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EDITORIAL COMMENT

Women Are Complex Creatures*

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It has been long known that women with ischemic heart disease have a high burden of comorbidities including advanced age, diabetes, hypertension, previous stroke, and renal insufficiency. Their coronary arteries are generally smaller, tortuous, more calcified, and prone to dissection, and atherosclerosis may be diffuse, making recognition of significant lesions and treatment difficult. Symptoms are often atypical or absent, which may delay the diagnosis of coronary artery disease until the disease is far advanced. Women with ischemic heart disease are less likely to be treated with medication and revascularization according to guideline recommendations. Moreover, several early studies suggested that women have a worse prognosis compared with men with acute coronary syndrome, ST-segment elevation myocardial infarction, bypass surgery, and percutaneous coronary interventions (PCIs), not entirely explained by advanced age and comorbidities (1–3). Although many attribute higher morbidity and mortality to advanced age, in fact, younger women with ischemic heart disease are reported to be particularly prone to misdiagnosis, treatment delays, and poor outcomes (4,5).

With improved techniques and the advent of newer drugs and devices, it appears that women are now doing as well as men. This was evident with the bare metal stents and first-generation drug-eluting stents (DES) (6,7). Smaller stent sizes, thinner struts, and improved polymers on newer generation DES appear to have superior outcomes compared with first-generation DES in both sexes. These changes in design may be particularly important in women with smaller coronary arteries, in which the lumen is too small to tolerate bulky stents or even small amounts of late lumen loss from mild restenosis. Not surprisingly, an analysis of 11,000 women enrolled in randomized stent trials found a reduced risk of death or myocardial infarction in women treated with newer DES compared with either first-generation DES or bare-metal stents (8).

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The study by Giustino et al. (9) in this issue of *JACC: Cardiovascular Interventions* provides further detail using pooled patient-level data from women enrolled in DES trials. The 10,241 women were evaluated on the basis of PCI complexity (long lesions, multiple stents, multiple lesions, bifurcation lesions) and followed for 3 years. Newer DES were associated with improved clinical events overall compared with early-generation DES. Women who underwent complex PCIs had a 1.6-fold increase in major adverse cardiac events at 3 years compared with noncomplex PCIs, but use of a new-generation DES reduced major adverse cardiac events (hazard ratio: 0.81) and stent thrombosis (hazard ratio: 0.50) compared with first-generation devices. This study is an important contribution and offers encouragement to physicians and patients who may be reluctant to perform PCIs in women with complex anatomy. However, women enrolled in device trials may not be representative of the real-world complexity. Indeed, large national registries of all-comers suggest that >33% of PCIs are performed in women (9), whereas <25% of patients enrolled in most PCI trials are women. Elderly women with renal insufficiency and complex anatomy are often considered ineligible for interventional trials. Unfortunately, Giustino et al. (9) did not provide data on PCI outcomes in calcified, tortuous vessels, chronic occlusions, or severe left ventricular dysfunction, all of which comprise the spectrum of complex coronary interventions.

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Although this study adds to our knowledge base, there is much that we still do not understand. The interplay between young women, risk factors, lack of recognition, and poor prognosis needs to be elucidated further. Defining the molecular and vascular biology for different risk factors for atherosclerosis in women and the unique pathophysiological mechanisms for myocardial infarction in women need further investigation. We need to clarify the mechanisms of an increased incidence of angina and heart failure despite less epicardial coronary disease and preserved left ventricular function in women. The consistent increase in bleeding (10) and vascular complications in women despite vascular closure devices (9), radial access (11,12), and bivalirudin (13) deserves further investigation. Sex differences in pharmacokinetics, pharmacodynamics and patient response to cardiovascular drugs need more attention (14,15). Better understanding of the patient and health care provider rationale for delays in presentation, treatment, withholding or refusing treatment as well as effective interventions to improve delays are necessary. Although we have come a long way in understanding heart disease in women, substantial gaps in our knowledge remain.

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