CARDIOLOGY GRAND ROUNDS

Presentation:  Approaching Efficiency in Randomized Clinical Trials in the US: The SAFE-PCI for Women Experience

Speaker:  Sunil V. Rao, MD, FACC, FSCAI
Associate Professor of Medicine with Tenure
Duke University Medical Center

Date:  Monday, January 12, 2015, 7:00 – 8:00 AM
Location:  ANW Education Building, Watson Room

OBJECTIVES
At the completion of this activity, the participants should be able to:
1. Review challenges facing clinical trials in the US
2. Discuss potential solutions to enhancing clinical trial conduct in the US
3. Describe the design and results of the SAFE-PCI for Women trial.

ACCREDITATION
Physicians: This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Allina Health and Minneapolis Heart Institute Foundation. Allina Health is accredited by the ACCME to provide continuing medical education for physicians.

Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses: This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.2 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

Others: Individuals representing other professional disciplines may submit course materials to their respective professional associations for 1.0 hours of continuing education credit.

DISCLOSURE STATEMENTS
Speaker(s):  Sunil V. Rao, MD, FACC, FSCAI, has declared the following relevant financial relationships: Terumo Medical and The Medicines Company.

Planning Committee: Dr. Michael Miedema and Eva Zewdie have declared that they do not have any conflicts of interest associated with the planning of this activity. Dr. Robert Schwartz declared the following relationships - stockholder: Cardiomind, Interface Biologics, Aritech, DSI/Transoma, InstyMeds, Intervalve, Medtronic, Osprey Medical, Stout Medical, Tricardia LLC, CoAptus Inc, Augustine Biomedical; scientific advisory board: Abbott Laboratories, Boston Scientific, MEDRAD Inc, Thomas, McNerney & Partners, Cardiomind, Interface Biologics; options: BackBeat Medical, BioHeart, CHF Solutions; speakers bureau: Vital Images; consultant: Edwards LifeSciences.
Approaching Efficiency in Randomized Clinical Trials in the US: The SAFE-PCI for Women Trial Experience

Sunil V. Rao MD
Associate Professor of Medicine
Duke University Medical Center
Duke Clinical Research Institute

Disclosures

- Consultant, Honoraria
  - The Medicines Company, Terumo Medical, ZOLL
- Research funding
  - Bellerophon
- Off-label uses of drugs/devices may be discussed
Case presentation: Let’s consider an industry…

- $29 billion industry\(^1\)
- 1100 contractors developing the final product
- 20-40% of the suppliers don’t supply any raw materials
- The process has little quality control
- The final product can be of poor quality
- The government cannot afford to bail it out any more

\(^1\)Goldman Sachs 2007
US Clinical Research in Crisis

- Increasing costs
- Prolonged timelines
- Poor enrollment
- Increased off-shoring
- Less value
Approaching efficiency in clinical research

- Perspectives on the current state
  - Industry
  - NIH
  - Sites
- Potential solutions
- The registry-based randomized trial concept
- SAFE-PCI for Women – piloting the National Cardiovascular Research Infrastructure
- Opportunities and Challenges
- Summary
R&D spending as a percent of sales revenue

Average R&D cost of a NME

Source: Tufts Center for the Study of Drug Development

Congressional Budget Office 2006
Number of patents awarded per dollar spent

Congressional Budget Office 2006

The cost of doing business

Research Spending Per New Drug

Company | Ticker | Number of drugs approved | R&D Spending Per Drug ($M) | Total R&D Spending 1997-2011 ($M)
--- | --- | --- | --- | ---
AstraZeneca | AZN | 5 | 11,790.93 | 58,955
GlaxoSmithKline | GSK | 10 | 8,170.81 | 81,768
Sanofi | SNY | 8 | 7,999.26 | 63,274
Roche Holding AG | RHHBY | 11 | 7,803.77 | 85,841
Pfizer Inc. | PFE | 14 | 7,279.03 | 108,178
Johnson & Johnson | JNJ | 15 | 5,883.65 | 88,285
Eli Lilly & Co. | LLY | 11 | 4,277.04 | 50,647
Abbott Laboratories | ABT | 8 | 4,916.21 | 35,970
Merck & Co Inc | MRK | 16 | 4,209.99 | 67,360
Bristol-Myers Squibb Co | BMY | 11 | 4,152.26 | 45,675
Novartis AG | NVS | 21 | 3,983.13 | 83,646
Amgen Inc. | AMGN | 9 | 3,692.14 | 23,229

