Clinical Trials are the Answer. What’s the Question?

John H. Alexander, MD, MHS
Director, Heart Center SBR
Co-Director, Cardiovascular Research DCRI

Thank You

Disclosures available:
https://dcri.org/about-us/conflict-of-interest
Nomenclature

- **Research**: A systematic evaluation to develop generalizable knowledge
- **Clinical Research**: Research involving human subjects or their protected health information (PHI)
- **Clinical Trial**: Clinical research where a specific research intervention is applied
- **Observational Study**: Clinical research without a specific research intervention where research subjects are “observed”

Medical Decision Making

**Reality**

For most medical decisions we simply do not know whether recommendations regarding therapies lead to better patient outcomes
Level of Evidence A

- 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%

Tricoci JAMA. 2009;301:831-41.

Life’s Questions

Diet Coke versus Sugar

Artificial Sweeteners
Life’s Questions

versus

Reading

Television

Quality of Evidence for Modestly Effective Therapies

<table>
<thead>
<tr>
<th>Method</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common sense</td>
<td>Nearly Worthless</td>
</tr>
<tr>
<td>Targeting disease process with surrogate endpoints</td>
<td>Terrible</td>
</tr>
<tr>
<td>Observational database analysis</td>
<td>Poor</td>
</tr>
<tr>
<td>Case-control study</td>
<td>Poor</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Good (66%)</td>
</tr>
<tr>
<td>Large randomized clinical trial</td>
<td>Best</td>
</tr>
</tbody>
</table>
Good Clinical Trial
Key Elements

- Relevant population included
- Randomized and Blinded
- Clinically meaningful endpoints
- Adequate size
- Quality
  - Protection of human subjects
  - Integrity of clinical trial data
Clinical Trials vs The Community

Clinical Trials
- White
- Male
- Adult
- Non-elderly
- Few comorbidities

Community

Comorbidity

Disease Severity

Age

Clinical Trials

“Flattening” of Clinical Research

- Conducting high quality clinical research in the US is an increasing challenge
  - Public Perception
  - Complexity / Regulation
  - Speed and Cost
- Clinical research is being “outsourced” from the US to India, China, Eastern Europe, and South America
Good Clinical Trial Key Elements

- Relevant population included
- **Randomized** and Blinded
- Clinically meaningful endpoints
- Adequate size
- Quality
  - Protection of human subjects
  - Integrity of clinical trial data

Hormone Replacement Therapy

**Background**

CHD in Women is Common and Often Fatal

Multiple Observational Studies Suggest:
- 35–50% Lower Risk for CHD in Estrogen Users
- Stronger Protection in Women with CHD
- Similar Benefit for Estrogen and Estrogen/Progestin
- Observed Benefit Could Be Due to Selection Bias

Millions of American Women using HRT

Randomized Trials Needed
HERS Study Overview

Post-menopausal women with CAD with an intact uterus
n=2763

- 0.625 mg conjugated equine estrogens + 2.5 mg medroxyprogesterone acetate qd
  n=1380

- Placebo qd
  n=1383

4.1 years treatment; clinic visits q 4 months

- Completed Closeout Contact (n=1222)
  Alive, But No Closeout (n=27)
  Lost-to-Follow-Up (n=0)
  Died (n=131)

- Completed Closeout Contact (n=1228)
  Alive, But No Closeout (n=32)
  Lost-to-Follow-Up (n=0)
  Died (n=123)

Primary endpoint: CHD death or non-fatal myocardial infarction

HERS Changes In Lipids

- LDL
- HDL
- Triglycerides

- Placebo
- Estrogen + Progestin
HERS Cardiovascular Events

Follow-Up, y (No. at Risk)
Log Rank p=0.91

Duke University
Symposium for Research Administrators

Good Clinical Trial
Key Elements

• Relevant population included
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• Clinically meaningful endpoints
• Adequate size
• Quality
  – Protection of human subjects
  – Integrity of clinical trial data
The CAST Trial

Important Outcomes

- Longer life
- Better quality of life
- Less cost

![Graph showing patients without event (%) over days after randomization.]

Placebo (n = 743)

Encainide or Flecainide (n = 755)

Odds of Death

Days after Randomization

\[ p = 0.0004 \]

—Echt, NEJM, 1991

Good Clinical Trial

Key Elements

- Relevant population included
- Randomized and Blinded
- Clinically meaningful endpoints
- Adequate size
- Quality
  - Protection of human subjects
  - Integrity of clinical trial data
### Sample Size

**Treatment Effect = 25%**

<table>
<thead>
<tr>
<th>Events</th>
<th>Patients Randomized (Risk = 10%)</th>
<th>Chance of Type II Error*</th>
<th>Comments on Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-50</td>
<td>&lt; 500</td>
<td>&gt; 90%</td>
<td>Utterly inadequate</td>
</tr>
<tr>
<td>50-150</td>
<td>1000</td>
<td>70-90%</td>
<td>Probably inadequate</td>
</tr>
<tr>
<td>150-350</td>
<td>3000</td>
<td>30-70%</td>
<td>Possibly inadequate</td>
</tr>
<tr>
<td>350-650</td>
<td>6000</td>
<td>10-30%</td>
<td>Probably adequate</td>
</tr>
<tr>
<td>&gt; 650</td>
<td>10000</td>
<td>&lt; 10%</td>
<td>Adequate</td>
</tr>
</tbody>
</table>

*Probability of failing to detect an important treatment effect if one exists.

