

EDITORIAL

# Sex-Based Differences in Revascularization Outcomes: Is It Time for a Dedicated Randomized Trial in Women?

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**R**evascularization for obstructive left main coronary artery disease (LMCAD) is the standard of care for patients who present with stable CAD or acute coronary syndromes.<sup>1,2</sup> With advances in drug-eluting stents (DES) and procedural technique, including intravascular imaging and physiologic guidance, selected patients with LMCAD are suitable candidates for revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). However, individual clinical and angiographic characteristics of each patient may pose different challenges for each procedure, affecting early and late outcomes. Identifying those features that might provide an improved prognosis with PCI versus CABG for the individual patient thus becomes paramount. For example, randomized trials comparing CABG with first-generation DES for LMCAD revascularization showed superiority of PCI in terms of fewer procedural complications, including stroke and myocardial infarction (MI), and earlier improvement in quality of life, noninferiority of PCI with respect to death or (MI) at 5 years, and a higher rate of target vessel revascularization with PCI.<sup>3,4</sup> However, patients with the greatest anatomic complexity according to the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) score had significantly worse outcomes after PCI compared with CABG.

## See Article by Yoon et al.

The EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Graft Surgery for Effectiveness of Left Main Revascularization) and NOBLE (Nordic-Baltic-British Left Main Revascularization) trials compared contemporary DES with CABG for LMCAD in patients with mostly low to intermediate risk SYNTAX scores. In the EXCEL trial, piecewise hazards models demonstrated that patients who underwent PCI had a lower upfront (30-day) risk of procedural complications and MI, similar outcomes between 30 days and 1 year, and a higher composite risk of death, MI, or target vessel revascularization between 1 and 5 years.<sup>5</sup> Quality of life was substantially better after PCI compared with CABG at 30 days, but then comparable at 1 year and beyond.<sup>6</sup> In the NOBLE trial, at 5 years, there were no significant 5-year differences in mortality after PCI and CABG, but PCI-treated patients had higher long-term rates of nonprocedural MI and repeat revascularization.<sup>7</sup> Recently, a meta-analysis of multiple trials showed no significant long-term differences in all-cause mortality, cardiac death, and MI between PCI with DES and CABG for treatment of LMCAD.<sup>8</sup> Ten-year outcomes from 2 of these randomized trials also showed comparable long-term mortality between the procedures.<sup>9,10</sup>

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The relative outcomes of PCI versus CABG may (surprisingly to some) vary in patients with LMCAD and multivessel disease (MVD). In the 10-year follow-up from the SYNTAX trial, mortality was lower after CABG compared with PCI in patients with MVD but not in patients with LMCAD.<sup>9</sup> A systematic review of 11 trials comparing PCI with CABG in patients with multivessel disease or LMCAD reported similar findings.<sup>11</sup> The LMCA is a large vessel and contains typically short lesions that are relatively easy to stent for experienced interventional cardiologists, even when the distal LM bifurcation is involved. In this regard the SYNTAX score may overweight the anatomic complexity of LMCAD. In contrast, severe MVD poses greater challenges for complete revascularization after PCI compared with CABG, and bypass grafts may prophylactically treat angiographically mild “vulnerable plaques,” contributing to the lower rate of late MI after CABG compared with PCI in such patients.

The role of sex in determining the optimal revascularization strategy for patients with LMCAD and MVD is less clear. Some studies have shown improved outcomes in women with intermediate to high SYNTAX scores undergoing CABG as opposed to PCI,<sup>12,13</sup> whereas in other studies, the benefit of CABG in women varied according to geography of treatment.<sup>14</sup> In the EXCEL trial, 30-day and 3-year outcomes tended to be worse in women compared with men undergoing PCI but not after CABG, although the relative risks between the procedures for the primary composite outcome of death, MI, or stroke were consistent in men and women at 5 years.<sup>5,15</sup> Other studies have demonstrated no significant interactions between sex and revascularization modality.<sup>7,11,16</sup>

In this issue of the *Journal of the American Heart Association (JAHA)*, Yoon et al address the important question of long-term outcomes in women undergoing PCI versus CABG for LMCAD.<sup>17</sup> This extended follow-up of the MAIN-COMPARE registry (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization from Multi-Center Registry) included consecutive patients who underwent PCI or CABG for LMCAD in South Korea from January 2000 to June 2006 with either bare metal stents or first-generation DES (the devices available at the time of treatment). To compensate for the nonrandomized design of the study, the authors used inverse-probability-treatment weighting for the primary analysis. Piecewise hazards models were assessed between 0 to 1 year, 1 to 5 years, and 5 to 10 years to examine short-term, mid-term, and long-term effects of PCI versus CABG.

