Cardiac Implantable Electronic Devices - What have we learned and where are we going?

Michael R Gold, MD, PhD
Medical University of South Carolina

Disclosures: Clinical Trials and Consulting – Medtronic and Boston Scientific
Breakthrough Innovation in Medical Devices

Requires alignment of:

- Unmet clinical needs
- Societal/market readiness
  - Global Megatrends
  - Healthcare trends
- Enabling technology
Pacemaker State-of-the-Art

- **Procedure:**
  - Radiation exposure
  - Surgical pocket + Transvenous leads

- **Device issues – Pocket:**
  - Discomfort
  - Hematomas
  - Infections
  - Cosmetic concerns

- **Leads**
  - Mechanical failures
  - Infections; Extractions
  - Mobility restrictions
  - Challenge in compatibility with MRI

Radiation Exposure varies by the square of the distance
Incidences of Lead & Pocket Complications

- Over 700,000 people are implanted annually worldwide
  - Nearly 50,000 experience post-implant related problems
- Over 4.4 million people WW currently have pacemaker
  - 65,000 chronic lead related problems annually

<table>
<thead>
<tr>
<th>Pacing complication</th>
<th>Average of Incremental cost per intervention in 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>$ 49,652</td>
</tr>
<tr>
<td>Lead revision</td>
<td>$ 16,285</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>$ 16,411</td>
</tr>
<tr>
<td>Pocket revision</td>
<td>$ 12,560</td>
</tr>
</tbody>
</table>

2: MDT, STJ, BSX Product Performance Reports
3: Danish Pacemaker Registry, www.pacemaker.dk
Incidence of Lead & Pocket Complications

- Over 700,000 people are implanted annually worldwide
  - Nearly 50,000 experience post-implant related problems
- Over 4.4 million people WW currently have pacemaker
  - 65,000 chronic lead related problems annually

<table>
<thead>
<tr>
<th>Pacing complication</th>
<th>Average of Incremental cost per intervention in 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>$ 49,652</td>
</tr>
<tr>
<td>Lead revision</td>
<td>$ 16,285</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>$ 16,411</td>
</tr>
<tr>
<td>Pocket revision</td>
<td>$ 12,560</td>
</tr>
</tbody>
</table>

2: MDT, STJ, BSX Product Performance Reports
3: Danish Pacemaker Registry, www.pacemaker.dk
Pacemaker Minutarization

- **Percutaneous femoral vein delivery**
  - 18F introducer /steerable catheter

- **Self-contained device in right ventricle**
  - No lead or surgical pocket
  - VVIR w/ Hysteresis
  - Inherently MRI compatible

- **Replacement options**
  - Catheter-based retrieval
  - Deliver additional leadless pacemakers
  - Revert to conventional pacing lead
LCP Long-Term Outcome:
Summary of Pacing/Sensing Parameters
LEADLESS Study

Safety Events

• Early Safety Events:
  • 1 inadvertent placement in LV (across PFO) → promptly removed and device placed in RV
  • 1 Tamponade → Surgery → f/u: Fatal stroke
  • 1 Minor Groin Hematoma → no treatment
  • 1 w/ VT 2 days after implant → LCP removed and ICD placed → ICD shock 2 wks later (same CL)

• Safety Events in follow-up:
  • No device migration / dislodgements
  • No infection
  • No mechanical failures / early battery depletion
  • No pro–arrhythmia
WiCS–LV System Provides LV Endocardial Pacing for CRT

- Transmitter implanted over an intercostal space
- Transfers ultrasound energy through the body, directed to a receiver in the LV.

- Receiver-Electrode implanted on the LV endocardial wall.
- Harvests ultrasound energy and converts it to electrical pacing pulse.
ICD Evolution of Devices and Programming

- ICDs have clearly been shown to reduce mortality in selective primary and secondary prevention cohorts.
- Despite 25 years of advancement in ICD therapy, lead failure and inappropriate shocks remain major clinical problem.
- Moreover, more recently there is a recognition of unnecessary appropriate shocks and concern has been raised regarding the long term risks of shocks.
- Multiple strategies have been developed to address these issues, including new algorithms and subcutaneous devices.
ICD Systems

The current ICD approach while effective, is not without significant risks

- 11% ICD patients suffer complications during or shortly after implant
- Acute complications add significant costs to the healthcare system (>7000/pt.)
- Infection rates are rising (one of the most serious complications)
Transvenous ICD Mortality After Extraction due to Infection

Analysis from Cleveland Clinic evaluated survival in patients who developed a CIED infection and found a 3-fold higher risk of death in those who had an endovascular infection compared to a pocket infection.

