Complications Following CRT Implantation: De Novo Procedures, Generator Changes, and Upgrades

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Disclosures: Consultant to Boston Scientific, Medtronic, Sorin, and St. Jude Medical
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBBB with QRS duration &gt; 150 msec</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>LBBB with QRS duration &gt; 120-150 msec</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Non-LBBB with QRS duration &gt; 150 msec</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>Non-LBBB with QRS duration 120-150 msec</td>
<td>I Ib</td>
<td>B</td>
</tr>
<tr>
<td>QRS &lt; 120 msec</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>
AMBITION

The Journey of a Thousand Miles Sometimes Ends Very, Very Badly.
Complications

- Pocket hematoma
- Lead dislodgement
- Phrenic nerve stimulation
- Infection
Pocket Hematoma

• 123 consecutive patients on chronic anticoagulation undergoing CRT-D implant

• Low risk patients: warfarin stopped 4 days prior to procedure and resumed evening prior to procedure

• High risk patients:
  • Continued warfarin (maintain INR 2-3)
  • Bridging therapy (IV heparin or LMWH pre and IV heparin post-procedure

High Risk Patients

• Mechanical prosthetic valve

• Atrial fibrillation patients undergoing full defibrillator threshold testing

• Atrial fibrillation patients with recent stroke, TIA, or systemic embolic event

• Venous thromboembolism within the past 3 months

Ghanbari H et al. PACE 2010; 33: 400-406
Pocket Hematoma

- 123 consecutive patients on chronic anticoagulation undergoing CRT-D implant

- Low risk patients: warfarin stopped 4 days prior to procedure and resumed evening prior to procedure

- High risk patients:
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  - Bridging therapy (IV heparin or LMWH pre and IV heparin post-procedure)

Ghanbari H et al. PACE 2010; 33: 400-406
Patients were eligible if they had an annual predicted risk of thromboembolism of 5% or more, were taking warfarin, and required non-emergency device (pacemaker or ICD) surgery.

Device surgery included implantation of a new device, pulse-generator change, lead replacement, or pocket revision.
Pocket Hematoma

• In the continued-warfarin group, INR on the day of surgery was ≤ 3.0 or lower, except for patients with one or more mechanical valves, for whom an INR of ≤ 3.5 was permitted.

• Patients in the heparin-bridging group discontinued warfarin 5 days before the procedure and started receiving full therapeutic doses of LMWH or IV heparin 3 days before the procedure.
  – For patients receiving bridging therapy with LMWH, the final dose was given the morning of the day before the procedure (i.e., >24 hours before the procedure).
  – For patients receiving bridging therapy with intravenous heparin, the infusion was discontinued at least 4 hours before surgery.
  – The administration of heparin was reinitiated 24 hours after the procedure and was continued until a therapeutic INR was achieved.

*NEJM* 2013; 368: 2084-2093
## Pocket Hematoma

- **Type of procedure:** *de novo* (47%) implant, generator change only (32%), generator change with additional procedure (21%)
- **Type of device:** CRT-D in 13%

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Heparin (n=338)</th>
<th>Warfarin (n=343)</th>
<th>RR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant hematoma</td>
<td>54 (16.0%)</td>
<td>12 (3.5%)</td>
<td>0.19 (0.10-0.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prolonged hospitalization</td>
<td>16 (4.7%)</td>
<td>04 (1.2%)</td>
<td>0.24 (0.08-0.72)</td>
<td>0.006</td>
</tr>
<tr>
<td>Interruption of anticoagulation</td>
<td>48 (14.2%)</td>
<td>11 (3.2%)</td>
<td>0.20 (0.10-0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Evacuation</td>
<td>09 (2.7%)</td>
<td>02 (0.6%)</td>
<td>0.21 (0.05-1.00)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*NEJM* 2013; 368: 2084-2093
LV Lead Dislodgement

- 226,724 patients in ICD NCDR database
  - 79,909 (35.2%) had CRT-D implant
- Dislodgement rates (acute, pre-discharge)
  - Single chamber: 0.56%
  - Dual chamber: 0.97%
  - CRT-D: 1.98%
- Increased LOS by 2.3 days; 11% associated with other complications

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined events</td>
<td>5.62</td>
<td>4.79-6.60</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>(cardiac arrest, tamponade,</td>
<td></td>
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</tr>
<tr>
<td>pneumothorax, infection)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital death</td>
<td>2.66</td>
<td>1.98-3.57</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Cheng A et al. JACC 2010; 56: 1651-1656
Quadripolar LV Leads

