Commercial Phase

S-ICD System Performance:
Implanted Systems...

S-ICD Systems Implanted (worldwide)
Q3-2012

- IDE Study Enrolled
  MAY-2011
- IDE Study Launch
  JAN-2010
- Commercial Launch
  SEP-2009
- CE Study
- CHRONIC II
- FDA Approval
  SEP-2012

1470

0 200 400 600 800 1000 1200 1400 1600
2008 2009 2010 2011 2012
S-ICD System Performance:
Commercial Age Distribution...

S-ICD System
Patient Age Distribution for Commercial Implants
Data available for 622 of 1079 commercial patients

S-ICD System Performance:
Therapy Delivery (episode analysis)…

EPISODE ANALYSIS
S-ICD System Performance:
Commercial Use…

Risk of Sudden Cardiac Death in Patients with “Hemodynamically Stable Sustained VT” After Myocardial Infarction

- 124 pts: 78 pts - AAD
  46 pts - surgical ablation
- Follow-up: 36 ± 30 month
- ICD in only 6 /124 pts

Total mortality: 45/124 (36.2%)
- Sudden Cardiac Death: 9 pts (7.2%) (Average 2.4% / year)
- Heart failure/ Recurrent MI: 20 pts (23.4%)
- Perioperative death: 9 pts (20% operative mortality)

(Sarter et al. JACC, 1996; 28: 122-9)