Sources: InnoPharm Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems

NIH Perspective

Coronary Intervention for Persistent Occlusion after Myocardial Infarction

Judit K. Hodany, M.D., Cesare A. Lemme, M.D., Christopher J. Beller, M.D., Vladimir Dzindz, M.D.,
Harvey P. Kazi, M.D., Toshi, Alexander M. P. H., Sirdaat Kerman, M.D., Whole Rage, M.D.,
Ala T. Maggi, M.D., Penny Whit, M.D., Zygmunt Sandow, M.D., Atanas C. Canev, M.D.,
Jason M. Kurnar, M.D., Jean P. Trachten, M.D., T. Gabriel F. N. F., St. M. Janes, M.D.,
Georgis P. M., Mathew T. Fiebine, M.D., James J. Janes, M.D., Victor F. Holt, M.D., Daniel R. Mark, M.D., F.A.C.C.,
and Gerald L. Keane, M.D., for the Unfilled Artery Trial Investigators*
The Costs of Conducting Clinical Research

By Ezekiel J. Emanuel, Lowell E. Schnipper, Deborah Y. Kamin, Jennifer Levinson, and Allen S. Lichter

<table>
<thead>
<tr>
<th>Activity</th>
<th>Industry Sponsored Total Costs ($)</th>
<th>Academic** Total Costs ($)</th>
<th>Organizations</th>
<th>Design/Group Practice</th>
<th>Total Costs ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-IRB submission and initiation of study</td>
<td>287</td>
<td>208</td>
<td>208</td>
<td>63-842</td>
<td>287</td>
</tr>
<tr>
<td>School recruitment and informed consent</td>
<td>287</td>
<td>208</td>
<td>208</td>
<td>63-842</td>
<td>287</td>
</tr>
<tr>
<td>Randomization and dispensing drugs</td>
<td>203</td>
<td>254</td>
<td>254</td>
<td>203</td>
<td>203</td>
</tr>
<tr>
<td>Office visits</td>
<td>2,902</td>
<td>1,369, 4,741</td>
<td>1,369, 4,741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management of adverse events</td>
<td>181</td>
<td>233</td>
<td>233</td>
<td>181</td>
<td>181</td>
</tr>
<tr>
<td>Data management and analysis</td>
<td>307</td>
<td>233</td>
<td>233</td>
<td>307</td>
<td>307</td>
</tr>
<tr>
<td>Audits and communications with the sponsor</td>
<td>197, 291</td>
<td>156</td>
<td>156</td>
<td>197, 291</td>
<td>197, 291</td>
</tr>
<tr>
<td>Poststudy follow-up and meetings</td>
<td>110</td>
<td>59, 195</td>
<td>59, 195</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>Total</td>
<td>18,285</td>
<td>8,993, 13,650</td>
<td>8,993, 13,650</td>
<td>18,285</td>
<td>18,285</td>
</tr>
</tbody>
</table>

NOTE: These are the average costs per n of treatment, and 12 months of follow-up

20-30% of sites
Enroll 70-80% of the Patients


Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

11% of all recs are LOE A
19% of Class I recs are LOE A

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 guideline 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 7,194 recommendations, were abstracted.

JAMA. 2009;301(3):831-841
How can we address these challenges?

- Comparative effectiveness research
  - Uses registries – cannot completely overcome the confounding
- Large, simple trials
  - Possible in the current era?
- “Pragmatic clinical trials”
  - Term coined in 1967 (Schwarz and Lellouch)
  - Many strategies – adaptive designs, cluster-based trials, registry-based trials

Slide credit to Michael Lauer MD
TASTE trial flow chart

Patients with suspected STEMI referred to primary PCI
N = 5000

STEMI diagnosis confirmed at coronary angiography. Informed consent obtained

Online 1:1 randomization in SCAAR, guidewire advancement, i.c. nitroglycerin

Thrombus aspiration and PCI  
P CI alone

Immediately after PCI: TIMI flow grade

30 days: all-cause death

1, 2, 5 and 10 years: all-cause death and additional secondary endpoints
Why SCAAR / Swedeheart?

- The most complete PCI registry in the world!
  - 100% complete. Nationwide
  - Validated
  - Complete follow-up
  - Merge with other national registries - Mortality, CV diagnoses, hospitalizations, re PCI
- Unique possibility to establish evidence in an area other trials will not or cannot
- Possibility to complete the world's largest randomized trials during the shortest period of time

When PCI with indication STEMI-primary/rescue PCI and PCI ad hoc is registered the system proposes randomization.
Two questions need to be answered:
Is the patient informed verbally and accepts participation?
Are inclusion and no exclusion criteria met?

