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

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ABSTRACT

OBJECTIVES This study sought to determine the effect of radial access on outcomes in women undergoing percutaneous coronary intervention (PCI) using a registry-based randomized trial.

BACKGROUND Women are at increased risk of bleeding and vascular complications after PCI. The role of radial access in women is unclear.

METHODS Women undergoing cardiac catheterization or PCI were randomized to radial or femoral arterial access. Data from the CathPCI Registry and trial-specific data were merged into a final study database. The primary efficacy endpoint was Bleeding Academic Research Consortium type 2, 3, or 5 bleeding or vascular complications requiring intervention. The primary feasibility endpoint was access site crossover. The primary analysis cohort was the subgroup undergoing PCI; sensitivity analyses were conducted in the total randomized population.

RESULTS The trial was stopped early for a lower than expected event rate. A total of 1,787 women (691 undergoing PCI) were randomized at 60 sites. There was no significant difference in the primary efficacy endpoint between radial or femoral access among women undergoing PCI (radial 1.2% vs. 2.9% femoral, odds ratio [OR]: 0.39; 95% confidence interval [CI]: 0.12 to 1.27); among women undergoing cardiac catheterization or PCI, radial access significantly reduced bleeding and vascular complications (0.6% vs. 1.7%; OR: 0.32; 95% CI: 0.12 to 0.90). Access site crossover was significantly higher among women assigned to radial access (PCI cohort: 6.1% vs. 1.7%; OR: 3.65; 95% CI: 1.45 to 9.17); total randomized cohort: (6.7% vs. 1.9%; OR: 3.70; 95% CI: 2.14 to 6.40). More women preferred radial access.

CONCLUSIONS In this pragmatic trial, which was terminated early, the radial approach did not significantly reduce bleeding or vascular complications in women undergoing PCI. Access site crossover occurred more often in women assigned to radial access. (SAFE-PCI for Women; NCT01406236) (J Am Coll Cardiol Intv 2014;7:857–67) © 2014 by the American College of Cardiology Foundation.
Ischemic heart disease is a leading cause of death among women. Although currently recommended treatment strategies such as antithrombotic therapy and revascularization improve outcomes in patients with unstable angina and myocardial infarction (1), they have been studied in predominantly male populations. Compared with men, women are at increased risk of adverse outcomes after acute coronary syndrome (2) and invasive procedures such as percutaneous coronary intervention (PCI) (3). They are also at increased risk of bleeding complications of both medical therapies for acute coronary syndrome (ACS) (4) and femoral artery access for PCI (5).

Women presenting for cardiac catheterization present a unique challenge because, although they are at higher risk of femoral arterial access site bleeding, radial artery access may not be feasible. Compared with males, females have smaller radial arteries (10) that may be more prone to spasm, which is a major cause of radial procedure failure (11). In addition, women have been significantly underrepresented in previous studies comparing radial with femoral access. Thus, the role of radial artery access in women undergoing PCI remains unclear. Accordingly, we performed a large simple multicenter, prospective, randomized trial to determine the efficacy and feasibility of transradial PCI in women.

Methods

Study Design. The SAFE-PCI for Women trial was a multicenter, prospective, open-label, randomized, controlled clinical trial that used the NCRI as the platform for randomization and data collection. This was an investigator-initiated trial, the design of which has been reported previously (12). All trial management activities including data management and statistical analyses were performed at the Duke Clinical Research Institute. Duke University Medical Center’s Institutional Review Board approved the study, as did the review Boards of each participating center. All subjects provided written informed consent before randomization. None of the trial’s funding sources had a role in the design or implementation of the study or in the reporting of the data. The authors wrote all drafts of the manuscript and vouch for the integrity of and completeness of the data and analyses. Members of the trial committees are listed and the trial protocol is given in the Online Appendix.

