The Critical Path & Cardiac Safety 2009
Plenary Presentation:
“ The Academic View ”

Cardiac Safety Research Consortium
Annual Meeting
Bethesda , MD
October 29, 2009

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Acknowledgments:

Dr. Richard Kovacs
Dr. Mark Carlson
Mitch Krucoff
The NCDR
The Triumvirate in Cardiac Safety

Industry Sponsors

Regulators - FDA

Academia
Academia View of The Individual Goals

• Industry Sponsors
  – Speed approval to maximize profitability
  – In best interest discover and avoid safety issues by thorough preclinical testing (potential harm for patients, liability and corporate image)
    - Generally less motivated for post-market surveillance of off-label uses
• Regulators - FDA
  – Carefully assess submission package according to policy and procedure. Somewhat rigid careful and thorough multidisciplinary body procedurally driven.
  – Identify safety issues (potential harm for patients, weigh in light of public safety, suggest monitoring strategies)
• Academia
  – Provide focused expert input (with transparency regarding conflicts of interest)
  – Serve on DSMB / DMC / CEC / Adjudication committees
  – Contribute to guideline development, whitepapers, writing groups
  – Act as a “trusted third party” - e.g. DCRI role in ECG Warehouse
  – Represent the patient - express opinions as to what might be acceptable safety risks in the clinic.
The Academic Balancing Act

- Intellectual curiosity
- Deliberate pace
- Publish results
- Career development based on discovery of safety signals
- Conflicts of interest

- Sponsor confidentiality
- Tight timelines
- Publication plans
- Appropriate balance of risk and benefit in clinical use
- Conflicts of interest
What has worked

• Individual contributions by academics to consensus documents, white papers, and intellectual discussions.
• Service as DSMB members, advisors, etc. both to sponsors and to the regulatory agencies.
• Service as a “trusted third party” for a data warehouse – as well as the demonstration of a viable public / private partnership as a vehicle for such a Registry or data repository.
Cardiac Safety Research Consortium

• Focused on QT Safety Effort earlier in decade
  – ECG Warehouse – collaborative arrangement (CREDA) with Mortara instruments (ECG manufacturer), FDA, and Duke
  – Academics advising drafts of ICH E14 document
    • Guides QT assessment in drug development worldwide
    • Collaboration on ECG warehouse
    • Co-authors on white papers addressing cardiac safety. Example: QT assessment in cancer drug development (Am Heart J 2009;157:827-836)
The Push for Comparative Effectiveness Research

Total Federal Spending for Medicare and Medicaid Under Different Assumptions About Excess Cost Growth, 1966 to 2050

(Percentage of gross domestic product)

- Excess Cost Growth of 2.5%
- Excess Cost Growth of 1.5%
- No Excess Cost Growth

Diagram showing:
- Large Health Care Databases
- Other Evidence and Studies
- Outcomes Research
- Other Evidence and Analysis
- Comparative Effectiveness Analysis

Image of a political event with a group of people and a flag.
2007 CBO Report

House Members Introduce Bill To Fund Comparative Effectiveness Studies On Medications, Medical Devices

Main Category: Public Health News
Article Date: 18 May 2007 - 2:00 PDT

Legislation (HR 2184) introduced on Tuesday by Reps. Tom Allen (D-Maine) and Jo Ann Emerson (R-Mo.) would provide $3 billion over five years to fund comparative effectiveness studies conducted by the Agency for Healthcare Research and Quality on drugs, medical devices and treatments, CQ HealthBeat reports. Funding

As part of ARRA: $1.1 billion set aside for comparative effectiveness research (CER)
Health Care Reform

CER & Cardiac Safety

True “Tipping Point” for huge leaps in Cardiac Safety

• ARRA Grants for CER
  – Builds infrastructure also valuable for cardiac safety
  – Funding for longitudinal databases
• Improvement in patient matching
  – ? Ever attaining the holy grail of UPI !
• Increased alignment of payers (CMS), FDA, Industry and Academics
Another Tipping Point for Cardiac Safety