— Yusuf, *Prog in CV Disease*, 1985

### Good Clinical Trial Key Elements

- Relevant population included
- Randomized and Blinded
- Clinically meaningful endpoints
- Adequate size
- **Quality ≠ Complexity**
  - Protection of human subjects
  - Integrity of clinical trial data
King Nebuchadnezzar II ordered children of royal blood to eat only meat and wine. Several other children ate only legumes and porridge. After ten days the other children were noticeably healthier than those who ate meat and wine.

<table>
<thead>
<tr>
<th>Key Clinical Trial Elements</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant population included</td>
<td>No</td>
</tr>
<tr>
<td>Randomized and Blinded</td>
<td>No and no</td>
</tr>
<tr>
<td>Clinically meaningful endpoints</td>
<td>No</td>
</tr>
<tr>
<td>Adequate size</td>
<td>No</td>
</tr>
<tr>
<td>Quality</td>
<td></td>
</tr>
<tr>
<td>Protection of human subjects</td>
<td>No</td>
</tr>
<tr>
<td>Integrity of clinical trial data</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Coronary Artery Bypass Graft Surgery in Patients with Ischemic Heart Failure

Eric J. Velazquez, MD
on behalf of the STICH Investigators
April 4, 2011
**All-Cause Mortality — As Randomized**

HR 0.86 (0.72, 1.04)  
**P** = 0.123

Adjusted HR 0.82 (0.68, 0.99)  
Adjusted **P** = 0.039

**Study population**

**Randomized (n=7141)**

**Placebo (n=3577)**
- Did not receive study drug (n=66)
  - Hypotension (n=28)
  - Exclusion criteria (n=8)
  - Physician decision (n=6)
  - Participant withdrew consent (n=14)
- Other reason (n=10)

**Nesiritide (n=3564)**
- Did not receive study drug (n=68)
  - Hypotension (n=26)
  - Exclusion criteria identified (n=9)
  - Physician decision (n=6)
  - Participant withdrew consent (n=16)
- Other reason (n=11)

Placebo MITT=3511  
Nesiritide MITT=3496
Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization

**Hazard Ratio 0.93 (95% CI: 0.81, 1.08)**

**P=0.31**

<table>
<thead>
<tr>
<th>30-day Death/HF Rehospitalization</th>
<th>Placebo</th>
<th>Nesiritide</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day Death</td>
<td>10.1</td>
<td>9.4</td>
</tr>
<tr>
<td>HF Rehospitalization</td>
<td>4.0</td>
<td>3.6</td>
</tr>
<tr>
<td>%</td>
<td>6.1</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Risk Diff (95% CI)
- 0.7 (-2.1; 0.7)
- 0.4 (-1.3; 0.5)
- 0.1 (-1.2; 1.0)

**Study Design**

**Atrial Fibrillation**

- **Rivaroxaban**
  - 20 mg daily
  - 15 mg for Cr Cl 30-49 ml/min

- **Warfarin**
  - Randomize Double Blind / Double Dummy (n ~ 14,000)
  - INR target - 2.5 (2.0-3.0 inclusive)

**Monthly Monitoring Adherence to standard of care guidelines**

**Primary Endpoint:** Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
Primary Efficacy Outcome
Stroke and non-CNS Embolism

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.71</td>
<td>2.16</td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI): 0.79 (0.66, 0.96)
P-value Non-Inferiority: <0.001

No. at risk:
Rivaroxaban 6958 6211 5786 5468 4406 3407 2472 1496 634
Warfarin 7004 6327 5911 5542 4461 3478 2539 1538 655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Costs of Clinical Trials

- Large Global Phase III Clinical Trial
  - 18,000 patients w/ atrial fibrillation
  - Randomized to warfarin vs. oral fXa inhibitor
  - Outcome = stroke or systemic embolism

- Time (enrollment / follow-up) > 4 years
- Cost > $400,000,000 (almost half a billion!)
- Result = definitive answer to 1 question
- Is something wrong with this picture?
The Medical / Academic Community

Our Responsibilities in Clinical Research

• **Demand** (on behalf of our patients) adequate evidence to support the use of new therapies

• **Participate** (as investigators) in the generation of evidence through participation in clinical trials

• **Educate** other physicians, medical institutions and the public about the importance of collaboration and participation in clinical research

“Science is organized common sense where many a beautiful theory was killed by an ugly fact.”

Thomas Huxley

Thank You