National Cardiovascular Research Infrastructure. The NCRI is an investigator network created through collaboration between the Duke Clinical Research Institute and the American College of Cardiology and funded by the National Heart, Lung, and Blood Institute (grant 1RC2HL101512-01). The network includes sites participating in the National Cardiovascular Data Registry’s CathPCI Registry, an ongoing PCI registry co-sponsored red by the American College of Cardiology and the Society for Cardiovascular Angiography and Intervention. Under

Analysis, and interpretation of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication. Some funding sources reviewed the manuscript before submission. Dr. Rao is a consultant for The Medicines Company and Terumo Medical. Dr. Jolly has received research funding from Medtronic. Dr. Waksman has received consulting fees and honoraria from Biotronik, Medtronic, Boston Scientific, Abbott Vascular, and AstraZeneca; is on Speakers’ Bureau of AstraZeneca; and is a shareholder in Endothelix, Inc. Dr. Mehran has received research grant support from The Medicines Company, Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly & Co./Daichi Sankyo, Regado Biosciences, and STENTYS and consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen (JNJ), Maya Medical, and Merck and is on the Advisory Board of Covidien, Janssen Pharmaceuticals, and Sanofi-Aventis. Dr. Harrington has received research grants from Merck, The Medicines Company, Sanofi-Aventis, Bristol-Myers Squibb, and Portola Pharma and consulting fees from Merck, Bristol-Myers Squibb, AstraZeneca, Gilead, Janssen/J&J, Merck, WebMD, CSL Behring, MyoKardia, The Medicines Company, and Amgen. Dr. Krucoff has received consulting fees and research support from Medtronic, Abbott Vascular, Terumo, and Acris. Dr. Anstrom has received research support from AstraZeneca, Lilly, Medtronic and consulting fees from Abbott Vascular, AstraZeneca, BMS, Pfizer, GSK, and Ikaria. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 3, 2014; accepted April 7, 2014.
the construct of the NCRI, the data stream of registry-participating sites is accessed electronically to populate a clinical trial database for patients consented and enrolled in the SAFE-PCI for Women trial. Patient demographics, medical history, concomitant medications, procedure details, and in-hospital clinical outcomes routinely entered in the registry’s data collection system using standardized data elements are transferred to an electronic case report form. Additional trial-specific information including procedure information related to vascular access site and outcomes of interest not obtained as part of the registry are collected using additional electronic case report form pages per usual clinical trial standards. The NCRI computer systems, including randomization components, are formally validated, and the integrated registry and trial-specific data conform to the same quality requirements. Because radial access accounts for a minority of procedures in the United States (9), initial study sites were identified through the CathPCI Registry on the basis of their actual transradial PCI volume as described previously (12). Participating sites and principal investigators are listed in the Online Appendix.

**STUDY POPULATION.** Women undergoing urgent or elective PCI or diagnostic cardiac catheterization with the possibility of PCI were considered eligible for the trial if they were older than 18 years of age, able to provide informed consent, and undergoing evaluation or treatment for ischemic heart disease. Exclusion criteria included conditions precluding arterial access in either the femoral or radial artery (peripheral arterial disease severe enough to preclude arterial access, absence of collateral flow in both hands assessed by use of the Allen or the Barbeau (13) test, active hemodialysis fistula or graft in an arm to be used in case of assignment to radial access, international normalized ratio $\geq 1.5$ in the presence of ongoing treatment with vitamin K antagonists, receipt of an oral factor IIa or Xa inhibitor in the 24 h before the PCI procedure), known valvular heart disease requiring valve surgery, planned right heart catheterization, primary PCI for ST-segment elevation myocardial infarction (STEMI), known presence of bilateral internal mammary coronary bypass grafts, participation in an investigational drug or device study within 30 days before enrollment, and planned staged PCI within 30 days after index PCI.

Two patient cohorts were pre-specified: the total randomized cohort and the PCI cohort. The total randomized cohort included all patients randomized regardless of whether they underwent PCI. The PCI cohort was a subgroup of the total randomized cohort and included patients who underwent PCI as defined in the following. The primary analysis of efficacy and feasibility was performed in the PCI cohort, and a sensitivity analysis was performed in the total randomized cohort.

**RANDOMIZATION.** After providing written informed consent, patients were randomized 1:1 to either radial or femoral arterial access. Randomization was performed via an online randomization module incorporated into the registry trial database.

