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

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Disclaimer

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SAFE-PCI for Women

- Background and Rationale
- NCRI construct
  - Advantages
  - Challenges
- Trial results
- Lessons Learned

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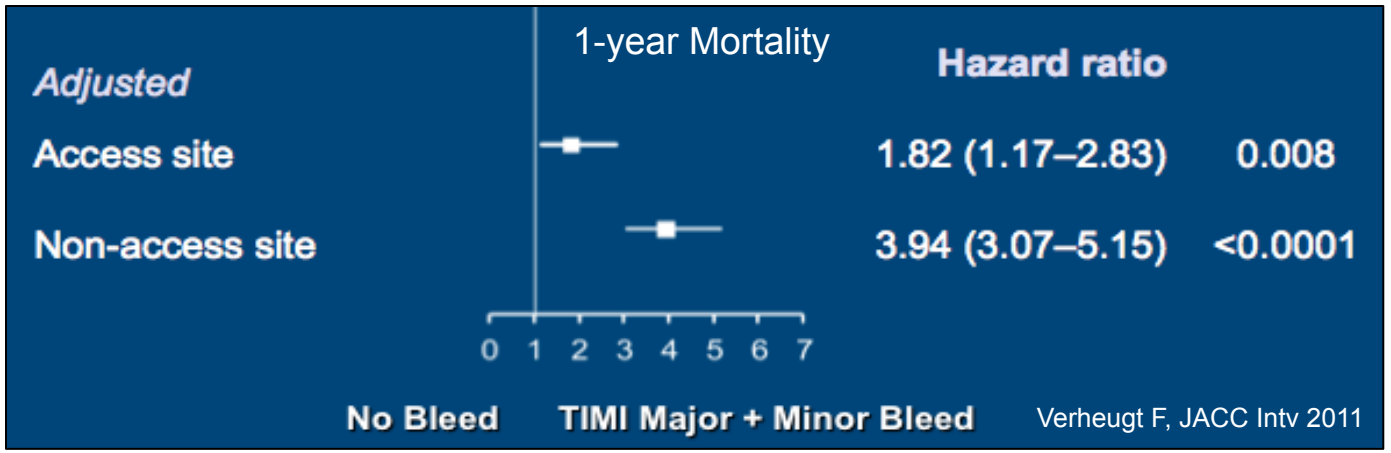
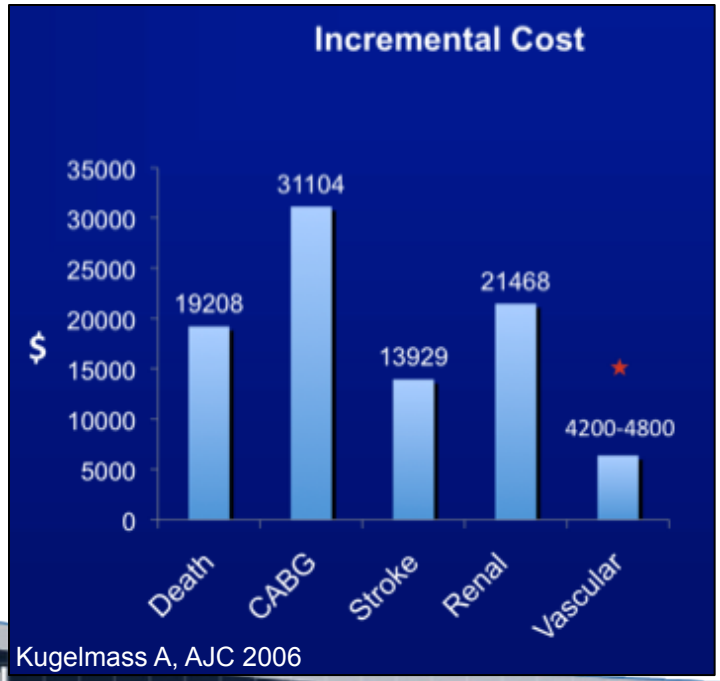
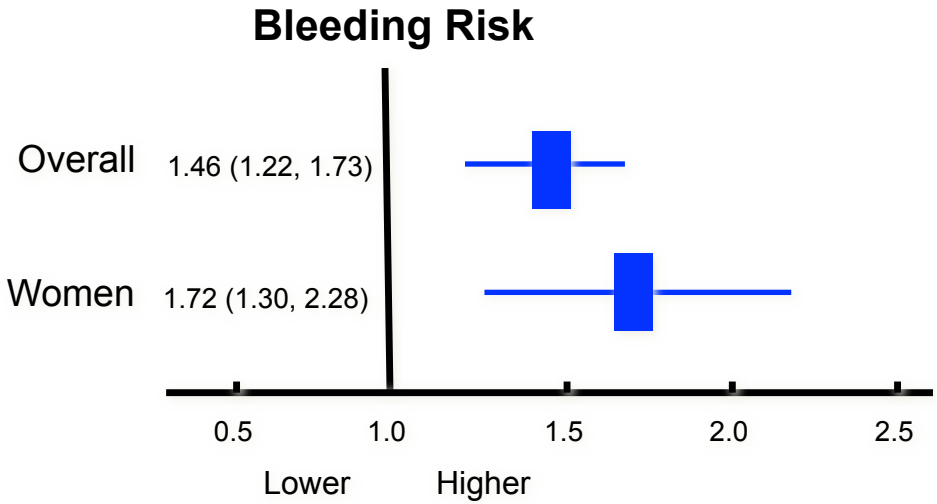
TREATT I ThinkTank