Risk factors for 1-year mortality among patients with cardiac implantable electronic device infection undergoing transvenous lead extraction: the impact of the infection type and the presence of vegetation on survival

- All patients with CIED infections who underwent device and lead removal at the Cleveland Clinic from January 2002 through 2008
- For patients with CIED infection, 20.3% mortality within the first year
  - Pocket infection 12% mortality
  - Endovascular infection 31% mortality

Kaplan–Meier survival curves over 1 year among TV-ICD patients with pocket infection and endovascular infection following TV-ICD system removal

- 12% mortality at 1 year
- 31% mortality at 1 year

ICD Pace-Sense Lead Failures
Present Most Commonly as Shocks

Riata Insulation Breach

Images taken from published Case Reports and Studies on Riata ICD lead failures.
Incidence of Lead Failures in Defibrillation Systems

S-ICD System

- Entirely Subcutaneous
- This avoids the acute and chronic complications associated with transvenous leads
- However, it creates other challenges
  - Defibrillation with subcutaneous rather than intracardiac coils
  - Sensing of subcutaneous signals
To avoid the complications of intravascular leads, a subcutaneous ICD was developed. The S-ICD produces more horizontal vector LV apex towards parasternal electrode.


- Slightly greater absolute safety margin in S-ICD due to potential 80J output

S-ICD Sensing

- Pre-implant screening required
- Three possible sensing vectors:
  - Distal and Proximal Electrodes, Pulse Generator
  - Automatically selects best vector determined by QRS to T wave ratio
  - Can manually select vector
- Sinus rhythm template stored at implant

Lewis GF and Gold MR. Clinical Experience with Subcutaneous implantable cardioverter-defibrillators. Nat Rev Cardiol.
Subcutaneous equivalent cutaneous connections

Transvenous pocket and lead connections

Gold et al, JCE 2011
## The S-ICD System Algorithm

**START Study... *Equivalent sensitivity* vs. transvenous systems**

- The S-ICD system appropriately delivered therapy in 100% of cases
- Equivalent to standard ICD

### START Study Results

<table>
<thead>
<tr>
<th>S-ICD</th>
<th>SINGLE CHAMBER TV</th>
<th>DUAL CHAMBER TV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSC</td>
<td>SJM</td>
</tr>
<tr>
<td>Rate Only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Appropriate</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>S-ICD</th>
<th>SINGLE CHAMBER TV</th>
<th>DUAL CHAMBER TV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSC</td>
<td>SJM</td>
</tr>
<tr>
<td>Dual Zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Appropriate</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

### The S-ICD System Algorithm

- The S-ICD system appropriately delivered therapy in 100% of cases.
- Equivalent to standard ICD.

References:

Gold et al, JCE 2011
The S-ICD Algorithm

- The S-ICD appropriately withheld therapy in 98% of cases
- Significant improvement over inappropriate shock rates with conventional ICDs

### START STUDY RESULTS

<table>
<thead>
<tr>
<th>SPECIFICITY</th>
<th>SINGLE CHAMBER TV</th>
<th>DUAL CHAMBER TV</th>
<th>S-ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BSC</td>
<td>SJM</td>
<td>MDT</td>
</tr>
<tr>
<td>Dual Zone - Nominal</td>
<td>70.0%</td>
<td>42.0%</td>
<td>92.0%</td>
</tr>
<tr>
<td>Appropriate</td>
<td>35</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>Inappropriate</td>
<td>15</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Adjusted* Appropriate</td>
<td>37</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>Dual Zone - SRD OFF</td>
<td>74.0%</td>
<td>64.0%</td>
<td>-</td>
</tr>
</tbody>
</table>

* Sustained rate timers (i.e. SRD) programmed OFF if nominally active (BSX = 3 min, SJM = 30 secs)

Gold et al, JCE 2011
ICD with Subcutaneous Leads

- Advantages
  - No transvenous lead complications
  - Fluoroscopy not required for implant
  - Ultra far field signals for arrhythmia discrimination
  - MRI Safe

- Disadvantages
  - Post shock pacing only (No Brady, CRT, ATP)
  - Larger Pulse generator
# S-ICD System Annualized Mortality Comparable to ICD Studies

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Annualized Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-ICD System IDE Study(^1)</td>
<td>3.7%</td>
</tr>
<tr>
<td>MADIT(^2)</td>
<td>5.8%</td>
</tr>
<tr>
<td>MADIT II(^3)</td>
<td>6.2%</td>
</tr>
<tr>
<td>AVID(^4)</td>
<td>8.2%</td>
</tr>
<tr>
<td>SCD-HeFT(^5)</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

\(^1\) Weiss et al, *Circulation* 2013;128:944-953
\(^2\) Moss, NEJM 1996
\(^3\) Goldenburg, Circulation 2010
\(^4\) AVID Investigators, N Engl J Med 1997;337:1576-83
\(^5\) Bardy, NEJM 2005
MADIT RIT: Cumulative Probability of First Inappropriate Therapy