**STUDY PROCEDURES.** Patients assigned to radial access underwent radial artery puncture by either the counterpuncture technique or the anterior wall technique (14) on the basis of operator preference. For femoral arterial access, it was recommended that operators use either fluoroscopic or ultrasound guidance. Cardiac catheterization and PCI technique was per operator preference. Adjunctive antithrombotic therapy was recommended for all transradial procedures at a minimal dose of 40 IU/kg unfractionated heparin bolus to minimize the risk of radial artery occlusion (15). For transfemoral diagnostic procedures, antithrombotic therapy was at the discretion of the operator. Bivalirudin was recommended for PCI in all patients, at a dose per the package insert, in conjunction with aspirin and an oral P2Y12 inhibitor. Use of glycoprotein Ilb/Ilia inhibitors was also by operator preference.

An immediate post-procedure “patent” hemostasis technique (16) was recommended for all patients after radial access; femoral arterial sheaths were removed $\leq 2$ h after the discontinuation of bivalirudin or when the activated clotting time was $<150$ s if unfractionated heparin was used for the PCI. Manual compression or closure devices were permitted at the operator’s discretion.

**ENDPOINTS AND DEFINITIONS.** There were 2 primary endpoints: the primary efficacy endpoint was bleeding or vascular complications requiring intervention occurring within 72 h of the procedure or by hospital discharge, whichever came first; the primary feasibility endpoint was access site crossover. Bleeding was defined according to the Bleeding Academic Research Consortium (BARC) definition (17), and the endpoint of interest for the study included a composite of BARC type 2, 3, or 5 bleeding events (definitions given in the Online Appendix). Vascular complications included a composite of arteriovenous fistula, arterial pseudoaneurysm, or arterial occlusion requiring intervention. Access site crossover was defined as the inability to complete the procedure from the assigned arterial access site,
requiring conversion from radial to femoral access or vice versa for procedure completion. Conversions to the contralateral radial artery in case of assignment to the radial approach (or contralateral femoral artery in case of assigned femoral approach) were not considered access site crossovers. Secondary endpoints included procedure duration, total procedure radiation dose to the patient measured as air kerma in milligrays (mGy), total contrast volume used during the procedure measured in milliliters, and the 30-day occurrence of death, vascular complications (as defined previously), or unplanned revascularization. At 30 days, we also assessed the patient’s access site preference for their next procedure should the patient require one. Secondary and 30-day outcomes were assessed only in patients who underwent PCI. A clinical events committee adjudicated all suspected primary efficacy endpoint events.

Because the risk of the primary efficacy endpoint (bleeding or vascular complications) is dependent on the combination of intensive anticoagulation and arteriotomy, a patient was grouped in the PCI cohort if a coronary guidewire exited the coronary guide catheter for the purpose of diagnosis or treatment, and systemic antithrombotics were given to achieve therapeutic levels of anticoagulation. This included diagnostic procedures such as fractional flow reserve, intravascular ultrasound, and optical coherence tomography as well as coronary angioplasty and/or stenting.

STATISTICAL ANALYSIS. On the basis of the actual rate of bleeding events using a definition approximating BARC type 2, 3, or 5 bleeding among women without STEMI undergoing PCI in the CathPCI Registry, we assumed that the rate of bleeding or vascular complications in the femoral access arm would be 8% (18). Using an estimate of bleeding reduction associated with radial access from observational and previous clinical trial data (8), we assumed a 50% decrease in the rate of the primary efficacy endpoint in the radial access arm. A sample size of 1,576 women undergoing PCI provided 90% power to detect statistically significant differences at a 2-sided alpha of 0.05. The sample size was set at 1,800 patients (900 patients per arm) due to uncertainty in event rates. Because of the common practice of ad-hoc PCI, we planned to randomize 3,000 women undergoing cardiac catheterization to obtain 1,800 undergoing PCI. No formal power calculation was used for the primary feasibility endpoint.

After 1,120 patients had been randomized (446 of whom had undergone PCI), an unplanned meeting of the Data Safety Monitoring Board (DSMB) was convened due to a lower than expected rate of the primary efficacy endpoint. The DSMB recommended terminating the trial because it was unlikely that the trial would show a difference between the access site strategies on the basis of the planned sample size. There was no evidence of harm in either arm. The steering committee met to discuss the recommendation and, because there were no safety issues, decided to continue enrollment until enrollment in a quality-of-life substudy was completed (300 patients undergoing coronary angiography or PCI). The results of this substudy will be reported separately.