- $800,000 USD including MRI sub study with 160 patients core lab evaluation
- All start up meetings on the web
- CRF incorporated in the registry
- Automated data and inconsistency checks
- Monitoring (approximately 10% of variables) included in the registry
- No reimbursement to sites
The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?
Michael S. Lauer, M.D., and Ralph B. D’Agostino, Sr., Ph.D.

The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for the effects of unmeasured factors, as well as inadequate representativeness. What good are trials if the results aren’t applicable to real-world patients and if, because of excessive expense, they can be used to answer only a tiny fraction of our important clinical questions? The randomized registry trial may provide an alternative.

- What kinds of trials can we do?
- What is different operationally?
- Can it really provide high quality data?
- Can it really save money?
Radial mega-analysis

N=76 studies (15 rand; 61 obs); 761,919 patients

Bertrand OF, et. al. 

International distribution of TRI - 2008

Radial Penetration

Saito, FDA 2011
RIVAL Study Design

Key Inclusion:
• Intact dual circulation of hand required
• Interventionalist experienced with both (minimum 50 radial procedures in last year)

Randomization

Radial Access (n=3507)
Femoral Access (n=3514)

Blinded Adjudication of Outcomes

Primary Outcome: Death, MI, stroke or non-CABG-related Major Bleeding at 30 days


TREATT I ThinkTank – 2011 White Oak Campus

- The rate of radial approach is lower in the US compared with other countries
- Lack of education and perhaps lack of large US-based randomized data may be responsible
- Large appetite for a randomized trial looking at clinical outcomes
- Challenge #1 is randomization
  - Femoralists unable to randomize to radial
  - Radialists unwilling to randomize to femoral
- Challenge #2 is funding
- Challenge #3 is identifying radial expert investigators

Duke Clinical Research Institute
**Post-PCI Bleeding and Vascular complications**

<table>
<thead>
<tr>
<th>Access site</th>
<th>1-year Mortality</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Non-access site</td>
<td></td>
<td>1.82 (1.17–2.83) 0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.94 (3.07–6.15) &lt;0.0001</td>
</tr>
</tbody>
</table>

**1-year Mortality**

- Death
- CABG
- Stroke
- Pectal
- Vascular

**Incremental Cost**

<table>
<thead>
<tr>
<th>Access site</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Non-access site</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Pectal</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
</tr>
</tbody>
</table>

**Bleeding Risk**

- Overall: 1.46 (1.22, 1.73)
- Women: 1.72 (1.30, 2.28)

**Challenge #1 – which patient population?**

- Women significantly underrepresented in prior radial trials
- Women present a unique challenge
  - Higher bleeding risk but radial approach underused
  - Smaller radial arteries
  - Potentially higher transradial procedure failure rate

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Alexander K, et. al.

From the NCDR CathPCI Registry®

Bartrum Of, et. al. AHA 2012

Feldman DN, et. al. Circ 2013
Challenge #2: A platform for a cheaper trial

- NCRI - Funded by the NHLBI
- Embeds randomization into the NCDR CathPCI Registry®
- Mechanism for identifying appropriate trial sites
- Leverages the workflow of registry participants by electronically exporting trial-relevant data into an electronic case report form
  - Reduction of redundant data entry (~60% data needed for study patients from CathPCI registry)
  - Reduced trial costs due to reduced site-level workload
- Data output using CDISC SDTM standards
- 21 CFR 11 compliant – IND and IDE applications
A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches In Women Undergoing Percutaneous Coronary Intervention: The Study of Access site For Enhancement of PCI for Women (SAFE-PCI for Women) Trial

Disclosures

• Sunil V. Rao
  – Consultant: The Medicines Company, Astra Zeneca

• The SAFE-PCI for Women Trial was conducted in collaboration with the American College of Cardiology and funded by a consortium of academic, industry, and government entities
  – Terumo Medical, Medtronic, The Medicines Company, Abbott Vascular, Daiichi-Sankyo Inc./Eli Lilly & Company, ACIST Medical, Guerbet
  – The FDA Office of Women’s Health
  – The Duke Clinical Research Institute

• The National Cardiovascular Research Infrastructure was funded by the National Heart, Lung, and Blood Institute (grant #1RC2HL101512-01)

SAFE-PCI for Women Objective

To determine the efficacy and feasibility of transradial PCI in women
Study design