- 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



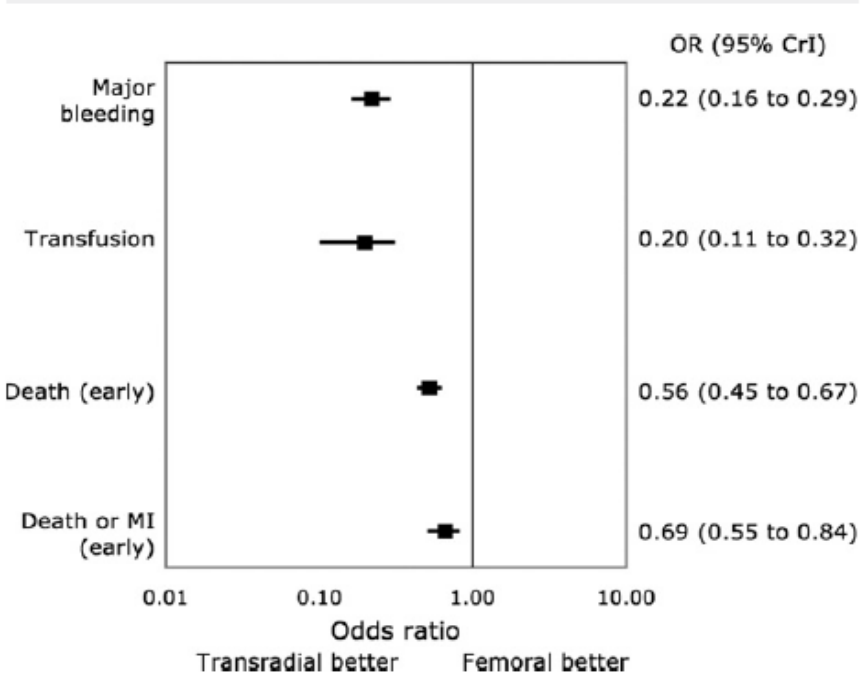




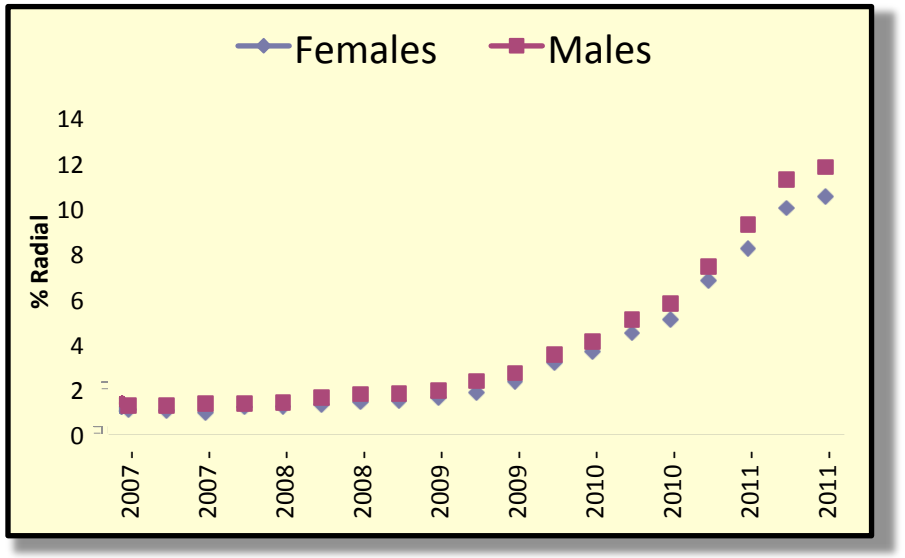
Alexander K, et. al. *Circ* 2006

DCRI

Radial approach



Radial approach in men vs. women