Descriptive summaries of the distribution of continuous variables are presented as mean ± SD, or median, 25th, 75th percentiles, and subject counts. Categorical variables are summarized in terms of frequencies and percentages. The primary analysis of efficacy and feasibility was performed by modified intention-to-treat in the PCI cohort, and sensitivity analyses of efficacy and feasibility were performed in the total randomized cohort. Odds ratios for the primary efficacy and feasibility endpoints were generated using logistic regression with indicator variables for randomized assignment, planned use of glycoprotein IIb/IIIa inhibitors during PCI, and elective PCI for stable angina versus ACS. Analyses of secondary endpoints also followed modified intention-to-treat principles and were conducted within the PCI cohort. Secondary analysis of 30-day death, vascular complications, or unplanned revascularization used the logistic regression and included indicator variables for randomized assignment, planned use of glycoprotein IIb/IIIa inhibitors during PCI, and elective PCI for stable angina versus ACS. Analyses of secondary continuous outcome measures of procedure duration, total radiation dose, total contrast volume were conducted using linear models with a binary indicator variable for randomized assignment.

Two pre-specified subgroup analyses for the primary efficacy endpoint were performed: ACS versus non-ACS in the PCI cohort and quartiles of site radial volume in the total randomized cohort. A post-hoc interaction for the primary efficacy endpoint was examined in the total randomized cohort between patients who underwent PCI and those who did not. We also performed an analysis according to the access site used to complete the procedure (as treated analysis) in both the randomized and PCI cohorts. Exploratory comparisons between the radial and femoral groups were conducted for 72 h or hospital discharge bleeding events using the Thrombolysis In Myocardial Infarction (19) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) (20) trial definitions, as well as bleeding and vascular
complications that were identified by sites and reported in the CathPCI Registry. Except for Thrombolysis In Myocardial Infarction major, the definitions were slightly modified on the basis of data availability (Online Appendix). These exploratory endpoints were reconstructed from events reported by sites and were not adjudicated. A 2-sided p value \( \leq 0.05 \) was used for statistical significance. All analyses were performed at the Duke Clinical Research Institute using SAS version 9.2 (SAS Institute, Cary, North Carolina).

**RESULTS**

Between September 2011 and July 2013, 1,787 women were randomized, 691 (38.7%) of whom underwent PCI, at 60 sites in the United States; 44 of 62 (70.9%) activated sites enrolled at least 10 patients. Of the total randomized cohort, 893 were assigned to radial access and 894 were assigned to femoral access; of the PCI cohort, 345 and 346 were assigned to radial and femoral access, respectively (Fig. 1). Follow-up for the primary endpoints was available for 99.9% of the PCI cohort and 99.3% of the total randomized cohort. Baseline characteristics of the total randomized and PCI cohorts are shown in Tables 1 and 2. There were no significant differences between the randomized groups in either cohort. The majority of procedures were performed for non-ST-segment elevation ACS. Unfractionated heparin was given during the diagnostic catheterization to 65.9% of the

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**FIGURE 1** Randomization and Follow-up

Women undergoing urgent or elective PCI or coronary angiography with the possibility of PCI were randomized to either radial or femoral arterial access. Shown are the number of patients in each group, the number of patients in each group who underwent PCI, and the number of patients assessed at 30 days for the secondary endpoint. FFR = fractional flow reserve; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.
TABLE 1 Baseline Characteristics of the Total Randomized Cohort

<table>
<thead>
<tr>
<th></th>
<th>Radial (n = 893)</th>
<th>Femoral (n = 894)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>63.3 (55.1, 72.2)</td>
<td>63.9 (55.7, 72.0)</td>
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<td>BMI, kg/m²</td>
<td>30.5 (26.1, 35.1)</td>
<td>30.8 (26.5, 35.8)</td>
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<td>Current or recent smoking</td>
<td>243 (27.2)</td>
<td>216 (24.2)</td>
<td>0.14</td>
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<tr>
<td>Hypertension</td>
<td>710 (79.5)</td>
<td>714 (79.9)</td>
<td>0.85</td>
</tr>
<tr>
<td>Previous MI</td>
<td>160 (17.9)</td>
<td>175 (19.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>40 (4.5)</td>
<td>57 (6.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>3 (0.3)</td>
<td>3 (0.3)</td>
<td>0.99</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>51 (5.7)</td>
<td>54 (6.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>314 (35.2)</td>
<td>313 (35.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-ACS: 418 (46.8) 389 (43.5)
NSTEACS: 471 (52.7) 503 (56.3)
STEMI: 4 (0.4) 2 (0.2)

