Piloting the National Cardiovascular Research Infrastructure: The SAFE-PCI for Women Trial

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Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
SAFE-PCI for Women

- Background and Rationale
- NCRI construct
  - Advantages
  - Challenges
- Trial results
- Lessons Learned
SAFE-PCI for Women

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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.
Post-PCI Bleeding and Vascular complications

**1-year Mortality**

<table>
<thead>
<tr>
<th>Access site</th>
<th>Hazard ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted</td>
<td>1.82 (1.17–2.83) 0.008</td>
<td></td>
</tr>
<tr>
<td>Non-access site</td>
<td>3.94 (3.07–5.15) &lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**Bleeding Risk**

- **Overall**
  - Hazard ratio: 1.46 (1.22, 1.73)

- **Women**
  - Hazard ratio: 1.72 (1.30, 2.28)

**Incremental Cost**

- Death: $19,208
- CABG: $31,104
- Stroke: $13,929
- Renal: $21,468
- Vascular: $4,200-4,800

**Post-PCI Bleeding and Vascular complications**

Kugelmass A, AJC 2006

Verheugt F, JACC Intv 2011

Alexander K, et. al. Circ 2006
Radial approach

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

Bertrand OF, et. al. AHJ 2012
Feldman DN, et. al. Circ 2013
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Study of Access site For Enhancing PCI for Women (SAFE-PCI for Women)*

Female patient undergoing urgent or elective PCI

Best background medical therapy
Bivalirudin, Clopidogrel, Prasugrel
2b3a at investigator’s discretion

N=1800 pts, 30 sites
Sites from NCRI
Patient hemostasis required
Vascular closure devices allowed

Radial

Primary Efficacy Endpoint: BARC Types 2, 3, or 5 bleeding or Vascular Complications requiring surgical intervention

Primary Feasibility Endpoint: Procedural failure

Secondary endpoints: Procedure duration, total radiation dose, total contrast volume

Femoral

*Planned in collaboration with ACC, CSRC, FDA Office of Women’s Health
Methods – The National Cardiovascular Research Infrastructure

- 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
Site identification
Using actual data rather than PI recall!

NCDR PCI records from 2009Q3 through Jan 2011

NATIONAL CARDIOVASCULAR RESEARCH INFRASTRUCTURE
Methods - SAFE-PCI for Women workflow

Randomization

Demographics
Medical Hx
Procedural data

Autopopulate

Unique pages for trial

Analytic Database

ORACLE

NCDR®
National Cardiovascular Data Registry

CathPCI Registry®
NCRI - Advantages

• Streamlines data collection/entry
• Encourages collaboration between multiple stakeholders at the site level
  – Research coordinators
  – Registry coordinators
  – Site Pis
  – Quality managers
• Minimizes costs by reducing site payments
• Costs are generally up front – creation of the software interface
NCRI Disadvantages

• Specific to the clinical trial data platform (e.g. InForm)

• Registry often is disease state specific
  – Data input may be automated and not conform to clinical trial schedule
  – Fees for change may be high and not accounted for in study budget

• Multiple stakeholders = multiple priorities

• Collaboration can be challenging at the site level
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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
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
    - intraocular 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

• **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
    • 3000 women randomized to obtain 1800 women undergoing PCI

• **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

\(^1\)Rao 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 – 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>
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<th>Femoral (N=894)</th>
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<th>P</th>
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<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
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Lessons learned

- Get all parties involved EARLY
- Budget for the unexpected
- Consider the different missions of the registry vs. the trial
  - SAFE-PCI for Women – FFR example
- Control the “trialist urges” and streamline the data collection
- Don’t overestimate the cost savings
  - Comes from reduced site work/payments
  - Adjudication may be needed
  - Core labs may be needed