Patients at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
<th>Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Conventional</td>
<td>514</td>
<td>420</td>
<td>305</td>
<td>149</td>
<td>56</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: High Rate</td>
<td>500</td>
<td>454</td>
<td>339</td>
<td>191</td>
<td>70</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: Duration Delay</td>
<td>486</td>
<td>445</td>
<td>342</td>
<td>177</td>
<td>82</td>
<td>13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MADIT RIT: Cumulative Probability of Death

![Graph showing cumulative probability of death over time for different treatment groups. The graph includes lines for Conventional, High Rate, and Duration Delay treatments. The table below the graph lists the number of patients at risk at each time point for each group.](image)
The Promise of Remote Monitoring

**Device-related**
- Elective replacement indicator (ERI) or end of life (EOL)

**Lead-related**
- Significant Δ in pacing Ω
- Significant increase in pacing thresholds
- Significant increase in the % of RV pacing
- Significant decrease in the % of LV pacing

**Arrhythmia-related**
- New onset of AT/AF
- Rapid ventricular rates during ongoing AT/AF
- Non-sustained or sustained VT/VF, including information about ATP and delivery of ICD shocks

**Heart failure-related**
TRUST Trial

Varma N et al. Circulation 2010; 122: 325-332
Hospitalization related to atrial arrhythmias and stroke observed:

- 6 active pts
- 18 control pts

(OR = 0.33; 95% CI: 0.14-0.87; p = 0.02)

IN-TIME Study

Mortality: 3.4% vs. 8.7%
HR 0.36 (95% CI: 0.17-0.74)
P=0.004

Hindricks G et al. Lancet 2014; 384: 583-590
Impact on Survival

Saxon LA et al. Circulation 2010 122: 2359-2367
Survival, Pacemakers

**Survival, Pacemaker**

- **Numbers at Risk**
  - **High**: 30,733, 28,732, 12,784, 1,217
  - **Low**: 20,763, 19,104, 9,496, 1,079
  - **None**: 61,173, 54,700, 25,805, 2,403

- **HR Adherence**
  - **RM** High vs. None: HR: 2.3 [2.1–2.4], p<0.001
  - **RM** High vs. Low: HR: 1.6 [1.3–1.5], p<0.001
  - **RM** Low vs. None: HR: 1.4 [1.5–1.7], p<0.001

**Survival, CRT-P**

- **Numbers at Risk**
  - **High**: 1,930, 1,786, 689, 55
  - **Low**: 1,460, 1,343, 565, 49
  - **None**: 4,310, 3,664, 1,416, 116

- **HR Adherence**
  - **RM** High vs. None: HR: 2.1 [1.8–2.5], p<0.001
  - **RM** High vs. Low: HR: 1.2 [0.9–1.5], p<0.111
  - **RM** Low vs. None: HR: 1.7 [1.5–2.1], p<0.001
Survival, Defibrillators

Survival, ICD

Survival, CRT-D

### Survival, ICD

**Number at Risk**

- **High:** 18,605
- **Low:** 18,854
- **None:** 45,139

**Number at Risk**

- **High:** 14,217
- **Low:** 13,602
- **None:** 31,704

**Years from Implant**

- 0
- 1
- 2
- 3
- 4

**RM Adherence**

- **High**
- **Low**
- **None**

**Probability of Survival**

<table>
<thead>
<tr>
<th>Years from Implant</th>
<th>High</th>
<th>Low</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>3</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
</tr>
</tbody>
</table>

### Survival, CRT-D

**Number at Risk**

- **High:** 14,217
- **Low:** 13,602
- **None:** 31,704

**Number at Risk**

- **High:** 13,342
- **Low:** 12,572
- **None:** 27,448

**Years from Implant**

- 0
- 1
- 2
- 3
- 4

**RM Adherence**

- **High**
- **Low**
- **None**

**Probability of Survival**

<table>
<thead>
<tr>
<th>Years from Implant</th>
<th>High</th>
<th>Low</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>3</td>
<td>0.85</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
<td>0.80</td>
<td>0.80</td>
</tr>
</tbody>
</table>

### Comparison of HRs

- **RM High vs. None**
  - HR: 2.5
  - [2.3–2.7], p<0.001
- **RM High vs. Low**
  - HR: 1.4
  - [1.3–1.5], p<0.001
- **RM Low vs. None**
  - HR: 1.8
  - [1.7–1.9], p<0.001
- **RM High vs. None**
  - HR: 2.4
  - [2.2–2.6], p<0.001
- **RM High vs. Low**
  - HR: 1.5
  - [1.4–1.6], p<0.001
- **RM Low vs. None**
  - HR: 1.6
  - [1.5–1.7], p<0.001
The Future CRT Device???
SUMMARY

- CIEDs have gone through a remarkable evolution over the years and are now smaller, smarter and have greater longevity.
- Leadless pacing, subcutaneous defibrillation and remote monitoring reduce complications, improve outcomes and likely survival.
- Leadless CRT devices, algorithms for prediction and prevention of heart failure and automated/remote programming are being developed.