Values shown are number (%) or median (25th, 75th percentiles).
BMI = body mass index; MI = myocardial infarction; CABG = coronary artery bypass grafting; ACS = acute coronary syndrome; NSTEACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Baseline Clinical and Procedure Characteristics of the PCI Cohort

<table>
<thead>
<tr>
<th></th>
<th>Radial (n = 345)</th>
<th>Femoral (n = 346)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65.1 (56.5, 73.7)</td>
<td>63.9 (56.5, 72.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.1 (25.9, 34.5)</td>
<td>30.5 (26.9, 35.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Current or recent smoking</td>
<td>106 (30.7)</td>
<td>102 (29.5)</td>
<td>0.72</td>
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<tr>
<td>Hypertension</td>
<td>296 (85.8)</td>
<td>295 (85.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Previous MI</td>
<td>82 (23.8)</td>
<td>96 (27.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>25 (7.2)</td>
<td>34 (9.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
<td>0.99</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>23 (6.7)</td>
<td>29 (8.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>144 (41.7)</td>
<td>154 (44.5)</td>
<td>0.46</td>
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<td>Clinical presentation</td>
<td>0.50</td>
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<tr>
<td>Non-ACS</td>
<td>98 (28.4)</td>
<td>94 (27.2)</td>
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<tr>
<td>NSTEACS</td>
<td>244 (70.7)</td>
<td>251 (72.5)</td>
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<tr>
<td>STEMI</td>
<td>3 (0.9)</td>
<td>1 (0.3)</td>
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<td>PCI status*</td>
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<td>Elective</td>
<td>133 (46.5)</td>
<td>123 (43.6)</td>
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<tr>
<td>Urgent</td>
<td>149 (52.1)</td>
<td>157 (55.7)</td>
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<tr>
<td>Emergent</td>
<td>4 (1.4)</td>
<td>2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Bivalirudin*</td>
<td>166 (59.1)</td>
<td>181 (65.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor*</td>
<td>32 (11.4)</td>
<td>32 (11.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Vascular closure device*</td>
<td>15 (5.1)</td>
<td>194 (65.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values shown are number (%) or median (25th, 75th percentiles). *Excludes patients who underwent fractional flow reserve, intravascular ultrasound, or optical coherence tomography without coronary angioplasty or stenting. †Patients who had any femoral arterial access.
PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

patients assigned to radial access and 25.7% of the patients assigned to femoral access in the PCI cohort. Bivalirudin was used as the anticoagulant during PCI for 59.1% and 65.8% of procedures in the radial and femoral groups, respectively. Vascular closure devices were used for hemostasis in 65.5% of the patients assigned to femoral access.

The primary efficacy and feasibility outcomes and secondary outcomes for the PCI and total randomized cohorts are shown in Table 3. The rate of BARC type 2, 3, or 5 bleeding or vascular complications requiring intervention in the femoral arm of the PCI cohort, which was the primary analysis cohort, was lower than predicted (2.9%). Compared with femoral access, radial access reduced the primary efficacy endpoint in this cohort by 60% in the PCI cohort, which did not reach statistical significance. There were no significant interactions noted in the pre-specified subgroups of ACS versus non-ACS in the PCI cohort (Fig. 2). In the total randomized cohort, radial access significantly reduced bleeding and vascular complications by 70% compared with femoral access. There was no significant interaction by volume of radial procedures performed at participating sites; similarly, the post-hoc analysis of the interaction between patients who underwent PCI and those who did not was also not significant (p = 0.58) (Fig. 2). With respect to the primary feasibility endpoint, the rate of conversion to femoral access from radial access was significantly higher than the rate of conversion to radial access from femoral access in both cohorts. Only 1 patient, who was assigned to femoral access, did not have her diagnostic catheterization procedure successfully completed from either access site. The major reason for conversion from radial to femoral access was radial artery spasm occurring in 42.9% of crossover patients in the PCI cohort and 43.6% of crossover patients in the total randomized cohort. Other reasons for access site crossover are listed in the Online Appendix, as are the primary efficacy results in the as-treated analysis in both cohorts, which were similar to the intention-to-treat results.

