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EDITORIAL COMMENT

Bioresorbable Vascular Scaffolds in Women*

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Iterations in metallic drug-eluting stents (DES) with enhanced polymer biocompatibility, drug release kinetics, and reduced strut thickness overcame the limitations of early-generation DES, including in high-risk patient subsets (1-3). However, even with new-generation metallic DES, phenomena such as incomplete strut endothelialization, polymer hypersensitivity, and very late accrual of target lesion failure (TLF) still exist (4-6). Bioresorbable vascular scaffolds (BVS) were created with the intent of providing transient mechanical support coupled with release of an antiproliferative drug to prevent restenosis (within 1 year), followed by complete scaffold resorption in the very late periods (beyond 1 year) (4). The Food and Drug Administration approval of the Absorb BVS (Abbott Vascular, Santa Clara, California) was achieved on the basis of its noninferiority in terms of TLF at 1 year compared with the best-in-class metallic everolimus-eluting stent (EES) (7). However, subsequent evidence suggested that the currently approved BVS is associated with lower efficacy and higher risk for thrombotic complications at a median time of follow-up of 2 years (8). Smaller reference vessel diameter (RVD), lesion complexity, and the lack of a standardized implantation protocol emerged as potential reasons for BVS failure (8). In this regard, the Food and Drug Administration recently released a safety alert recommendation (9) for strict adherence to dual-antiplatelet therapy in all patients who receive the currently approved Absorb BVS, and its off-label use is discouraged.

Women have been historically under-represented in randomized controlled trials (RCTs) that established the efficacy and safety of DES (1-3). Whereas men tend to have in general higher anatomic complexity, greater plaque burden, and longer lesions, women frequently have narrower and more tortuous vessels at the time of coronary revascularization. In addition, at clinical presentation, women tend to be older and to have a greater prevalence of comorbidities (10). In fact, women undergoing coronary stent implantation have been reported to experience a significantly higher risk for coronary perforations, dissections, access-site complications, and death (1-3). Within this background, whether sex differences in outcomes exist between BVS and EES remains unknown.

SEE PAGE 1881

To address this gap in knowledge, in this issue of *JACC: Cardiovascular Interventions*, the ABSORB investigators report the results of a patient-level pooled analysis of 4 RCTs of the ABSORB trials program (ABSORB II, ABSORB III, ABSORB Japan, and ABSORB China), evaluating sex differences in outcomes with the Absorb BVS versus the XIENCE EES (Abbott Vascular) (11). Patient-level data were aggregated into a single dataset, and the analysis was performed using the intention-to-treat approach. The primary endpoint was the 2-year rate of TLF. Effect estimates were generated using Cox proportional hazard models in which trial identifiers were included as fixed effects. A total of 3,384 patients were included, of whom 27.5% (n = 932) were women. As expected, female participants were older, more often had diabetes, and had a greater prevalence of comorbidities but less extensive coronary artery disease. In

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addition, women were more likely to have smaller baseline RVD and moderate or severe calcification. Overall 2-year adherence to dual-antiplatelet therapy was roughly 50%, with no significant differences between sexes.

At 2 years of follow-up, BVS were associated with an absolute 2.7% (study-level adjusted hazard ratio [HR]: 1.47; 95% confidence interval [CI] [10]: 0.88 to 2.46) and 2.5% (study-level adjusted HR: 1.40; 95% CI: 1.02 to 1.92) increase in TLF in both women and men, respectively, without evidence of an interaction for a differential effect ($p_{interaction} = 0.85$). BVS were associated with similar risk for definite or probable stent thrombosis (ST) in women, compared with an absolute 1.6% increased risk in men (HR: 5.54; 95% CI: 1.69 to 18.14), with borderline statistical interaction for lower risk in women ($p_{interaction} = 0.06$). Importantly, by visual inspection of the Kaplan-Meier curves, it is apparent that the accrual of TLF and definite or probable ST events in the BVS arm continues over time, especially beyond 1 year. The increased risk for TLF and definite or probable ST with BVS versus EES was also uniform between sexes in the subgroup of patients with RVD <2.25 mm ($p_{interaction} = 0.66$ and $p_{interaction} = 0.69$, respectively). By means of multivariable Cox regression modeling, in the overall population, RVD <2.25 mm was independently associated with an increased risk for TLF (adjusted HR: 1.69; 95% CI: 1.28 to 2.23) and for definite or probable ST (adjusted HR: 2.45; 95% CI: 1.33 to 4.51). Within sex strata, RVD <2.25 mm emerged as an independent predictor of increased risk for TLF in men (adjusted HR: 1.56; 95% CI: 1.11 to 2.20) and of increased risk for definite or probable ST in women (adjusted HR: 6.74; 95% CI: 2.02 to 22.49). In conclusion, compared with EES, the currently Food and Drug Administration–approved Absorb BVS was associated with increased risk for TLF and ST that was consistent between sexes, including the subgroup with RVD <2.25 mm. Of note, the latter factor appears to be a strong determinant of outcomes in the overall population, regardless of the type of stent implanted.

Strengths of the study are its inclusion of prospective, multicenter RCTs with blinded event adjudication and angiographic core laboratory analysis. Although the present report constitutes a significant contribution to sex-specific analysis in the field of coronary stents, many questions remain unanswered. First, it is unknown if the resorption kinetics of the scaffolds differ between sexes. Second, whether sex differences exist in the mechanism of BVS thrombosis remains to be determined. Intravascular imaging studies suggest that the predominant mechanisms underlying BVS thrombosis are undersizing with respect to RVD, inadequate lesion preparation with poor BVS expansion, late scaffold fracture or discontinuity, and excessive positive vessel remodeling with subsequent malapposition (12). Third, whether the vascular response to BVS implantation differs between sexes remains unclear, and whether this may influence stent-specific outcomes is still uncertain. For example, in a recent intravascular imaging study from the ABSORB II trial, expansive vessel wall remodeling was more frequent and intense with the BVS than the metallic DES (13). Of note, female sex was a strong independent predictor of expansive remodeling (13). Whether the greater expansive remodeling with BVS in women may account for the numerically lower risk for ST observed in the present large-scale clinical study or just represents a chance finding remains to be determined.

Despite the unfavorable results in RCTs with the current bioresorbable devices, iteration in BVS technology may overcome the limitations of first-generation BVS. Enhancement in device deliverability, radial strength, scaffold resorption and drug elution kinetics may establish BVS in routine clinical practice. BVS will need to find their role in a field dominated by the excellent performance of permanent-polymer and bioresorbable-polymer metallic DES (14). Data sharing and pooling of RCTs, like the present study, will be key to estimate the risk and benefits of different stent types across relevant subsets of patients, such as women and minorities.

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