Dislodgement of the LV lead was observed in 6 (3.5%) of 170 patients

Tomassoni G et al. JCE 2013; 24: 449-455
Quadipolar LV Leads

- LV lead dislodgement: 1.4%

Crossley GH et al. *Heart Rhythm* (accepted; in press)
Active Fixation LV Leads

Crossley GH et al. Heart Rhythm 2010; 7: 472-478
Active Fixation LV Leads

Medtronic 20066 LV Lead

Yee R et al. *Heart Rhythm* 2014; 11: 1150-1155
Active Fixation LV Leads

Yee R et al. *Heart Rhythm* 2014; 11: 1150-1155
Phrenic Nerve Stimulation

Randhawa A et al. PACE 2014; 37: 1477-1484
Phrenic Nerve Stimulation

Crossley GH et al. *Heart Rhythm* (accepted; in press)
Phrenic Nerve Stimulation

- PNS: 7.2% (97% resolved with device reprogramming)

Crossley GH et al. *Heart Rhythm* (accepted; in press)
Rates of and Factors Associated With Infection in 200,909 Medicare Implantable Cardioverter-Defibrillator Implants
Results From the National Cardiovascular Data Registry

Jordan M. Prutkin, MD, MHS; Matthew R. Reynolds, MD, MSc; Haikun Bao, PhD; Jeptha P. Curtis, MD; Sana M. Al-Khatib, MD, MHS; Saurabh Aggarwal, MD; Daniel Z. Uslan, MD

<table>
<thead>
<tr>
<th>Adverse Infection</th>
<th>No Infection (n=197519)</th>
<th>Infection (n=3390)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematoma</td>
<td>1828 (0.925%)</td>
<td>127 (3.746%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lead Dislodgement</td>
<td>1884 (0.954%)</td>
<td>056 (1.652%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Circulation 2014; 130: 1037-1043
CIED Infection

• The burden of CIED infections is increasing over time (and out of proportion to the increase in implantation rates) and is associated with prolonged hospital stays and high costs.

Greenspon AJ et al. *JACC* 2011; 58: 1001-1006
CIED Infection

• Additionally, in August 2012, CMS published the Inpatient Prospective Payment System (IPPS) fiscal year 2013 final rule, which added surgical site infection following CIED implantation as a hospital acquired condition.

  – As such, CMS considers these infections to be reasonable preventable; thus, hospitals in the United States are no longer eligible for payment for treating these infections.

• PQRS # 393 took effect January 1, 2015

  – Infection within 180 days of CIED implantation

  – Failure to report = 2% payment cut starting 2017
CIED Infection

- A number of risk factors for CIED infection have been reported. These include the following:1-7
  - Male gender
  - Diabetes
  - Renal insufficiency
  - Use of oral anticoagulants
  - Fever within 24 hours of device implantation
  - Use of temporary pacing before device implantation
  - Presence of > 2 leads
  - Lack of antibiotic prophylaxis
  - A defibrillator procedure (as opposed to a pacemaker procedure)
  - A non-de novo procedure
  - Need for early pocket exploration

CIED Infection

• To date, the only intervention shown in the context of a randomized clinical trial to reduce CIED infections is the routine administration of intravenous antibiotics (targeted to gram positive organisms) prior to the incision.¹

• Unproven, yet commonly employed strategies
  – Intra-procedure pocket rinse with or without antibiotics
  – Pocket debridement (capsulectomy) at time of generator change
  – Post-procedure intravenous and/or oral antibiotics

• Available but not yet commonly used strategy
  – Tyrx antibacterial envelope: releases rifampin and minocycline into the generator pocket after CIED implantation

De Oliveira JC et al. Circ Arrhythm Electrophysiol 2009; 2: 29-34
Tyrx Antibacterial Envelope

• 624 consecutive patients who received an envelope¹
  – PM (35%), ICD (29%), and CRT-D (36%)
  – Mean follow-up: 1.9 months
  – 3 (0.48%) infections
    • None occurred in a patient undergoing a de novo procedure

• 260 consecutive patients who received an envelope because of >1 risk factor for infection propensity matched to a control cohort²
  – Minimum 3 months of follow-up
  – Infection occurred in 1 (0.4%) envelope patient and 19 (3%) controls, OR; 0.13 [0.02–0.95], p = 0.04

¹ Bloom HL et al. PACE 2011; 34: 133-142
² Kolek MJ et al. PACE 2013; 36: 354-361
• However, the risk of infection in any individual patient may be more dependent on the specific combination of risk factors rather than just the absolute number of risk factors.