Secondary outcomes of procedure duration and total radiation dose were not statistically different between the radial and femoral access groups (Table 4); the mean total contrast volume was significantly higher among patients assigned to femoral access. Thirty-day follow-up was available for 582 patients in the PCI cohort (84.2%). The rate of 30-day death, vascular complications, or unplanned revascularization was not significantly different between the 2 arms. Exploratory analyses using different bleeding definitions also showed no significant differences in either the total randomized or PCI cohort (Table 5). At 30-day follow-up, 71.9% of patients assigned to the radial approach preferred radial access for their next procedure; 23.5% of patients...
assigned to the femoral approach preferred femoral access for their next procedure.

**DISCUSSION**

The SAFE-PCI for Women trial represents several “firsts” for clinical trials. It is the first U.S.-based multicenter, prospective, randomized trial comparing radial and femoral approaches to cardiac catheterization or PCI and is the first randomized trial of PCI strategies performed solely in women. In addition, it is the first registry-based trial in the United States with patient-level randomization. Importantly, this registry-trial infrastructure provided several efficiencies in site selection, data collection, and site workload. Thus, the results and methodology of the trial inform clinical practice and provide a unique model for future clinical research.

This study was terminated early at the recommendation of the DSMB on the basis of a lower than expected rate of bleeding or vascular complications. Although there was a trend toward benefit, radial access did not significantly reduce bleeding or vascular complications among women undergoing PCI. The PCI cohort was essentially a subgroup of the total randomized cohort in which radial access did significantly reduce bleeding and vascular complications. Thus, this lack of a significant difference may be due to the limited sample size of women undergoing PCI. There was no significant interaction between patients undergoing PCI and those undergoing diagnostic catheterization for the primary efficacy endpoint, suggesting that the benefit of radial access is consistent across both the PCI and total randomized cohorts. Although the reduced sample size limits the statistical certainty of this interpretation, it is encouraging that the findings in the total cohort of women undergoing diagnostic catheterization or PCI are consistent with the benefits of the radial approach to bleeding reduction in mixed-sex populations (8).

Also consistent with previous studies was the need to convert to femoral access from radial, which was statistically higher than the need to convert to radial access from femoral access. The major reason was arterial spasm, and the rate of conversion was similar to that seen in the RIVAL (Radial Versus Femoral Access for Coronary Intervention) trial, which included both men and women (21). Future iterations in PCI catheters and devices, such as improved hydrophilic coatings for catheters and extremely slender 3- and 4-French systems (22), may permit the application of the radial approach to more women and reduce access site crossover rates. In addition, ulnar artery access may also be an alternative if proven to be as safe as the radial approach. Taken together with previous studies, the results of the SAFE-PCI for Women trial suggest that an initial radial access strategy is reasonable in women undergoing cardiac catheterization or PCI with the recognition that a proportion of patients may require conversion to femoral access.

Although ischemic heart disease is a leading cause of mortality in women, they are significantly underrepresented in clinical trials. For example, women have often comprised less than a third of the populations of clinical trials of recommended secondary prevention strategies (23). In addition, trials that have defined the role of revascularization strategies for high-risk ACS patients or failure of medical therapy in stable angina have included mostly men (24,25). There is reason to believe that women may respond to treatment strategies differently from men, and it is clear that women are at significantly higher risk of bleeding with antithrombotic therapy for ACS and after PCI (18). Such bleeding complications often occur at the vascular access site and are associated with subsequent adverse events such as myocardial infarction, stroke, stent thrombosis, and even death (26). The majority of PCI procedures in the United

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| TABLE 3 Primary Efficacy and Feasibility Endpoints in the Total Randomized and PCI Cohorts |
|---------------------------------------------|------------------|------------------|-----|-------|
| PCI Cohort                                  | Radial (n = 345) | Femoral (n = 345) | OR (95% CI) | p Value |
| BARC type 2, 3, or 5 bleeding or vascular complications | 4 (1.2) | 10 (2.9) | 0.39 (0.12-1.27) | 0.12 |
| Type 2                                      | 3 (0.9) | 6 (1.7) |            |       |
| Type 3                                      | 1 (0.3) | 4 (1.2) |            |       |
| Type 5                                      | 0 | 0 |            |       |
| Arteriovenous fistula                       | 0 | 0 |            |       |
| Arterial pseudoaneurysm                     | 1 (0.3) | 0 |            |       |
| Arterial occlusion                          | 0 | 0 |            |       |
| Access site crossover                       | 21 (6.1) | 6 (1.7) | 3.65 (1.45-9.17) | <0.01 |

