Medical Device Surveillance Using “Big Data” Methods

Yale FDA Safety Signal Detection Project
MDEpiNet Live Webcast
January 5th, 2016
Yale Team

- Joseph Ross, MD, MHS
- Harlan Krumholz, MD, SM
- Jonathan Bates, PhD
- Shu-Xia Li, PhD
- Craig Parzynski, MS
- Erin Singleton, MPH

- Expertise from wider CORE community of clinicians and scientists ...
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Tom Gross
Ben Eloff
Vahan Simonyan

**American College of Cardiology (ACC)**
Fred Masoudi
Dick Shaw

**MDEpiNet Methodology Workgoup**
Sharon-Lise Normand
Fred Resnic

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Myoung Kim
Kade Etter
Andrew Yoo
Purpose of Today’s Meeting

- Provide study methods and analytic approaches, including explanation of the endpoints identified and decision on appropriate ‘comparators’
- Share preliminary results from the novel and traditional analytic methods
- Describe options for evaluating the quality of propensity score matching
- Invite the MDEpiNet community to provide feedback and suggest alternate approaches
FDA-Yale Background and Objectives

• FDA is actively strengthening national post-market surveillance system

• Goal is to understand potential uses, advantages of big data analytic approaches for detecting device-related safety (and effectiveness?) signals

• Methods will have wider implications once UDI system is adopted by routinely collected health data systems
Safety Signal Detection Project

• Development of signal detection “use case” that will be undertaken within the Yale BD2K Center
• Application of both traditional and “big data” analytic methods
• Partnered with ACC-NCDR to utilize Medicare-linked ICD registry, 2006-2010 data on implantations with follow-up data through 2011
• Working within MDEpiNet collaboration …
Yale Big Data To Knowledge (BD2K)

- Robust Computing Infrastructure to process & safely store data
- World-Class Data Scientists develop & apply novel analytic methods
- Strong Partnerships with data owners & policy makers around the world
- Clinical Capability to inform research and validate findings
Approach based around “use cases” that address high-impact questions

1. Define use case
   - Articulate high-impact questions

2. Acquire data
   - Apply to public / private sources for access to clinical & claims data

3. Data preparation
   - Store securely
   - Pre-processes
   - Share with collaborators

4. Analysis
   - Multiple teams of collaborators apply and develop novel techniques

5. Interdisciplinary problem-solving
   - Refine models to ensure clinically-meaningful output

6. Disseminate findings
   - Write papers
   - Develop posters
Types of “use cases” to pursue

<table>
<thead>
<tr>
<th></th>
<th><strong>Classification</strong></th>
<th>Identify “phenotypes” of disease and of health systems with novel approaches to classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><strong>Signal detection</strong></td>
<td>Identification of meaningful signals from background noise</td>
</tr>
<tr>
<td>3</td>
<td><strong>Prediction</strong></td>
<td>Predict outcomes to facilitate targeting of existing interventions &amp; those in development</td>
</tr>
<tr>
<td>4</td>
<td><strong>Causation</strong></td>
<td>Develop methods that allow causal inference from large observational data sets</td>
</tr>
<tr>
<td>5</td>
<td><strong>Discovery</strong></td>
<td>Explore relationships between data and understand how they interact</td>
</tr>
</tbody>
</table>
Research Objectives

• Characterize “signals detected”: device-related complications / outcomes after ICD therapy

• Utilize big data analytic approaches for signal detection of device-related complications / outcomes after ICD therapy

• Compare the big data analytic approaches with traditional analytic approaches for signal detection of device-related complications / outcomes after ICD therapy
Safety Signal Detection Project: ICDs?

Advantages
- Many manufacturers, models
- Highly effective therapy
- But not without risks: ~10% experience in-patient complications, ~10% per year long-term events

Disadvantages
- Many manufacturers, models
- No information on leads
- Only claims data for longitudinal events
ICD Sample in NCDR

- Many manufacturers, models
- Reviewed and reclassified as needed all other implanted ICDs, ensuring correct designation as single chamber vs. dual chamber vs. CRT

<table>
<thead>
<tr>
<th>Device Type</th>
<th>Manufacturers, No.</th>
<th>Model Names, No.</th>
<th>Model Numbers, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Chamber</td>
<td>6</td>
<td>~20</td>
<td>~40</td>
</tr>
<tr>
<td>Dual Chamber</td>
<td>6</td>
<td>~20</td>
<td>~45</td>
</tr>
<tr>
<td>CRT</td>
<td>6</td>
<td>~20</td>
<td>~45</td>
</tr>
</tbody>
</table>
ICD Sample in NCDR

- Included patients who received any top 10 implanted ICD over the whole period

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</tr>
</thead>
<tbody>
<tr>
<td>Single Chamber</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Dual Chamber</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>CRT</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Defining Safety Endpoints