Female patient undergoing PCI or cardiac cath w/poss. PCI

Best background medical therapy
Bivalirudin, P2Y12 inhibitors
2b3a at investigator’s discretion

N=3000 pts randomized for 1800
PCI pts
Patent hemostasis required
Vascular closure devices allowed

Primary Efficacy Endpoint (72 hrs or hospital discharge):
BARC Types 2, 3, or 5 bleeding or Vascular
Complications requiring intervention

Primary Feasibility Endpoint: Access site crossover
Secondary endpoints: Procedure duration, total radiation dose, total contrast
volume, 30-day death/vascular complications/unplanned revascularization

Methods – Patient population

Inclusion

- Age > 18 years
- Female patient undergoing elective or urgent PCI or
- Undergoing diagnostic angiography to evaluate ischemic symptoms with the possibility of PCI
- Have capacity to sign informed consent

Exclusion

- Conditions precluding safe arterial access
  - Non-palpable radial or femoral pulses
  - Bilateral abnormal Barbeau tests
  - Hemodialysis AV fistula or graft in arm to be used for arterial access
  - INR ≥ 1.5 if on warfarin
- Bilateral IMA grafts
- Planned staged PCI within 30d of index PCI
- Valvular heart disease requiring surgery
- Planned RHC
- Primary PCI for STEMI

Two cohorts specified:

- **Total randomized** – all women who are randomized regardless of whether they undergo PCI
- **PCI cohort (primary analysis cohort)** – Guidewire exiting the guide catheter for diagnosis or treatment and therapeutic anticoagulation given
Methods - Endpoint definitions

Primary efficacy endpoint

- **BARC Bleeding**
  - Type 2: Overt, actionable bleeding not meeting criteria for type 3, 4, or 5 bleeding
  - Type 3:
    - Overt bleeding with hgb drop ≥ 3 g/dL (corrected for transfusion)
    - Transfusion with overt bleeding
    - Cardiac tamponade
    - Bleeding requiring surgical intervention or intravenous vasoactive drugs
    - Intracranial bleeding or ICH
  - Type 5: Fatal bleeding
- **Vascular complications requiring intervention**
  - AV fistula
  - Pseudoaneurysm
  - Arterial access site occlusion

Primary Feasibility Endpoint

- **Access site crossover**
  - Inability to complete the procedure from the assigned access site

CEC Adjudication of all suspected bleeding or vascular complication events

Methods - Secondary endpoints

*Assessed only in PCI cohort*

- Procedure duration
- Total radiation dose (Air Kerma, mGy)
- Total contrast volume (mL)
- 30-day death, vascular complications, or unplanned revascularization
- Access site preference for next procedure
Methods - SAFE-PCI for Women workflow

Randomization

Demographics
Medical Hx
Procedural data

Autopopulate

Unique pages for trial

Analytic
Database

Site Workflow

Entry and harvest of registry data within 7 days post discharge for study patients

Study Objective:
To compare the efficacy and feasibility of the transluminal approach to PCI in women compared with the transluminal approach.

Trial Study Coordinator (SC) Flow
1. Identify and screen potential subjects
2. Confirm inclusion/exclusion criteria
3. Obtain informed consent
4. Perform baseline test before randomization

Record Subject ID (Men & Women)
Patient Data in BMRCathPCI System

Study Subject ID
(Gender)

Demographics

Unique pages for trial
Methods

- **Sample size calculation**
  - Rate of BARC-type bleeding in NCDR CathPCI Registry among women without STEMI ~ 8.7%¹
  - Assumptions
    - Femoral access bleeding or vascular complication rate – 8%
    - 50% reduction with radial access; 1576 patients provides 90% power at alpha 0.05
    - Sample size increased to 1800 due to uncertainty around event rates
  - All primary analyses performed by modified intention-to-treat
  - Primary analysis in PCI cohort; Sensitivity analysis in Total Randomized Cohort
  - Three subgroups examined for primary efficacy endpoint
    - Prespecified in PCI cohort: ACS vs. non-ACS, Site radial volume
    - Post-hoc in Total Randomized Cohort: PCI vs. no PCI

¹Rao SV. et. al. JACC Intv 2013

Trial conduct

- After 1120 women had been randomized, routine review of trial endpoints by DSMB
  - Primary efficacy event rate markedly lower than expected
  - Trial unlikely to show a difference at the planned sample size
  - Recommended termination of the trial
- No harm noted in either the radial or femoral groups
- Steering committee voted to continue study until enrollment in a quality-of-life substudy was complete (N=300)
Results - Final Recruitment