<table>
<thead>
<tr>
<th>Total Randomized Cohort</th>
<th>Radial (n = 891)</th>
<th>Femoral (n = 884)</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC type 2, 3, or 5 bleeding or vascular complications</td>
<td>5 (0.6)</td>
<td>15 (1.7)</td>
<td>0.32 (0.12-0.90)</td>
<td>0.03</td>
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<td>Type 2</td>
<td>4 (0.4)</td>
<td>10 (1.1)</td>
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<td>Type 3</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
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<td>Type 5</td>
<td>0</td>
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</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial pseudoaneurysm</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial occlusion</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Access site crossover</td>
<td>60 (6.7)</td>
<td>17 (1.9)</td>
<td>3.70 (2.14-6.40)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BARC = Bleeding Academic Research Consortium; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention.
States are performed via femoral artery access (9). The femoral artery is large and readily accommodates PCI equipment, and spasm is rare. On the other hand, hemostasis after femoral access requires the effect of procedural anticoagulation to wane, thus necessitating prolonged post-PCI bed rest. In addition, the femoral artery is deeply situated, particularly in overweight or obese patients, can have atherosclerotic narrowing, needs relatively intense manual compression to achieve hemostasis after PCI, and is difficult to monitor for occult bleeding such as retroperitoneal hematomas, which are associated with increased morbidity and mortality (26).

Several strategies have emerged to reduce the risk of post-PCI bleeding and are termed “bleeding avoidance strategies,” which include the direct thrombin inhibitor bivalirudin, potentially the use of vascular closure devices, and radial access (27). In observational studies, radial artery access is associated with a large reduction in access site bleeding and major vascular complications compared with femoral access (8). The radial artery is superficial and readily compressible and rarely has atherosclerosis. In patients at high risk of bleeding, such as those with STEMI, radial access for primary PCI may also reduce mortality by reducing major bleeding events (28).

<table>
<thead>
<tr>
<th>TABLE 4 Secondary Endpoints</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Procedure duration, min</td>
</tr>
<tr>
<td>Total radiation dose, air kerma, mGy</td>
</tr>
<tr>
<td>Total contrast volume, ml</td>
</tr>
<tr>
<td>30-day death, vascular complications, or unplanned revascularization*</td>
</tr>
<tr>
<td>Patient preference for next procedure†</td>
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Values shown are mean ± SD or number (%). *Odds ratio: 1.58; 95% confidence interval: 0.71 to 3.48. †Available in 320 patients assigned to radial access and 319 patients assigned to femoral access.

FIGURE 2 Odds Ratios for the Primary Efficacy Endpoint in Subgroups of Patients

Odds ratios for the incidence of Bleeding Academic Research Consortium type 2, 3, or 5 bleeding events or vascular complications requiring intervention occurring within 72 h of the index PCI or at hospital discharge, whichever occurred first. Analysis of the interaction between ACS and non-ACS patients was performed in the PCI cohort; analysis of the interaction by site radial volume and between patients who underwent PCI versus those who underwent diagnostic catheterization was performed in the total randomized cohort. Analysis of the interaction between patients who underwent PCI versus those who underwent diagnostic catheterization was performed post-hoc. ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.
Women trial, which included endpoint adjudication translated into faster enrollment and decreased trial radial procedure volumes. This strategy achieved trial CathPCI Registry to identify sites using actual trans-
whic his h am per e dB yr e c a l b i a s,w el e v e ag e dt h e method of using site surveys to determine eligibility, 
pulated with data from the registry, thus reducing proportion of the trial case report form was autopo-
enrolled at least 10 patients. In addition, a large clinical trial operations. More than 96% of sites 
metrics for enrollment that far exceed traditional 
necessitating conversion to the femoral approach(11). 
large-bore catheters in some patients, and arterial 
caliber radial arteries than men(10), and thus spasm 
may be a more prevalent technical issue. Hence, our 
rationale for performing the SAFE-PCI for Women 
trial was rooted in the lack of data on radial access 
in women and the equipoise that although the 
radial approach may reduce post-procedure bleeding, 
it may require conversion to femoral access in some 
patients.
Performing a study to address this equipoise in an 
underrepresented patient subgroup like women 
posed several challenges including identifying in-
vestigators with requisite transradial procedure pro-
ficiency and the costs of conducting a prospective, 
randomized trial (12,29). An important aspect of the 
SAFE-PCI for Women trial was the embedding of the randomization into an ongoing PCI registry. At 
the time that enrollment began, radial access accounted for <10% of PCI procedures performed in the United States (9). Therefore, it was fundamentally important to include sites with proficiency in the radial approach. Rather than rely on the traditional method of using site surveys to determine eligibility, which is hampered by recall bias, we leveraged the CathPCI Registry to identify sites using actual trans-
radial procedure volumes. This strategy achieved trial metrics for enrollment that far exceed traditional 
clinical trial operations. More than 96% of sites 
enrolled at least 1 patient and nearly 71% of sites 
enrolled at least 10 patients. In addition, a large proportion of the trial case report form was autopo-
pulated with data from the registry, thus reducing 
site-level workload. These efficiencies in workflow 
translated into faster enrollment and decreased trial 
costs. The overall budget for the SAFE-PCI for 
Women trial, which included endpoint adjudication