From the NCDR CathPCI Registry®



- 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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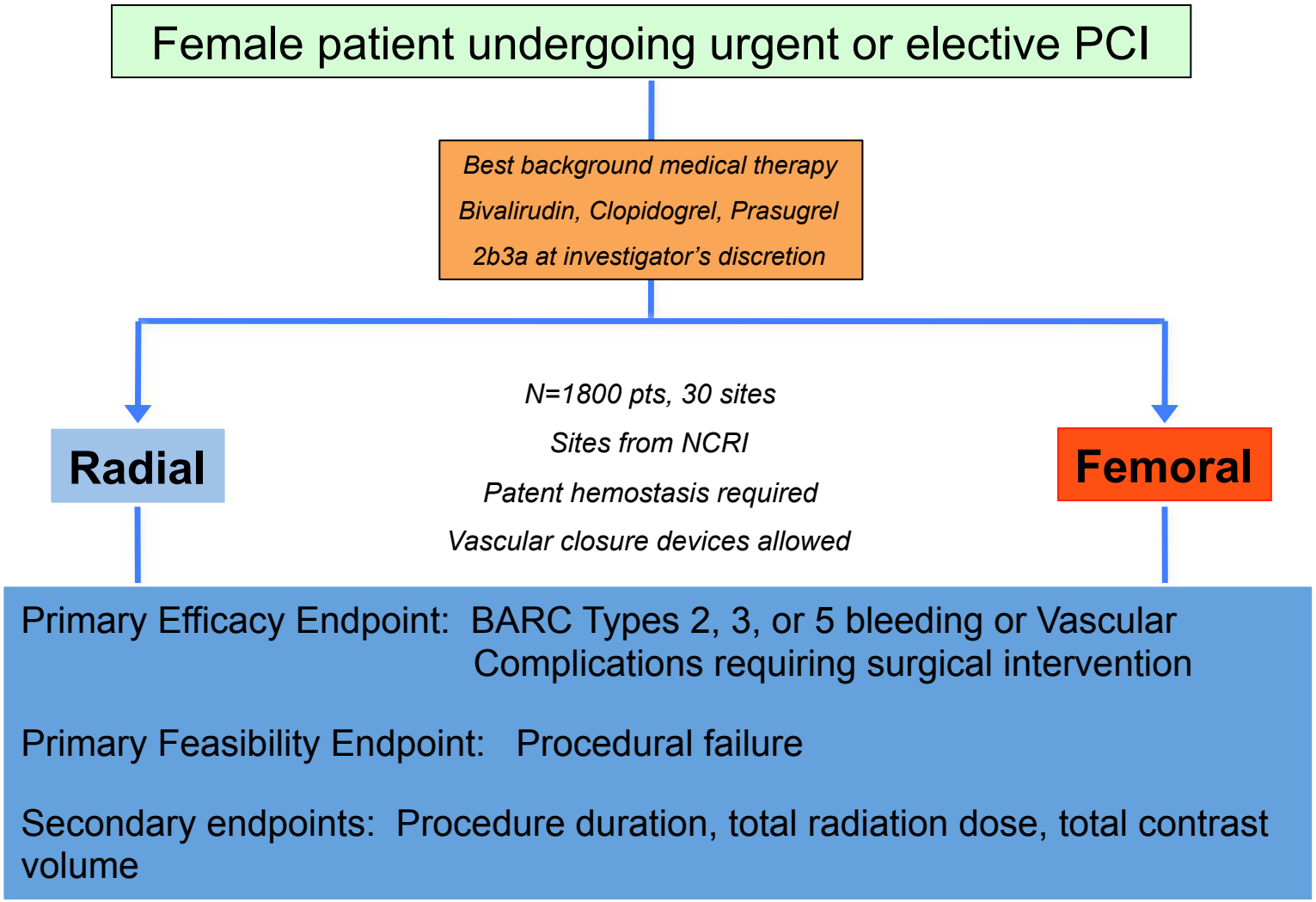
Study of Access site For Enhancing PCI for Women (SAFE-PCI for Women)*



