Lessons Learned from Cardiovascular Clinical Trials
March 3, 2016

Adrian Hernandez, MD, MHS
Director, Health Services & Outcomes Research
Associate Director, DCRI
What problems are we trying to solve?
Cultural Demand: A Persistent Problem – Closing Major Gaps in Evidence

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.
Level of Evidence A
Current Guidelines*

- AF: 11.7%
- Heart failure: 26.4%
- PAD: 15.3%
- STEMI: 13.5%
- Perioperative: 12.0%
- Secondary prevention: 22.9%
- Stable angina: 6.4%
- SV arrhythmias: 6.1%
- UA/NSTEMI: 23.6%
- Valvular disease: 0.3%
- VA/SCD: 9.7%
- PCI: 11.0%
- CABG: 19.0%
- Pacemaker: 4.9%
- Radionuclide imaging: 4.8%

*Guidelines expressing Level of Evidence
Level of Evidence C
Current Guidelines*

- AF: 58.6%
- Heart failure: 54.3%
- PAD: 25.1%
- STEMI: 47.2%
- Perioperative: 32.0%
- Secondary prevention: 8.3%
- Stable angina: 54.5%
- SV arrhythmias: 56.5%
- UA/NSTEMI: 29.6%
- Valvular disease: 70.6%
- VA/SCD: 58.5%
- PCI: 47.8%
- CABG: 20.0%
- Pacemaker: 58.2%
- Radionuclide imaging: 26.3%
How do we fill in the knowledge gaps?
Looking Back at a Disruptive Technology

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCIINASI NELL’INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11,806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11,712. At 21 days overall hospital mortality was 10.7% in SK recipients versus 13% in controls, an 18% reduction (p = 0.0002, relative risk 0.81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0.74, 0.80, 0.87, and 1.19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

“It started with no funding and skepticism in some quarters but today GISSI is recognized as an Italian achievement that has changed cardiology treatment worldwide.”

http://eurheartj.oxfordjournals.org/content/31/9/1023.full
Evolving Technology!

1989
GUSTO
40,000+ pts
3-page faxed CRF
100's of papers!

1969
Duke Databank
1st and largest CV clinical registry

Global Utilization of Streptokinase and t-PA
For Occluded Coronary Arteries

2016
ADAPTABLE
Patient Centric RCT
20,000 pts; EHR driven
Mobile based pt follow-up
Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

- **ADAPTABLE Enrollee**
  - Baseline Data

- **DCRI FOLLOW-UP**
  - Patient Reported Outcomes
  - Medication use
  - Health outcomes

- **Portal FOLLOW-UP**
  - Patient Reported Outcomes
  - Medication use
  - Health outcomes

- **PCORNet Coordinating Center FOLLOW-UP**
  - Via Common Data Model
  - Longitudinal health outcomes

- **CMS & Payer Virtual Data Warehouse FOLLOW-UP**
  - Longitudinal health outcomes
3

Relevant Question?
NATRECOR®

FDA approved on Aug 10, 2001

- Intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity
Real World Challenges- Equipoise?

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure
A Pooled Analysis of Randomized Controlled Trials

Risk of Worsening Patients With Acute Heart Failure

Nesiritide — Not Verified

Expert Panel Gives Advice That Surprises A Drug Maker
Design of ASCEND-HF: Guiding Principles

• Investigator independence in context of joint Executive Committee/large Steering Committee

• Large, pragmatic trial model
  – Focused
  – Efficient study design
  – Streamlined procedures
  – Simple follow-up

• Enroll clinical heart failure

• Meaningful outcomes

• ‘Real world’ treatment (standard of care)

• Feasible sub-studies to advance knowledge in acute heart failure
ASCEND-HF North American Enrollment