- Paper based records being replaced with:
  - Electronic Health Records
  - Device Telephonic Assessments
  - Computerized Databases
  - Standardized Data Definitions
  - Robust National Registries – although siloed and episodic/procedure based
  - Development of Linked Databases for true longitudinal assessment
Siloed Enterprises to Collaboratives

- “Mission Statement” of CSRC
- With CER infrastructure, IT developments, and the increased penetration of EHRs
  - Increasing “ease” of post-market surveillance
- Government now with increasing focus on CER but also Medical Errors and Safety
- Financial support ARRA and elsewhere along with the political climate offers huge opportunity
- We must through avenues such as CSRC build the collaboratives to leverage these wins
Registries for Evidence Development and Dissemination

Concept → Clinical Evidence → Multicenter Clinical Registries → Guidelines → Performance Indicators

Outcomes → Multicenter Clinical Registries → Measurement + Feedback → QI Initiatives

Adapted from Califf RM, Peterson ED et al. JACC 2002;40:1895-901
Bill Weintraub: NCDR Founding Father, CV Epidemiologist, Clinical Trialist and Outcomes Thought Leader
“Science tells us what we can do;
Guidelines what we should do;
Registries what we are actually doing.”

Registries what we will be doing!

Registries what we are doing safely!
Timeline of building a true National CardioVascular Data Registry

- CathPCI Registry
- ICD Registry
- CARE Registry
- ACTION Registry
- SPECT MPI Registry
- IC3 Registry
- IMPACT Registry
- ICD Long Registry
- EP Registry
- PAD Registry

- 1998
- 2004
- 2005
- 2006
- 2007
- 2008
- beyond
<table>
<thead>
<tr>
<th>Hospital/Practice</th>
<th>Name</th>
<th># of Participants</th>
<th># of Patient Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>CathPCI</td>
<td>1200</td>
<td>10 million</td>
<td></td>
</tr>
<tr>
<td>ICD</td>
<td>1500</td>
<td>400,000</td>
<td></td>
</tr>
<tr>
<td>ACTION-GWTG</td>
<td>425</td>
<td>150,000</td>
<td></td>
</tr>
<tr>
<td>CARE</td>
<td>160</td>
<td>15,000</td>
<td></td>
</tr>
<tr>
<td>IMPACT</td>
<td>Launched July 2009</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Practice</td>
<td>IC3</td>
<td>600</td>
<td>400,000</td>
</tr>
</tbody>
</table>

Influence of NCDR Research

• Public Policy
• Quality Improvement: Guideline Adherence
  – Reducing D2B Times
  – Clinical Indications & Outcomes
• Quality Improvement: Translational Research
• Post Market Surveillance
  – Adverse Events in Closure Devices
• New Technologies and Effectiveness
  – Diffusion of New Technology
## Executive Summary Performance Metrics

### PCI Quality Measures

1. **Proportion of STEMI Pts with DBT \(\leq 90''\)**
   - **My Hospital:** 65.5\% (Rank: 87 of 389, Rank Percentile: 78)
   - The proportion of primary PCI patients with DBT (door to balloon time) \(\leq 90\) minutes. The goal is to have a DBT of \(\leq 90\) minutes for all non-transferred patients pts having an ST elevated MI and having primary PCI. [Detail Line: 1767]

2. **Risk Adjusted Mortality**
   - **My Hospital:** 1.02\% (Rank: 118 of 366, Rank Percentile: 68)
   - Your hospital’s PCI mortality rate adjusted using the ACC-NCDR® risk adjustment model [Detail Line: 1732]

3. **Incidence of Vascular Complications**
   - **My Hospital:** 2.7\% (Rank: 286 of 401, Rank Percentile: 30)
   - Includes procedures with at least one vascular complication. [Detail Line: 2029]
Trends : Age & PCI Mortality