*Planned in collaboration with ACC, CSRC, FDA Office of Women's Health

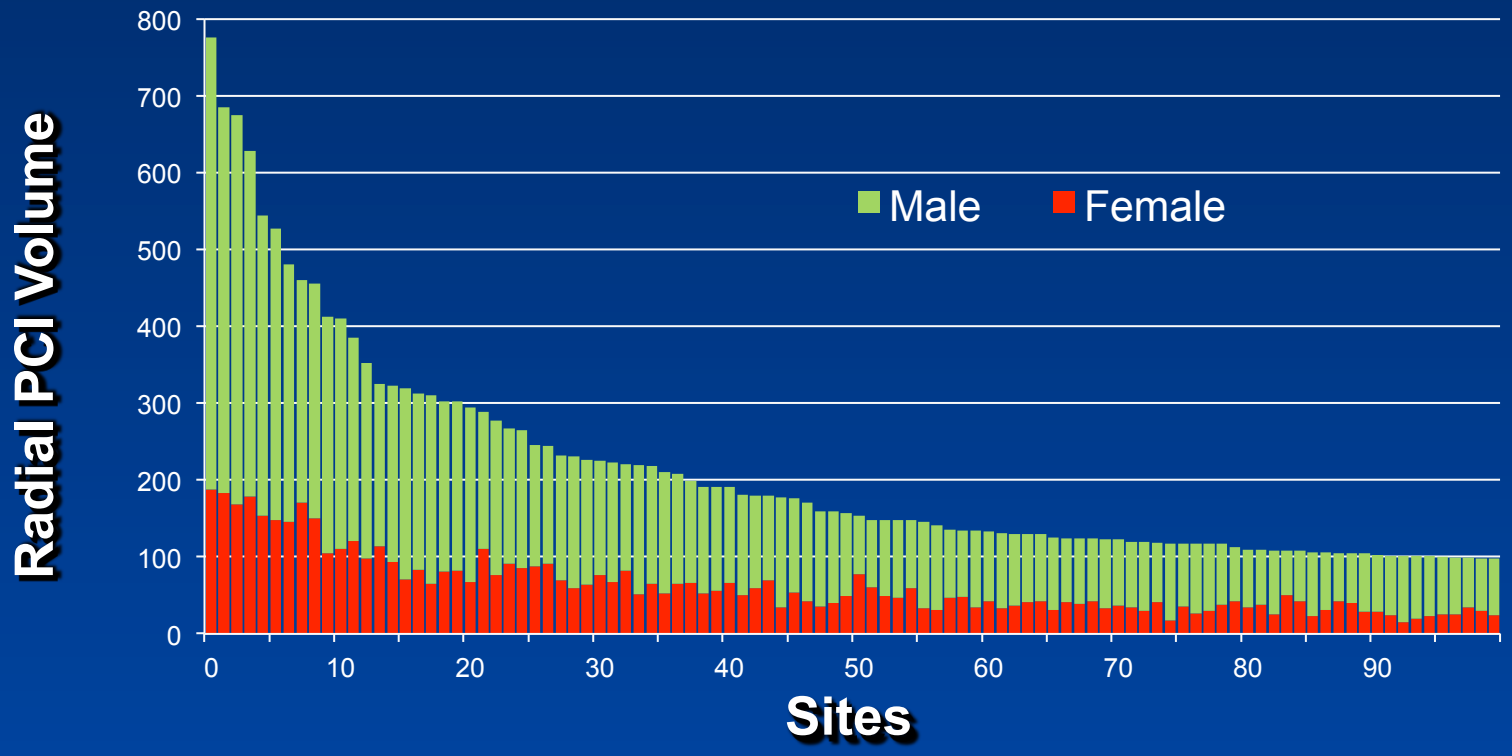
Methods – The National Cardiovascular Research Infrastructure

- **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**

NCRI
NATIONAL CARDIOVASCULAR RESEARCH INFRASTRUCTURE

Site identification
Using actual data rather than PI recall!

NCDR PCI records from 2009Q3 through Jan 2011



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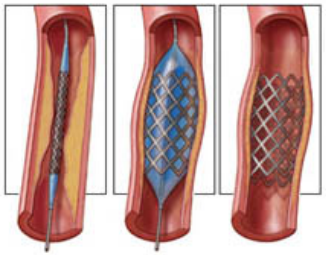
Methods - SAFE-PCI for Women workflow

Randomization



Demographics
Medical Hx
Procedural data

NCDR® National Cardiovascular Data Registry
CathPCI Registry®

Autopopulate

Unique pages for trial

Analytic Database

ORACLE

DCRI

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:

- **<u>Total randomized</u> – all women who are randomized regardless of whether they undergo PCI**
- **<u>PCI cohort</u> (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
    - 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