Months

Patients

projection
actual
Benchmarking…

<table>
<thead>
<tr>
<th></th>
<th>XXXXXXX (&gt;10,000)</th>
<th>ASCEND-HF (n=7142)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Trial</strong></td>
<td>Chronic CV</td>
<td>Acute Heart Failure</td>
</tr>
<tr>
<td><strong>Traditionally Reported SAEs</strong></td>
<td>10,373</td>
<td>964</td>
</tr>
<tr>
<td><strong>Triggered Events</strong></td>
<td>10,895</td>
<td>1480</td>
</tr>
<tr>
<td><strong>Coded AEs</strong></td>
<td>65,296</td>
<td>386</td>
</tr>
<tr>
<td><strong>Concomitant Therapies</strong></td>
<td>332,677</td>
<td>&lt;50,000</td>
</tr>
<tr>
<td><strong>Visits</strong></td>
<td>478,001</td>
<td>14,200</td>
</tr>
<tr>
<td><strong>eCRF pages</strong></td>
<td>&gt;2.5 million</td>
<td>&lt;200,000</td>
</tr>
<tr>
<td><strong>Data Points</strong></td>
<td>&gt;30 million</td>
<td>&lt;3 million</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>+++++++++++</td>
<td>++</td>
</tr>
</tbody>
</table>
Right Treatment?
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrok, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington for the PLATO Investigators

HR 0.84 (95% CI 0.77–0.92), p=0.0003
## Geographic Regions

### CV Death, MI, Stroke

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>Total patients</th>
<th>KM at month 12</th>
<th>Interaction p-values HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tic</td>
<td>Clop</td>
</tr>
<tr>
<td>Asia / Australia</td>
<td>1714</td>
<td>11.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Central America / South America</td>
<td>1237</td>
<td>15.2</td>
<td>17.9</td>
</tr>
<tr>
<td>Europe / Middle East / Africa</td>
<td>13859</td>
<td>8.8</td>
<td>11.0</td>
</tr>
<tr>
<td>North America</td>
<td>1814</td>
<td>11.9</td>
<td>9.6</td>
</tr>
</tbody>
</table>

Clopidogrel better

Ticagrelor better

HR (Hazard Ratio), CI (Confidence Interval)
# Primary Efficacy Outcome

## US and Non-US and by ASA Dose

<table>
<thead>
<tr>
<th>Region</th>
<th>ASA Dose (mg)</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>E</td>
<td>N</td>
</tr>
<tr>
<td>US</td>
<td>≥300</td>
<td>324</td>
<td>40</td>
<td>352</td>
</tr>
<tr>
<td></td>
<td>&gt;100–&lt;300</td>
<td>22</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>≤100</td>
<td>284</td>
<td>19</td>
<td>263</td>
</tr>
<tr>
<td>Non-US</td>
<td>≥300</td>
<td>140</td>
<td>28</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>&gt;100–&lt;300</td>
<td>503</td>
<td>62</td>
<td>511</td>
</tr>
<tr>
<td></td>
<td>≤100</td>
<td>7449</td>
<td>546</td>
<td>7443</td>
</tr>
</tbody>
</table>

*Hazard ratio not calculated due to small number of events.*
Right Outcome?
Diabetes and Cardiovascular Outcomes: Surrogate vs. Outcomes

- Interventions
- HbA1c
- Glycemic Control
- End Organ Complications
  - Myocardial Infarction
  - Heart Failure
- Unintended negative effects
  - e.g., Hypoglycemic Events
- Alternative beneficial effects
Potential Modifiable factors related to CV risk

- BP
- Arterial stiffness
- Albuminuria
- Sympathetic nervous system activity
- Glucose
- Insulin
- Uric acid
- Weight
- Visceral adiposity
- Oxidative stress
- \( \uparrow \) LDL-C
- \( \uparrow \) HDL-C
- \( \downarrow \) Triglycerides

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus


Hazard ratio, 1.00 (95% CI, 0.89–1.12)
P<0.001 for noninferiority
P=0.99 for superiority
2-yr Kaplan–Meier rate:
Saxagliptin, 7.3%
Placebo, 7.2%

No. at Risk
Placebo:
Saxagliptin:

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo</th>
<th>Saxagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8212</td>
<td>8280</td>
</tr>
<tr>
<td>180</td>
<td>7983</td>
<td>8071</td>
</tr>
<tr>
<td>360</td>
<td>7761</td>
<td>7836</td>
</tr>
<tr>
<td>540</td>
<td>7267</td>
<td>7313</td>
</tr>
<tr>
<td>720</td>
<td>4855</td>
<td>4920</td>
</tr>
<tr>
<td>900</td>
<td>851</td>
<td>847</td>
</tr>
</tbody>
</table>

Scirica BM et al NEJM 2013; Scirica BM et al Circ 2014
EMPA-REG-Outcomes: Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)

\(p=0.0017\)

Impact of Endpoints on Dissemination…

Publication of Trials Funded by the National Heart, Lung, and Blood Institute

Real World Integration?
Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Cimerovic, M.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerå, Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., Ulf Jansen, M.D., Ph.D., Agneta C. Johansson, M.D., Amra Kårgren, M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertson, M.D., Lennart Sandhall, M.D., Ivar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harne, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches in Women Undergoing Percutaneous Coronary Intervention

The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) Trial

Sunil V. Rao, MD,* Connie N. Hess, MD, MHS,* Britt Barham, BA,* Laura H. Aberle, BSPhI,* Kevin J. Anstrom, PhD,* Tejjan B. Patel, MD,* Jesse P. Jorgensen, MD,* Ernest I. Mazzaferri Jr., MD,* Sanjit S. Jolly, MD,* Alice Jacobs, MD,* L. Kristin Newby, MD,* C. Michael Gibson, MD,* David F. Kong, MD,* Roxana Mehran, MD,* Ren Waksman, MD,* Ian C. Gilchrist, MD,* Brian J. McCourt,* John C. Messenger, MD,* Eric D. Peterson, MD, MPH,* Robert A. Harrington, MD,* Mitchell W. Krueger, MD*
Swedish Registry-Trial Hybrids

TASTE Trial: Thrombus-Aspiration in MI

Cost (incremental) = US $300,000 ($50 per patient)

Frobert O et al NEJM 2013
Retention!
Months After Randomization

**PRIMARY EFFICACY ENDPOINT:**

CV Death / MI / Stroke* (Ischemic + Hemg.)

*Rivaroxaban (both doses)*

HR 0.84
(0.74-0.96)
ARR 1.7%

mITT p = 0.008
ITT p = 0.002
NNT = 59

---

* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata. Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; ARR=Absolute Relative Reduction; NNT=Number needed to treat; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.
The ATLAS ACS 2–TIMI 51 Trial and the Burden of Missing Data

(Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51)

Mori J. Krantz, MD,*† ‡ Sanjay Kaul, MD§||

Aurora and Denver, Colorado; and Los Angeles, California

<table>
<thead>
<tr>
<th>Trial</th>
<th>Enrolled (N)</th>
<th>Median Follow-up (days)</th>
<th>Incomplete F/U</th>
<th>Withdrawal of consent</th>
<th>Vital Status Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS-ACS-2</td>
<td>15,526</td>
<td>484</td>
<td>2402 (15.5%)</td>
<td>1294 (8.3%)</td>
<td>1117 (7.2%)</td>
</tr>
<tr>
<td>TIMI 51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLATO</td>
<td>18,624</td>
<td>277</td>
<td>562 (3.0%)</td>
<td>545 (2.9%)</td>
<td>2 (0.01%)</td>
</tr>
<tr>
<td>APPRAISE-2</td>
<td>7,392</td>
<td>241</td>
<td>131 (1.8%)</td>
<td>81 (1.1%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Final Thoughts
What is A Quality Clinical Trial?

1. Relevant question being addressed
2. A protocol that is clear, practical, focused
3. Adequate number of events to answer question with confidence
4. In a general practice setting to make results generalizable
5. With proper randomization
6. With reasonable assurance that patients receive (and stay on) assigned treatment
7. With reasonably complete follow-up and ascertainment of primary outcome (and other key outcomes like death)
8. With a plan for ongoing measurement, feedback, improvement of quality measures during trial conduct
9. With safeguards against bias in determining clinically relevant outcomes
10. With protection of rights of research patients