• Death

• Any Adverse Event
  • Inpatient/outpatient visit for ICD site reoperation
<table>
<thead>
<tr>
<th>Reoperation Category</th>
<th>Identified Through</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pocket reoperation</td>
<td>Specific ICD9 Procedure Code or CPT Code</td>
<td>Any</td>
</tr>
<tr>
<td>Generator replacement (± lead replacement)</td>
<td>Select ICD9 Codes in combination with Specific ICD9 Procedure Code or CPT Codes:</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td><em>Mechanical complications with system revisions</em></td>
<td></td>
</tr>
<tr>
<td>Lead replacement only (no generator replacement)</td>
<td>Select ICD9 Codes in combination with Specific ICD9 Procedure Code or CPT Codes:</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td><em>Mechanical complications with system revisions</em></td>
<td></td>
</tr>
</tbody>
</table>
Defining Safety Endpoints

• Death

• Any Adverse Event
  • Inpatient/outpatient visit for ICD site reoperation
  • ED visit/hospitalization for an ICD-related adverse event, defined as:
    • Events resulting from the implantation, presence, performance, or failure of ICD therapy
    • But do not involve re-operation
## ED/Admission for ICD-Related AEs

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>Identified Through</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Failure</td>
<td>Select ICD9 Codes from CCs 78, 79, 92, 93: Respiratory failure, cardio-respiratory failure, shock, heart arrhythmia, other rhythm &amp; conduction disorders</td>
<td>Any</td>
</tr>
<tr>
<td>Infections</td>
<td>Select ICD9 Codes from CCs 2, 6, 85, 86 152: Septicemia, specific gram-positive and gram-negative infections, heart and heart valve infections (endocarditis, myocarditis, pericarditis), and cellulitis of neck or trunk</td>
<td>Any</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Select ICD9 Codes from CCs 55, 58, 59: Major depressive, depression, and anxiety disorders</td>
<td>Any</td>
</tr>
<tr>
<td>Other Device Malfunctions</td>
<td>Select ICD9 Codes from CCs 164: Malfunctioning cardiac device / graft / pacemaker</td>
<td>Any</td>
</tr>
</tbody>
</table>
## ED/Admission for ICD-Related AEs

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>Identified Through</th>
<th>Time Frame</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural Complications 1</td>
<td>Select ICD9 Codes from CCs 104, 105, 106, 164: Aortic aneurysms, aortic dissections, cardio-embolic events (including PE and DVT), hemorrhage, and other surgical complications (wound infection, air embolism)</td>
<td>90 days</td>
</tr>
<tr>
<td>Procedural Complications 2</td>
<td>All ICD9 Codes from CC 114: Pneumothorax or pleural effusion</td>
<td>90 days</td>
</tr>
<tr>
<td>Procedural Complications 3</td>
<td>Select ICD9 Codes from CC 131: Acute renal failure</td>
<td>90 days</td>
</tr>
<tr>
<td>Procedural Complications 4</td>
<td>Select ICD9 Codes from CC 165: Other surgical complications</td>
<td>90 days</td>
</tr>
</tbody>
</table>
Brief Methods

• All analyses stratified by ICD-type (single-chamber, dual-chamber, CRT)

• Will start with overall analysis to determine whether there is a signal to detect ...

• Then will compare and contrast 3 methods
  • Traditional time-to-event methods, risk-adjusted for patient and procedural characteristics
  • DELTA method, prospective propensity score matching
  • Big Data methods
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Top 10 Dual-Chamber ICDs
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>71,948</td>
</tr>
<tr>
<td>Age - Mean (SD)</td>
<td>75.2 ± 6.4</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>17,162 (23.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>64,215 (89.3)</td>
</tr>
<tr>
<td>Black</td>
<td>5,017 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>2,716 (3.8)</td>
</tr>
<tr>
<td>Admission Reason</td>
<td></td>
</tr>
<tr>
<td>Admitted for Procedure</td>
<td>46,062 (64)</td>
</tr>
<tr>
<td>Cardiac - CHF</td>
<td>5,171 (7.2)</td>
</tr>
<tr>
<td>Cardiac - Other</td>
<td>18,168 (25.3)</td>
</tr>
<tr>
<td>Non-Cardiac</td>
<td>2,547 (3.5)</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>13,861 (19.3)</td>
</tr>
<tr>
<td>II</td>
<td>35,936 (49.9)</td>
</tr>
<tr>
<td>III</td>
<td>20,597 (28.6)</td>
</tr>
<tr>
<td>IV</td>
<td>1,554 (2.2)</td>
</tr>
<tr>
<td>Atrial Fibrillation or Flutter</td>
<td>26,105 (36.3)</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>37,127 (51.6)</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>55,149 (76.7)</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>12,910 (17.9)</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>16,476 (22.9)</td>
</tr>
<tr>
<td>Renal Failure Dialysis</td>
<td>2,571 (3.6)</td>
</tr>
<tr>
<td>ICD Indication</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>51,241 (71.2)</td>
</tr>
<tr>
<td>Secondary</td>
<td>20,707 (28.8)</td>
</tr>
<tr>
<td>Optimal Medical Therapy Received</td>
<td>46,258 (64.3)</td>
</tr>
</tbody>
</table>