1787 women randomized
At 60 US sites

893 women assigned to Radial
894 women assigned to Femoral

891 women
345 underwent PCI
ITT: Primary 72 hr or discharge endpoints
884 women
345 underwent PCI

290 PCI pts Secondary 30-day endpoints 292 PCI pts

96.7% of sites enrolled ≥ 1 patient
70.9% of sites enrolled ≥ 10 patients

Results – Baseline characteristics
Total randomized cohort

<table>
<thead>
<tr>
<th></th>
<th>Radial (N=893)</th>
<th>Femoral (N=894)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>63.4 (55.1, 72.2)</td>
<td>63.9 (55.7, 72.0)</td>
</tr>
<tr>
<td>Median BMI, kg/m2</td>
<td>30.5 (26.1, 35.1)</td>
<td>30.8 (26.5, 35.8)</td>
</tr>
<tr>
<td>Current or Recent smoker</td>
<td>27.2%</td>
<td>24.2%</td>
</tr>
<tr>
<td>HTN</td>
<td>79.5%</td>
<td>79.9%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>17.9%</td>
<td>19.6%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>4.5%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Dialysis</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>PAD</td>
<td>5.7%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35.2%</td>
<td>35.0%</td>
</tr>
<tr>
<td>CAD presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-ACS</td>
<td>46.8%</td>
<td>43.5%</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>52.7%</td>
<td>56.3%</td>
</tr>
<tr>
<td>STEMI</td>
<td>0.4%</td>
<td>0.2%</td>
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</table>
### Results – Baseline characteristics

**PCI cohort**

<table>
<thead>
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<th></th>
<th>Radial (N=345)</th>
<th>Femoral (N=346)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>65.1 (56.5, 73.7)</td>
<td>63.9 (56.5, 72.9)</td>
</tr>
<tr>
<td>Median BMI, kg/m2</td>
<td>30.1 (25.9, 34.5)</td>
<td>30.5 (26.9, 35.4)</td>
</tr>
<tr>
<td>Current or Recent smoker</td>
<td>30.7%</td>
<td>29.5%</td>
</tr>
<tr>
<td>HTN</td>
<td>85.8%</td>
<td>85.0%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>23.8%</td>
<td>27.7%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>7.2%</td>
<td>9.9%</td>
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<tr>
<td>Dialysis</td>
<td>0.6%</td>
<td>0.6%</td>
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<tr>
<td>PAD</td>
<td>6.7%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>41.7%</td>
<td>44.5%</td>
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### Results – Procedure characteristics

**PCI cohort**

<table>
<thead>
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<th></th>
<th>Radial (N=345)</th>
<th>Femoral (N=346)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>46.5%</td>
<td>43.6%</td>
</tr>
<tr>
<td>Urgent</td>
<td>52.1%</td>
<td>55.7%</td>
</tr>
<tr>
<td>Emergent</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Bivalirudin used</td>
<td>59.1%</td>
<td>65.8%</td>
</tr>
<tr>
<td>Glycoprotein Iib/Illa</td>
<td>11.4%</td>
<td>11.6%</td>
</tr>
<tr>
<td>Vascular closure device</td>
<td>5.1%*</td>
<td>65.5%</td>
</tr>
</tbody>
</table>

*Table excludes patients who underwent FFR, IVUS, or OCT

*Patients who had any femoral access*
Results – Primary efficacy and feasibility endpoints

**PCI cohort**

<table>
<thead>
<tr>
<th></th>
<th>Radial (N=345)</th>
<th>Femoral (N=346)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC 2, 3, 5 bleeding or Vasc Complications</td>
<td>1.2%</td>
<td>2.9%</td>
<td>0.4 (0.1-1.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>Access site crossover</td>
<td>6.1%</td>
<td>1.7%</td>
<td>3.6 (1.5-9.2)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

- Interactions for primary efficacy endpoint not significant for ACS vs. Non-ACS, tertiles of site radial volume
- Most common reason for needing to convert from radial to femoral access to complete the procedure was radial artery spasm (42.9% of crossovers)

Results – Primary efficacy and feasibility endpoints

**Total randomized cohort**

<table>
<thead>
<tr>
<th></th>
<th>Radial (N=893)</th>
<th>Femoral (N=894)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC 2, 3, 5 bleeding or Vasc Complications</td>
<td>0.6%</td>
<td>1.7%</td>
<td>0.3 (0.1-0.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Access site crossover</td>
<td>6.7%</td>
<td>1.9%</td>
<td>3.7 (2.1-6.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Interaction term for primary efficacy endpoint not significant for PCI vs. no PCI
- Most common reason for needing to convert from radial to femoral access to complete the procedure was radial artery spasm (43.6% of crossovers)
- Only one patient did not have the procedure successfully completed – was randomized to femoral
### Results – Secondary endpoints