• We conducted a study to examine the incidence and risk factors for CIED infection in a large contemporary cohort, developed a novel scoring index to risk stratify patients with respect to their risk of infection, and analyzed the effect of the TYRX Antibacterial Envelope on 6-month CIED infection rates.

Mittal S et al. *Heart Rhythm* 2014; 11: 595-601
## Patients, n=2891

<table>
<thead>
<tr>
<th>Age, years</th>
<th>77 ± 12</th>
<th>Device Used</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1802 (62%)</td>
<td>PPM</td>
<td>1740 (60%)</td>
</tr>
<tr>
<td>Co-Morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>2281 (79%)</td>
<td>CRT-PPM</td>
<td>48 (02%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>820 (28%)</td>
<td>CRT-ICD</td>
<td>426 (15%)</td>
</tr>
<tr>
<td>CHF</td>
<td>1084 (38%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>42 ± 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>53 ± 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6-Month Infection</td>
<td>No Infection</td>
<td>P Value</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Patients, n</td>
<td>33 (1.1%)</td>
<td>2858</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>74 ± 11</td>
<td>77± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>30 (91%)</td>
<td>1772 (62%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Co-Morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HTN</strong></td>
<td>27 (82%)</td>
<td>2254 (79%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>15 (46%)</td>
<td>805 (28%)</td>
<td>0.026</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>22 (67%)</td>
<td>922 (32%)</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>35 ± 12</td>
<td>42 ± 17</td>
<td>0.030</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>51 ± 15</td>
<td>53 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Device Type</td>
<td>6-Month Infection</td>
<td>No Infection</td>
<td>P Value</td>
</tr>
<tr>
<td>---------------</td>
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<td>---------</td>
</tr>
<tr>
<td><strong>PPM</strong></td>
<td>10 (30%)</td>
<td>1730 (61%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>CRT-PPM</strong></td>
<td>00 (00%)</td>
<td>48 (02%)</td>
<td></td>
</tr>
<tr>
<td><strong>ICD</strong></td>
<td>08 (24%)</td>
<td>669 (23%)</td>
<td></td>
</tr>
<tr>
<td><strong>CRT-ICD</strong></td>
<td>15 (46%)</td>
<td>411 (14%)</td>
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</tbody>
</table>
6-Month CIED Infection Rate: Stratified by Device Type

<table>
<thead>
<tr>
<th>Device Type</th>
<th>Patients</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT-P</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>PPM</td>
<td>1740</td>
<td>10</td>
</tr>
<tr>
<td>ICD</td>
<td>677</td>
<td>8</td>
</tr>
<tr>
<td>CRT-D</td>
<td>426</td>
<td>15</td>
</tr>
</tbody>
</table>

Mittal S et al. *Heart Rhythm* 2014; 11: 595-601
6-Month CIED Infection Rate: Stratified by Procedure Type

- De Novo: 1.1% (19 infections out of 1,802 patients)
- Generator: 0.9% (8 infections out of 929 patients)
- Upgrade: 3.5% (4 infections out of 115 patients)
- Other: 4.4% (2 infections out of 45 patients)

Mittal S et al. *Heart Rhythm* 2014; 11: 595-601
6-Month CIED Infection Rate: Stratified by Device and Procedure Type

Mittal S et al. *Heart Rhythm* 2014; 11: 595-601
6-Month CIED Infection Rate: Pre-Envelope vs. Envelope Era

Mittal S et al. *Heart Rhythm* 2014; 11: 595-601

- **Envelope Era**: 1240 patients, 275 (22%) envelope, 8 (0.6%) infections
- **Pre-Envelope Era**: 1651 patients, 25 (1.5%) infections

**Graph Details**
- **Y-axis**: Freedom from 6-month infection
- **X-axis**: Time to Infection (days)
- **Statistical Significance**: p=0.029
6-Month CIED Infection Rate: Propensity Analysis

Infection rate: 1.1%
Infection rate: 3.6%

Freedom from 6-month Infection

Time to Infection (days)

<table>
<thead>
<tr>
<th>Envelope Era, n</th>
<th>275</th>
<th>270</th>
<th>267</th>
<th>262</th>
<th>260</th>
<th>257</th>
<th>256</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Envelope Era, n</td>
<td>275</td>
<td>267</td>
<td>265</td>
<td>261</td>
<td>259</td>
<td>257</td>
<td>255</td>
</tr>
</tbody>
</table>