* All included in DELTA method propensity score match.
<table>
<thead>
<tr>
<th>Safety Events</th>
<th>Dual chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, %</td>
<td>9.8 – 12.2</td>
</tr>
<tr>
<td>Outpt/Inpt ICD Reoperation, %</td>
<td>4.0 – 6.9</td>
</tr>
<tr>
<td>Pocket Reop</td>
<td>0.2 – 0.5</td>
</tr>
<tr>
<td>Gen ReplaceOp</td>
<td>1.9 – 4.9</td>
</tr>
<tr>
<td>Lead ReplaceOp</td>
<td>1.1 – 1.9</td>
</tr>
<tr>
<td>ED/Admit ICD-related AEs, %</td>
<td>5.3 – 6.6</td>
</tr>
<tr>
<td>Device failure</td>
<td>7.2 – 8.7</td>
</tr>
<tr>
<td>Infection</td>
<td>3.0 – 3.9</td>
</tr>
<tr>
<td>Behavioral</td>
<td>0.2 – 0.4</td>
</tr>
<tr>
<td>Oth device malfxn</td>
<td>1.6 – 2.7</td>
</tr>
<tr>
<td>Proc comp 1</td>
<td>0.3 – 0.6</td>
</tr>
<tr>
<td>Proc comp 2</td>
<td>0.1 – 0.3</td>
</tr>
<tr>
<td>Proc comp 3</td>
<td>0.0 – 0.0</td>
</tr>
<tr>
<td>Proc comp 4</td>
<td>0.2 – 0.5</td>
</tr>
<tr>
<td>Any Reop or AE, %</td>
<td>8.5 – 10.5</td>
</tr>
</tbody>
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DELTA Method

• Computerized automated safety surveillance tool, the Data Extraction and Longitudinal Trend Analysis (DELTA) system, that was developed and validated with support from MDEpiNet

• Several publications
  • Reproducing analyses from Resnic et al. 2010, JAMA

• Prospective propensity score matching
  • Clinically relevant variable from literature and experts
  • Greedy matching algorithm w/ .05 caliper
  • Matched within 6 months procedure date

• Quarterly analysis of adverse event rates of “qualifying” devices to matched devices, from among all others
  • Difference of proportions w/ CI (using Wilson method)
  • Overall alpha of 0.10, after accounting for multiple comparisons

• Sensitivity analyses when safety alerts identified (did not implement)

Covariate Balance, ICD 145
Safety Analyses, ICD 145

Any AE / Death

Any Death

Any AE
Covariate Balance, ICD 207
Safety Analyses, ICD 207

Any AE / Death

Any Death

Any AE
Covariate Balance, ICD 323
Safety Analyses, ICD 323

Any AE / Death

Any AE

Any Death
Brief Methods

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  • DELTA method, prospective propensity score matching
  • Big Data methods
Big Data Method

• Use sparse linear model for propensity score
  • SVM with L1 regularization
  • Start with many variables, then increase regularization penalty to increase covariate balance

• Matching
  • Use difference between decision values, large caliper
  • Use greedy 1-1 matching within 6mos implant date

• Cumulative analysis
  • CI generated for difference in proportions per quarter between exposed and matched
  • Wilson score method with continuity correction; significance level fixed at alpha=0.01
Propensity Score Covariates

• Analysis 1.
  • Patient demographics, clinical history, ICD indication, adverse events during implant stay
  • Period of implant
  • Operator certification, experience
  • Sites are dummy coded
  • 80 binary, 19 continuous, 52 categorical

• Analysis 2.
  • Same as Analysis 1, but with site indicator removed

• Analysis 3.
  • Dynamic feature selection with covariates from Analysis 2
Analysis 1
Analysis 1, ICD 145
Analysis 1
Propensity score covariates: Analysis 2

- Same as Analysis 1, but with no site indicator
Analysis 2
Analysis 2, ICD 145
Analysis 2, ICD 145
Analysis 2
Analysis 2, ICD 207
Analysis 2, ICD 207
Analysis 2, ICD 207
Propensity score covariates: Analysis 3

- Dynamic feature selection with covariates from Analysis 2
Analysis 3, dynamic feature selection
Analysis 3, ICD 145
Analysis 3, ICD 145
Analysis 3, ICD 145
Analysis 3, dynamic feature selection
Analysis 3, ICD 323
Analysis 3, ICD 323
Analysis 3
Next Steps

• Complete analyses ...
• Need to check “matched” groups – double-check that 2 methods used different comparators
• Finalize method to manage multiple comparisons
  • How long should active surveillance go on for?
  • Is 3 years (post-implantation) time enough?
Big Picture, for feedback

• How to compare methods?
  • Is it a matter of matching and variable balance?

• How to incorporate other safety information?
  • Complaint rates ascertained from MAUDE?

• Does Big Data move us forward?
  • Do “selected” variables make sense? Clinically?