Singh M et.al Circ Cardiovasc Intervent 2009;2:20-26
## Pre-CathPCI Risk Models

<table>
<thead>
<tr>
<th>Label</th>
<th>Full Model †</th>
<th></th>
<th>Precath Simple Model</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O.R.</td>
<td>95% CI</td>
<td>Wald Chi-Square</td>
<td>O.R.</td>
</tr>
<tr>
<td>Age (for age&lt;=70) ‡</td>
<td>1.55</td>
<td>1.44</td>
<td>1.69</td>
<td>115.33</td>
</tr>
<tr>
<td>Age (for age&gt;70) ‡</td>
<td>1.71</td>
<td>1.57</td>
<td>1.88</td>
<td>125.80</td>
</tr>
<tr>
<td>Previous History - CHF</td>
<td>1.29</td>
<td>1.13</td>
<td>1.47</td>
<td>13.85</td>
</tr>
<tr>
<td>Peripheral Vascular</td>
<td>1.53</td>
<td>1.35</td>
<td>1.74</td>
<td>42.39</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>1.48</td>
<td>1.31</td>
<td>1.66</td>
<td>43.04</td>
</tr>
<tr>
<td>GFR for stemi ‡</td>
<td>0.77</td>
<td>0.74</td>
<td>0.80</td>
<td>181.90</td>
</tr>
<tr>
<td>Cardiogenic Shock at Admission</td>
<td>8.35</td>
<td>7.40</td>
<td>9.44</td>
<td>1168.28</td>
</tr>
<tr>
<td>NYHA Class IV for STEMI</td>
<td>1.21</td>
<td>1.05</td>
<td>1.39</td>
<td>6.74</td>
</tr>
<tr>
<td>Urgent PCI Status-STEMI §</td>
<td>1.09</td>
<td>0.64</td>
<td>1.83</td>
<td>0.09</td>
</tr>
<tr>
<td>Emergency PCI Status-STEMI §</td>
<td>2.07</td>
<td>1.30</td>
<td>3.31</td>
<td>9.24</td>
</tr>
<tr>
<td>Salvage PCI Status-STEMI §</td>
<td>14.55</td>
<td>8.39</td>
<td>25.21</td>
<td>91.08</td>
</tr>
</tbody>
</table>

† Full model also includes Previous PCI, PreOp IABP, Ejection Fraction, Coronary Lesion >= 50%: Subacute Thrombosis (Y/N), Highest Risk Pre-Procedure TIMI Flow = none, Diabetes/Control, Highest Risk Lesion: SCAI Lesion Class 2 or 3, BMI for STEMI/non STEMI, Previous Dialysis for STEMI/non STEMI, Highest Risk Lesion Segment Category for STEMI/non STEMI. ‡ Per 10 unit increase. § Versus Elective
The doctor has explained to me that there are risks with this procedure. It is possible that unexpected things may happen. These might include, but are not limited to:

Risk of In-Hospital Complication
Ranges of outcome(s) for patients with similar clinical profiles

<table>
<thead>
<tr>
<th>Death</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>&gt;= 20</td>
</tr>
</tbody>
</table>

Percent (%) chance.
## In-Hospital Outcomes - STEMI vs. NSTEMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>STEMI (n=20,998)</th>
<th>NSTEMI (n=31,774)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death*</td>
<td>5.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Re-infarction</td>
<td>1.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>CHF</td>
<td>6.8%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>6.2%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.8%</td>
<td>0.7%</td>
</tr>
<tr>
<td>RBC Transfusion#</td>
<td>6.4%</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

* Unadjusted mortality
# Transfusion among non-CABG patients

ACTION Registry-GWTG DATA: January 1 – December 31, 2008
Excessive Dosing of Anticoagulants by Age

Alexander KP, et. al. JAMA 2005
% DES Use NCDR CathPCI

Overall

"Basket-Late" FDA Statement
% DES Use NCDR CathPCI

- Age<65
- Age=65-75
- Age>=75

Calendar Year/Quarter:

- 2003Q1
- 2003Q3
- 2004Q1
- 2004Q3
- 2005Q1
- 2005Q3
- 2006Q1
- 2006Q3
- 2007Q1
- 2007Q3
- 2008Q1
- 2008Q3

%DES

- 0
- 20
- 40
- 60
- 80
- 100
Percutaneous Coronary Interventions in Facilities without On-Site Cardiac Surgery: A Report from the National Cardiovascular Data Registry (NCDR)