**PCI cohort**

<table>
<thead>
<tr>
<th></th>
<th>Radial (N=290)</th>
<th>Femoral (N=291)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure duration (min)</td>
<td>51.6 ± 32.3</td>
<td>49.9 ± 30.5</td>
<td>0.46</td>
</tr>
<tr>
<td>Total radiation dose (mGy)</td>
<td>1604 ± 1394</td>
<td>1472 ± 1274</td>
<td>0.26</td>
</tr>
<tr>
<td>Total contrast volume (mL)</td>
<td>152.7 ± 76.9</td>
<td>165.6 ± 82.7</td>
<td>0.03</td>
</tr>
<tr>
<td>30-day death, vascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications, or unplanned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>revasc</td>
<td>5.2%</td>
<td>3.4%</td>
<td>0.26</td>
</tr>
<tr>
<td>Patient prefers assigned</td>
<td>71.9%</td>
<td>23.5%</td>
<td></td>
</tr>
<tr>
<td>access site for next</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions

- **The SAFE-PCI for Women Trial represents several “firsts”**
  - The first randomized trial comparing interventional strategies in women
  - The first multicenter randomized trial comparing radial with femoral access in the United States
  - The first registry-based randomized trial in the United States

- **In this trial that did not reach its planned enrollment due to early termination, radial access**
  - Did not significantly reduce bleeding or vascular complications in the subgroup of women undergoing PCI
  - Did significantly reduce bleeding or vascular complications in the larger sample size of all women undergoing cardiac catheterization or PCI
  - Was preferred over femoral approach by the majority of women undergoing PCI
  - Increased the need for conversion to femoral access in ~6% of cases
Clinical implications

- Given the consistency of these results with prior data in lower risk groups
  - Proportional bleeding reduction with radial approach similar to that seen in prior studies\(^1\)
  - Conversion to femoral rate (6%) similar to that seen in the RIVAL trial (7.6%)\(^2\)
- The SAFE-PCI for Women trial suggests an initial strategy of radial access is reasonable and may be preferred by some operators for women undergoing cardiac catheterization or PCI, with the recognition that a proportion of patients will require conversion to femoral access.

\(^1\)Bertrand OF, et al. AHA/2012

Research implications

- As the first registry-based randomized trial in the US, the SAFE-PCI for Women trial demonstrates a new paradigm for conducting efficient pragmatic clinical trials using The National Cardiovascular Research Infrastructure
  - High quality data
  - Adjudication possible
  - CFR Part 11 compliant – IND and IDE applications
  - Faster enrollment, Reduced site workload
  - Reduced costs (total budget for SAFE-PCI for Women ~ $5 million)
- This trial construct is a promising approach for future clinical investigations
NCRI Challenges

- Specific to the clinical trial data platform (e.g. InForm)
- US only (for now)
- Registry often is disease-state specific
- Changes of the registry and case report forms are not synchronized
  - Registry form changes are Decision by Committee
- **Multiple stakeholders = multiple priorities**
  - FFR example
  - Funding

NCRI Challenges

- Collaboration can be challenging at the site level
  - Registry managers and Trial Coordinators separated by mission, distance, and time
- **Timeliness of data entry**
  - Many sites enter data into the registry on a quarterly basis
  - Contractually may be challenging to change the schedule
- **For sites - two sets of queries (registry and trial data)**
- **Format not applicable to all trials**
  - e.g., Early phase trials with lots of PK/PD sampling
- **Don’t overestimate the cost savings**
  - As designed, the savings are at the site level (reduced workload)
  - May need adjudication, core labs, monitoring, long-term outcomes, etc.
- **Temptation to indulge the “trialist” urges and collect lots of additional unnecessary data**
Summary

- There is a clear need to alter the way we do clinical trials in the USA
  - Take too long to get up and running and to complete
  - Too expensive
  - The ROI is questionable
- There is broad recognition of this problem and many strategies are underway to address it
- The registry-based RCT is a viable alternative
  - SAFE-PCI experience suggests that it is feasible, provides high quality data, and allows for adjudication at an acceptable costs
- The future of this platform depends on whether “we” have the will to overcome the challenges

Questions

- Thank you!