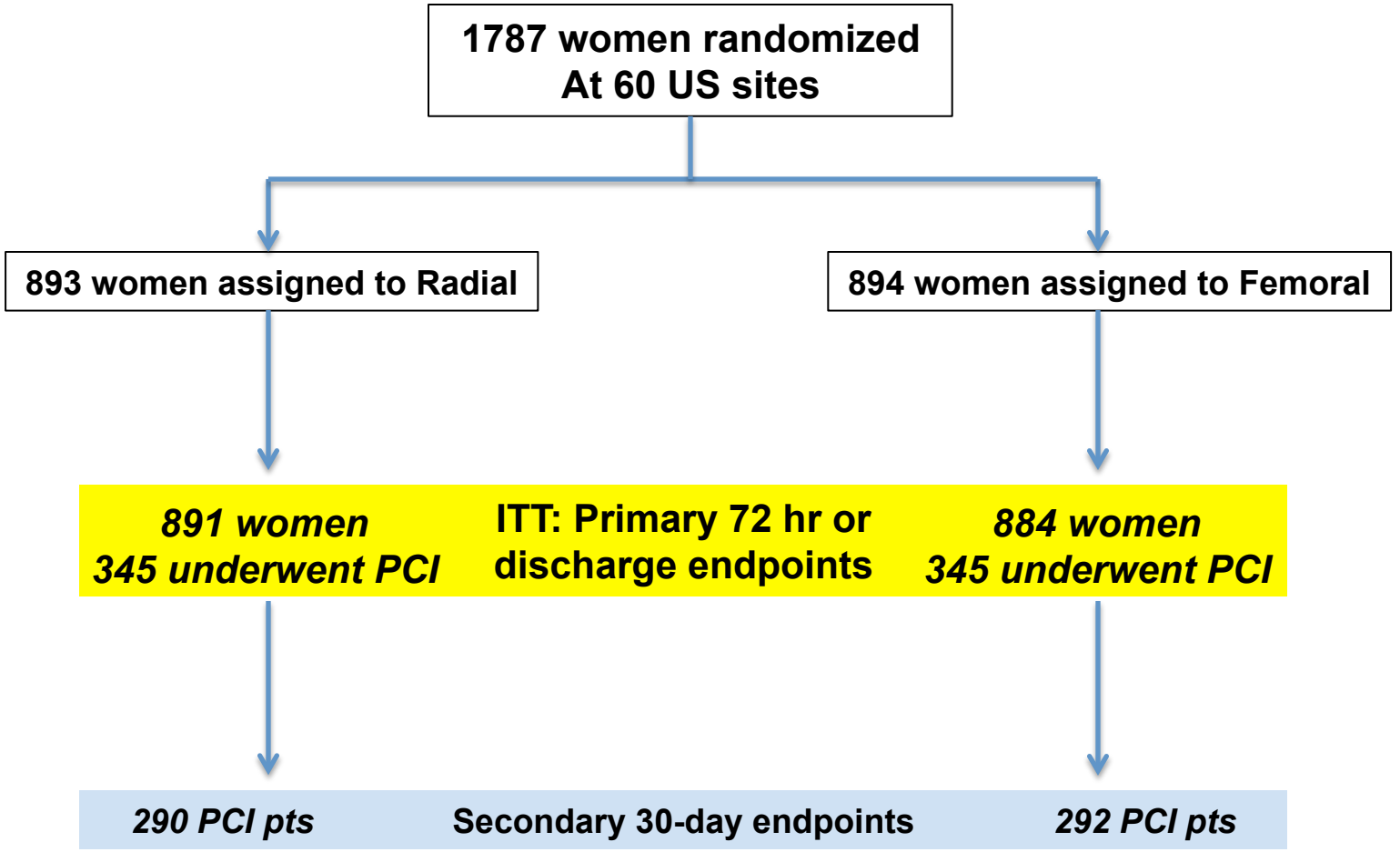
- **Sample size calculation**
  - Rate of BARC-type bleeding in NCDR CathPCI Registry among women without STEMI ~ 8.7%[1]
  - Assumptions
    - Femoral access bleeding or vascular complication rate – 8%
    - 50% reduction with radial access; 1576 patients provides 90% power at alpha 0.05
    - Sample 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



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

Results – Primary efficacy and feasibility endpoints

PCI cohort

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

- 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

	Radial (N=893)	Femoral (N=894)	OR (95% CI)	P
BARC 2, 3, 5 bleeding or Vasc Complications	0.6%	1.7%	0.3 (0.1-0.9)	0.03
Access site crossover	6.7%	1.9%	3.7 (2.1-6.4)	<0.001

- 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