## Safety and Efficacy of PCI Without On-site Surgical Back-up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total N</th>
<th>Favors Off-Site</th>
<th>Favors On-Site</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality - overall</td>
<td>308,120</td>
<td></td>
<td></td>
<td>0.90 (0.72 - 1.14)</td>
<td>0.388</td>
</tr>
<tr>
<td>Mortality - primary PCI pts</td>
<td>33,008</td>
<td></td>
<td></td>
<td>0.97 (0.75 - 1.25)</td>
<td>0.807</td>
</tr>
<tr>
<td>Mortality - non-primary PCI pts</td>
<td>275,098</td>
<td></td>
<td></td>
<td>0.86 (0.63 - 1.16)</td>
<td>0.319</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>308,121</td>
<td></td>
<td></td>
<td>0.60 (0.37 - 0.98)</td>
<td>0.042</td>
</tr>
<tr>
<td>Mortality - pts not requiring emergency CABG</td>
<td>306,962</td>
<td></td>
<td></td>
<td>0.93 (0.73 - 1.17)</td>
<td>0.533</td>
</tr>
</tbody>
</table>

### Sensitivity Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total N</th>
<th>Favors Off-Site</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality - impute to Yes for Off-site *</td>
<td>308,161</td>
<td></td>
<td>1.21 (0.95 - 1.54)</td>
<td>0.120</td>
</tr>
<tr>
<td>Mortality - impute to No for Off-site **</td>
<td>308,161</td>
<td></td>
<td>0.88 (0.70 - 1.11)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Odds Ratio (OR): outcomes for patients at Off-Site (vs. On-Site) facilities, adjusting for within site correlations and potential confounding variables

* Worst case scenario: patients with missing mortality data were considered as all died
* Best case scenario: patients with missing mortality data were considered as all alive
Risk of Local Adverse Effects Following Cardiac Catheterization by Hemostasis Device and Gender

A Report from the NCDR in Partnership with the FDA

Dale Tavris, Syamal Dey, Albrecht Gallauresi, Richard Shaw, William Weintraub, Kristi Mitchell, Ralph Brindis

Grant from Office of Women’s Health, Food and Drug Administration
Certification and Outcomes with ICDs

Issues

• Physician specialty impact on ICD outcomes = unknown

Findings

• ICD implantation by non-electrophysiologist associated with higher risk of complications and lower likelihood to receive an evidenced based CRT-D

Curtis et al., JAMA 2009; 301 (16) 1661:1670
Outcomes Following Coronary Stenting: A National Study of Long Term, Real-World Outcomes of Bare-Metal and Drug-Eluting Stents


Duke Clinical Research Institute
Duke University Medical Center
Goal and Population

Goal
- To examine comparative effectiveness and safety of DES vs BMS in a national PCI cohort

Study population
- All PCI pts ≥ 65 yo in NCDR CathPCI 1/04-12/06
- Follow up obtained through linkage to CMS inpatient claims data using indirect identifiers; 76% matched

Final cohort
- 262,700 pts
- 83% DES; 46% Cypher, 55% Taxus
Analysis

• **30 month outcomes**
  – Death, MI, Stroke, Revascularization, Major bleeding
  • Overall and in important subgroups

▪ **Outcomes adjustments**
  – Inverse propensity weighted model (102 covariates)
  – Cox proportional hazards model (60 covariates)

▪ **Sensitivity analyses**
  • Results in ‘RCT-like’ population
  • Non-CV ‘cause’ of death
Outcomes Following Coronary Stenting
A National Study of Long Term, Real-World Outcomes of Bare-Metal and Drug-Eluting Stents
Conclusions

• NCDR data can be linked to claims data
• Data analysis allows a robust, longitudinal assessment of clinical effectiveness
• Comparing outcomes of DES to BMS at 30 months
  – No major DES safety concerns
  – Lower death and MI rates in DES patients
  – Slightly lower revascularization, bleeding rates
  – Similar stroke rates
CER “Definition”

- CER is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions.

- The purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances.

- CER research must assess a comprehensive array of health-related outcomes for diverse patient populations.

- This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness.

Clinical Registries!
"There is a wealth of data available from large databases that enable us to research important clinical questions," "Robust methodology exists for comparing different therapies through observational database analysis."