<table>
<thead>
<tr>
<th>TABLE 5 Bleeding Outcomes at 72 H or Hospital Discharge Using Different Bleeding Definitions in the Total Randomized Cohort</th>
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<tbody>
<tr>
<td>Radial (n = 891)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>TIMI major</td>
</tr>
<tr>
<td>TIMI minor</td>
</tr>
<tr>
<td>ACUITY major</td>
</tr>
<tr>
<td>CathPCI Registry bleeding</td>
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<tr>
<td>CathPCI Registry vascular complications</td>
</tr>
</tbody>
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Events are reconstructed from site-reported events and not adjudicated; see Online Appendix for definitions.
TIMI = Thrombolysis In Myocardial Infarction.

However, its small caliber can exclude the use of large-bore catheters in some patients, and arterial 
spasm is a major cause of radial access site crossover necessitating conversion to the femoral approach (11). 
Women, in particular, are noted to have smaller 
caliber radial arteries than men (10), and thus spasm may be expected, thus permitting detection of a statistically significant benefit in the total randomized cohort. Although we used the CathPCI Registry to estimate the rate of bleeding or vascular complications, the rate in the trial was much lower than expected. This low underlying rate of the primary endpoint could be attributed to vascular access expertise at the sites that participated in the trial compared with the other sites in the registry, the Hawthorne effect (32), the preponderance of bivalirudin use, or a 
combination of these factors. Second, the investigators who participated in the trial were all 
involved in using the radial approach. It is likely that these results may not translate to novice radial approach operators who may initially experience higher rates of conversion to femoral approach. Studies indicate that although the learning curve for 
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involved in using the radial approach. It is likely that these results may not translate to novice radial approach operators who may initially experience higher rates of conversion to femoral access during the learning phase. Finally, we excluded patients undergoing primary PCI in our trial due to the relatively lower overall proficiency with radial approach in the United States at the time that the trial began, which could have led to prolonged times to reperfusion. Data that emerged during the conduct of the SAFE-PCI for Women trial suggests that transradial primary PCI may lower mortality compared with the femoral approach (34). On the basis of the site activity and experience in the SAFE-PCI for Women trial and the demonstrated efficiency of the NCRI model, a randomized trial comparing both clinical outcomes and door-to-balloon time metrics between radial and femoral access in STEMI patients seems both warranted and feasible.
CONCLUSIONS

In the SAFE-PCI for Women trial that was terminated early, radial access did not significantly lower the incidence of bleeding or vascular complications in women undergoing PCI; however, in the larger sample size of women undergoing cardiac catheterization or PCI, radial access significantly reduced bleeding or vascular complications. There was a need to convert from radial access to femoral access in 6.7% of patients. As the first registry-based, randomized trial performed in the United States, this study demonstrates a new paradigm for conducting efficient pragmatic clinical trials.

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REFERENCES


KEY WORDS PCI, radial approach, women and heart disease

APPENDIX For the list of trial committee members and the trial protocol, please see the online version of this article.