6-Month CIED Infection Rate: Limited to ICD and CRT-D Patients

# Logistic Regression Model

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Point Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Pocket Re-exploration</td>
<td>11</td>
</tr>
<tr>
<td>Male Gender</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
</tr>
<tr>
<td>Device Upgrade</td>
<td>2</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>GFR &lt; 60 ml/min</td>
<td>1</td>
</tr>
</tbody>
</table>

C-index: 0.72; 95% CI: 0.61-0.83  
Mittal S et al. *Heart Rhythm* 2014; 11: 595-601
6-Month CIED Infection Rate: Limited to ICD and CRT-D Patients

Pre-Envelope Era
- 0-7: 1.0%
- 8-14: 3.4%
- 15-25: 11.1%

Envelope Era
- 0-7: 1.4%
- 8-14: 0.7%
- 15-25: 0.0%

Composite Risk Score

Pre-Envelope, n = 204
Envelope, n = 140
Envelope Use, n (%)
- 47 (34%)
- 16 (40%)
- 21 (88%)

Mittal S et al. *Heart Rhythm* 2014; 11: 595-601
Randomized Clinical Trials

- World-wide Randomized Antibiotic Envelope CIED Infection Prevention Trial (WRAP-IT)
  - Nearly 7000 patients undergoing de novo CRT implant or any CIED (PPM or CRT device) generator change
  - Randomized: envelope vs. no envelope
    - Second generation envelope: fully absorbable (in about 9 weeks) polyarylate polymer
  - Primary endpoint: CIED infection at 12-months
    - Last enrolled patient followed out to 12 months
Randomized Clinical Trials

- Prevention of Arrhythmia Device Infection Trial (PADIT) Cluster Crossover Study
  - Antibiotic strategy randomized per center
    - Conventional antibiotic strategy
    - Incremental antibiotic strategy
  - 6 months, then crossover to alternative strategy
    - Continue alternating every 6 months
  - Cohort: 10800 replacement or upgrade procedures
  - Primary endpoint: hospitalization for device infection
Randomized Clinical Trials

• PADIT Antibiotic Strategy

  – Conventional antibiotic strategy
    • Pre-op administration of either cefazolin 1-2 gm IV OR vancomycin 1-1.5 gm IV

  – Incremental antibiotic strategy
    • Pre-op administration of either cefazolin 1-2 gm IV AND vancomycin 1-1.5 gm IV; AND
    • Intraoperative antibacterial wash of 50,000 units Bacitracin powder in saline; AND
    • 48 hours of post-op oral antibiotics
Complication Rates Associated With Pacemaker or Implantable Cardioverter-Defibrillator Generator Replacements and Upgrade Procedures

Results From the REPLACE Registry

Jeanne E. Poole, MD; Marye J. Gleva, MD; Theofanie Mela, MD; Mina K. Chung, MD; Daniel Z. Uslan, MD; Richard Borge, MD; Venkateshwar Gottipaty, MD, PhD; Timothy Shinn, MD; Dan Dan, MD; Leon A. Feldman, MD; Hanscy Seide, MD; Stuart A. Winston, DO; John J. Gallagher, MD; Jonathan J. Langberg, MD; Kevin Mitchell, RN, BS; Richard Holcomb, PhD; for the REPLACE Registry Investigators
Major Complications

Poole JE et al. Circulation 2010; 122: 1553-1561
Major Complications

Poole JE et al. *Circulation* 2010; 122: 1553-1561
Conclusions (1)

- Multiple randomized clinical trials support the role of CRT in appropriate patients
- Procedure continues to be plagued by certain complications
  - Acute
    - Pocket hematoma
    - LV lead dislodgement
    - Phrenic nerve pacing
  - Chronic: infection
    - Minimize pocket re-explorations
Conclusions (2)

• Strategies to avoid complications
  1. Pocket hematoma
     • Avoid bridging therapy in patients on anticoagulation
  2. LV lead dislodgement
     • LV lead shape tailored to patient’s anatomy
     • Innovative active fixation design
  3. Phrenic nerve pacing
     • Quadripolar LV leads
Conclusions (3)

• Infection remains the most feared complication
  1. Avoid early pocket re-exploration
  2. Anticipate need for a CRT device
  3. Upcoming clinical trials will define role of
     • Tyrx antibacterial envelope
       – In interim, consider use in patients at moderate-high risk of CIED infection
     • Pocket flushing and post-operative antibiotics
Problem Solving Requires New Approaches

“We can’t solve problems by using the same kind of thinking we used when we created them.” – Albert Einstein