Of the 2240 patients enrolled in the MAIN-COMPARE registry, 1609 were men and 631 were women. There were no significant differences in the

adjusted composite outcome of death, Q-wave MI, or stroke at 10 years after PCI versus CABG in either men or women, with no significant interactions suggesting long-term differences in relative risks. However, there were different time-related interactions noted according to sex and revascularization modality. Specifically, among women, the adjusted 10-year composite risk of death, Q-wave MI, or stroke was lower after PCI compared with CABG with the first year of revascularization (2.8% versus 6.5%, hazard ratio [HR], 0.41; 95% CI, 0.19–0.91;  $P=0.028$ ), was higher after PCI between years 1 and 5 (12.9% versus 4.6%, HR, 2.93; 95% CI, 1.59–5.39;  $P=0.001$ ), and was similar after PCI and CABG between 5 and 10 years (10.6% versus 11.5%, HR, 0.92; 95% CI, 0.58–1.49;  $P=0.75$ ). In contrast, there were no significant differences in the adjusted composite rates of death, Q-wave MI, or stroke in men undergoing PCI versus CABG, with consistent and similar risks during each of the 3 follow-up periods. Target vessel revascularization, an outcome of lesser importance, was higher after PCI compared with CABG in all time periods in both women and men. Unfortunately, other outcomes such as atrial fibrillation, chronic kidney disease, angina relief, and quality-of-life measures were not available.

The present study has numerous strengths, in particular its long-term follow-up (median 11.9 years) and excellent rate of major event ascertainment (98.7%). The use of piecewise hazards models provides useful insight when nonproportional hazards are present.<sup>18</sup> Its results are consistent in many ways with the recent 10-year outcomes reported from the SYNTAX (TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial. In SYNTAX, the 5-year mortality rate was significantly higher in women who underwent PCI compared with CABG (19.3% versus 10.3%,  $P=0.01$ ). However, at 10 years, there was no significant difference in mortality between PCI and CABG (33.0% versus 32.5%,  $P=0.60$ ).<sup>19</sup> Based on this study, the SYNTAX II 2020 risk prediction model removed female sex from the 10-year mortality calculator.<sup>20</sup>

There are several limitations to this study. Most important, the comparisons between PCI and CABG were drawn from nonrandomized data, precluding ruling out effects from important unmeasured confounders. Interaction testing is inherently underpowered, and the number of women enrolled was insufficient to draw stand-alone conclusions, a common problem with all revascularization trials. The MAIN-COMPARE registry enrolled a population that underwent PCI with bare metal stents and first-generation DES, both of which have been retired from current practice. Contemporary DES have markedly lower rates of MI and stent thrombosis, greater freedom from target vessel revascularization, and in some studies

enhanced survival. Additionally, MAIN-COMPARE was performed in South Korea, further limiting its generalizability to other populations. In this regard, differences in outcomes have been reported between East Asian and Western populations after revascularization with PCI or CABG.<sup>14</sup>

These limitations notwithstanding, the present study adds to the growing evidence for equipoise in women with LMCAD and MVD for revascularization with PCI or CABG, as long as other clinical or anatomic risk factors are not available that might strongly favor one procedure over the other. Nonetheless, in some studies women have tended to have higher mortality and MI rates compared with men, even after adjustment for differences in baseline characteristics. The extent to which hormonal factors, coronary artery size and lesion composition, and procedural and operative characteristics may underlie differences in early and late outcomes in women compared with men after both PCI and CABG is still uncertain.<sup>21</sup> What is certain is that the relative safety and effectiveness of PCI versus CABG in women with LMCAD and MVD can only be addressed by a dedicated, adequately powered randomized trial. The time for such a study is NOW!

## ARTICLE INFORMATION

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