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EDITORIAL COMMENT

The Efficacy of Drug-Eluting Stents in Women

A Window of Opportunity*

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During the past several decades, there have been numerous studies evaluating sex-based differences in patients undergoing coronary revascularization across the clinical spectrum of coronary artery disease, reporting remarkably consistent findings (1). Yet, the number and rate of studies comparing outcomes between women and men undergoing percutaneous coronary intervention (PCI) continue to increase, perhaps driven by the increasing awareness of the prevalence and adverse impact of coronary disease in women, by the mandate to include more women and sex-specific analyses in clinical trials, and by the lack of true understanding of the biologic basis for the differences observed.

See page 603

Notably, in the more recent studies, the sex difference in (adjusted) in-hospital mortality has nearly disappeared, even in large-scale registries, which are less likely to be underpowered (on the basis of the 25% to 30% of patients who are women) (2). However, the incidence of bleeding and vascular complications after the procedure continues to be significantly higher in women than in men (3). Moreover, both women and men in contemporary studies have, in comparison with earlier studies, more complex anatomy and concomitant disease. Yet, adjusted mortality after the procedure has decreased, particularly in women (4,5). The reasons for the reduction in the sex difference in mortality are unclear, but greater awareness of issues specific to women (such as peri-procedural heart failure due to hypertensive heart disease) and improved technology including smaller and more flexible stents (allowing access to smaller coronary vessels) have been implicated.

In fact, when coronary stents were initially introduced into clinical practice, it was hoped that they would negate the marked increase in mortality in women compared with men after balloon angioplasty (adjusted in-hospital mortality 5-fold higher in women within the 1985 to 1986 National Heart, Lung and Blood Institute's Coronary Angioplasty Registry) (6). Not surprisingly (because stents have rarely been shown to save lives), at least initially, stents did not fulfill this promise. For patients undergoing PCI with stents, the sex difference in in-hospital (7) and 30-day (8) mortality persisted in the setting of both acute myocardial infarction (MI) and elective/urgent procedures. However, the benefits of stents in reducing repeat revascularization are independent of sex. For patients treated with both bare-metal (BMS) (9) and drug-eluting (DES) (sirolimus [10] and paclitaxel [11]) stents, the reduction in restenosis and repeat target vessel (TVR) and target lesion revascularization have been reported to be similar in women and men (12).

In this issue of *JACC: Cardiovascular Interventions*, Onuma et al. (13) add to the growing body of evidence demonstrating improved outcomes in women (and men) undergoing PCI with DES and extend the observations to include longer-term follow-up. In a retrospective cohort study of 4,936 consecutive patients (of whom 1,394 or 28.2% were women) treated with PCI with stents within the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registries between 2000 and 2004, the sex differences in outcomes as well as the outcomes in women and men receiving BMS in comparison with DES were evaluated during the 3 years after the procedure.

As expected, for both BMS and DES groups, women were significantly older (5 years), with a higher risk profile and a lower prevalence of multi-vessel disease than men. In addition, the number of lesions treated, the number of stents, and total stent length were similar between women and men. Cumulative incidences of clinical end points through 3 years revealed the absence of a significant difference by sex for rates of all-cause death, MI, TVR, stent thrombosis, and major adverse cardiovascular event (MACE), although there was a trend toward a higher mortality in women in both stent groups at 1 year.

Among both women and men, there was a higher prevalence of risk factors, more complex coronary anatomy treated, and more frequent treatment for acute MI in the DES compared with the BMS group. Moreover, patients treated with DES had a longer stent length and more stents used although the average stent diameter was smaller in comparison with patients receiving BMS. Yet, rates of MACE and TVR were lower in both women and men treated with DES in comparison with BMS at any time point throughout 3 years of follow-up. However, subgroup multivariate analysis revealed a higher risk of MACE in women compared with men with acute MI treated with

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DES (hazard ratio: 1.37, 95% confidence interval: 1.02 to 1.85).

These experienced investigators who have significantly contributed to our understanding of the use of both BMS and DES in an evolving clinical practice have both confirmed and extended the observations of improved outcomes in women, absence of sex-based differences in MACE, and similar efficacy of DES in both sexes in patients undergoing contemporary PCI—the lack of propensity-matched samples for sex as well as type of stent and the absence of multivariate adjustment for left ventricular function and changes in the standard of care over time notwithstanding.

Several interesting observations have emerged from these analyses. Although the limitations of subgroup analyses (particularly when not pre-specified) and the small number of patients undergoing PCI for acute MI are well-recognized, the data suggest a significantly higher incidence of MACE in women compared with men receiving DES in this setting. These findings are consistent with other studies reporting sex differences in outcomes after ST-segment elevation myocardial infarction with higher in-hospital mortality in women in comparison with men (14). It should be noted, however, that the influence of time to treatment, which has been shown to be longer in women, and the use of guideline-recommended medical therapies that have been shown to be used less often in women were not measured in this study.

The observation that the benefits of DES are independent of sex is particularly encouraging. Although women have a higher prevalence of diabetes, diffuse coronary disease, and small vessels in comparison with men, the impact of these factors on the sex-difference in the incidence of restenosis after PCI has been variable, with some studies reporting a lower risk in women (15). The findings might be confounded by exclusion of women in many studies on the basis of these characteristics—their smaller, calcified, and diffusely diseased vessels that are often not ideally suited for PCI. Furthermore, it has been shown that the macrovasculature and microvasculature are stiffer and smaller and that there is more endothelial and smooth muscle dysfunction in women than in men (16). There are also data to suggest that estrogen attenuates the vessel wall response to injury, in part by reducing the rate of oxidative degradation of arterial wall nitric oxide and by promoting prostatcyclin formation and vasodilation (17,18). However, the potential contribution of these findings to clinical studies is unclear, particularly in the absence of information concerning the prevalence of hormone replacement therapy in the majority of trials.

Perhaps most important is that the efficacy of DES in reducing restenosis and repeat revascularization in women opens a window of opportunity. The development of device-based local drug delivery strategies could decrease the adverse impact of inherent sex-differences in pharmacodynamics and reduced glomerular filtration rate and delayed gastric emptying reported in women in comparison with men (19). This approach might, depending on the agents used, decrease the risk of bleeding and excess dosing of drugs seen more frequently in women (20). Ultimately, sex-based therapeutic strategies might emerge, perhaps actually initially developed in women and then translated to men, and lead to improved care and outcomes for all patients undergoing coronary revascularization in the years ahead.

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