Wilensky G Health Affairs Nov 2006:w572-w588
Registries can:

- capture high quality clinical data efficiently
- be used for scientific discovery
  - track patients’ longitudinal care
  - track drugs/devices
  - be linked to biological/imaging data
- complement/support RCTs
  - and perhaps be backbone for these
- helps drive new evidence into routine practice
ACC and Comparative Effectiveness Research

- Stimulus for evidence development
  - High scientific rigor, impact on diversity
- CER priorities set by Multi-stakeholder board
- Wise stewardship of resources
  - Quality of care first priority while reducing costs
    - Secondary aim
      - Separate entities that generate CER and those that determine coverage and benefit programs
- CER needs long-term support/investment
- CER policies/programs implementation monitoring
DES - DAPT Study

- **Issue:** Length of DAPT to prevent Late Stent Thrombosis
- **Leadership:** CSRC & ……
- **Partnership:**
  - FDA-device, FDA-Drug, CMS, Payers, AHRQ, Device Industry, Pharmaceutical Industry, Academics, Professional Societies, NCDR Registry
SAFARI
Safety of Atrial Fibrillation Ablation Registry Initiative - MISSION

• Facilitate national pan-stakeholder collaboration supporting the design, implementation and maintenance of feasible AF Ablation Registry
  – Safety and effectiveness of on- and off-label “real world” AF ablation
  – Inform development of reliable knowledge practice guidelines
  – Better inform regulatory processes to safety of medical products used in Dx, Ablation, and subsequent Rx of AF
SAFARI - Partnerships

• FDA under Critical Path Initiative developing a partnership with Cardiac Safety Research Consortium (CSRC)
  – ACC
  – NCDR
    • Data elements for Registry developed (Ben Eloff - FDA)
  – HRS (Heart Rhythm Society)
  – Industry
  – Government
  – Academia, Payers, Hospitals
National Data Repository for Comparative Effectiveness Research

- ClaimsNCDR
- CATHPCI
- NDI
- STS Registry
- UPI
- Pharm
- Claims
- CATHPCI
- NCDR
ACC/Duke Partnership: Develop a National Cardiovascular Research Infrastructure (NCRI)
NHLBI GO Grant Proposal: ACC/STS - CardioLINK

• **Purpose**
  – Compare CABG and PCI using linked databases from the CathPCI and STS Registries for in-hospital outcomes

• **Clinical data linked to MEDPAR data for long-term survival and economic outcomes**

• **Develop prediction models of death after initial revascularization in setting of chronic CAD**
Create propensity score for patients undergoing isolated CABG or PCI in stable CAD

Create a model to predict the SYNTAX score based on co-variables available in STS and NCDR databases

Compare long-term survival, hospitalization for MI, renal failure, stroke, and repeat revascularization using propensity scores from matched pairs and also by disease severity from derived SYNTAX scores
ACC/STS – CardioLINK

- Cost and incremental cost-effectiveness of CABG vs PCI for matched subgroups
- Outcomes in cost per life year gained and cost per quality-adjusted life year gained
CER and Registries

**Perfect Opportunity for Coverage with Evidence Development (CED)**

- Offers the “Carrots” and “Sticks” for Registry participation
- Realizes opportunities to assess new technology in real world applications – non-RCT and off label uses
- An ultimate national tool for assessing safety and efficacy of new devices/drugs with low adverse event rates

**Percutaneous Aortic Valves**

**Atrial Fibrillation Ablation**

**New CV Imaging Technologies**
What Now Needs to Be Done?

- Address the needs of small and mid-sized pharmaceutical companies for cardiac safety assessments that are timely, fair and accurate.
- Integrate these novel approaches to safety assessment.
- Replicate repositories like the ECG warehouse for research requiring large clinical datasets.
- Leverage existing clinical databases for safety assessment and ongoing safety monitoring.
Mutual Challenges

• Always putting the patient first.
• Maintaining confidentiality.
• Managing conflicts of interest.
• Maintaining the pace required by business.
• Balancing academic curiosity with corporate secrecy.
• Finding the time and funding for academics to participate in the process.