

EDITORIAL COMMENT

Female Sex and Low Flow

A Double Paradox in Aortic Stenosis?*



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As the treatment of aortic stenosis (AS) continues to evolve with expanding indications to a broader subset of patients, reduction in procedural risk, advances in valve design, and improved hemodynamics, it is of increasing importance that patients are selected for the right intervention for each specific subpopulation. Such subsets include low flow-low gradient, female population, multivalvular disease, and those with concomitant multivessel atherosclerotic disease among many other conditions. The approach to intervention in women with AS has been of particular interest for a variety of reasons. There are historically well-described differences in annuli size and hemodynamics among other features between men and women with women typically having smaller annuli on average than men. However, the sex-related issues in AS therapy are not just related to size. Women also have different left ventricular (LV) responses to AS and are known to have a higher prevalence of heart failure with preserved ejection fraction and paradoxical low flow-low gradient (PLF LG) AS. Sex-based disparities in AS care for women are also apparent, where women are less often referred for AS intervention.

It is the intersection of sex and flow status that is assessed in the study by Carter-Storch et al¹ in this issue of *JACC: Advances* who analyzed data from the PARTNER 2 and 3 trials to assess the impact of PLF on adverse outcomes after transcatheter aortic valve

replacement (TAVR) or surgical aortic valve replacement (SAVR).¹

Two-year occurrence of the composite of death or heart failure hospitalization (primary endpoint) and of all-cause mortality alone (secondary endpoint) were analyzed. Out of just over 2,000 patients, PLF was present in 390 men and 239 women (30% vs 26%, $P = 0.06$). PLF was associated with a higher rate of NYHA functional class III to IV dyspnea and a higher prevalence of atrial fibrillation. PLF was a significant predictor of the primary endpoint among women undergoing SAVR in multivariate analysis but was not associated with a worse outcome in any of the other groups that were studied according to sex or intervention. They conclude that in women with PLF, TAVR may be more appropriate compared to SAVR.

The authors have highlighted that sex in conjunction with PLF LG AS is an important consideration when assessing patients for TAVR vs SAVR. The intersection of these 2 subsets of AS patients is notable considering the unique considerations for AS intervention in women, and those patients with PLF LG or normal flow AS are at increased risk of mortality.² As TAVR continues to progress as the predominant mode of intervention for AS across all risk spectrums and is generally associated with low risk, the field of structural interventions pushes our understanding of tailoring therapy to each individual vs a “one size fits all” approach. Unlike many other fields in cardiovascular medicine, women have, relatively speaking, had a higher representation in TAVR studies compared to other cardiovascular studies. However, representation of women in such studies in and of itself is not sufficient, as the question of how sex factors into the discussion of appropriate mode of intervention is still in question. There are definitive anatomic differences between men and women, as mentioned earlier, as well as differences in left ventricular response to AS and outcomes after intervention. Valvular pathology is also different leading to

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differences in calcium score for men and women when evaluating AS severity, where the recommended cut-off valve for significant calcification is significantly less in women than in men.³ The issue of reference points such as valve calcification and differences in adaptive response is also important to consider. LV hypertrophy tends to be more concentric in women with predominant fibrosis and is associated with diastolic dysfunction,^{4,5} and women tend to also have smaller valve areas and lower gradients. As is examined in this study, analysis of the PLF LG population has historically relied on cutoffs of stroke volume index <35 ml/m² as the definition of low flow. Considering smaller LV cavities and annuli, PLF has been noted more frequently in women, but whether this dichotomous cutoff of stroke volume index is as predictive in women vs men is unclear and thus begs the question of whether such traditional cutoffs are appropriate for men and women comparatively.

The results found in this study and many others in regard to female sex and AS interventions continue to highlight the need for not only more data on women in this area but also tailored interventions. Early data from PARTNER I suggested a paradox that female sex is an adverse predictor of outcomes after SAVR with favorable outcomes in TAVR in high-risk patients despite a higher risk of vascular complications. However, subsequent data analyzed in mixed populations of intermediate and lower risk cohorts have been discordant in regards to outcomes after TAVR vs SAVR in women.⁶⁻¹⁰ A meta-analysis from 2018 with nearly 50% women noted increased vascular complications but greater 1-year survival.¹¹ The continued surge of transcatheter aortic interventions only furthers the need to dedicate studies of AS intervention in women to specifically account for sex-specific

factors such as low flow and small annuli. The recent VIVA study compared hemodynamic and clinical outcomes between TAVR and SAVR in patients with severe AS and small aortic annuli. The study population included 93% women with no differences between TAVR and SAVR in regard to prosthesis patient prosthesis mismatch and no differences in stroke or mortality at 30 days and 2 years.¹² Findings such as these also strengthen the need for such dedicated studies as WIN-TAVI, which is an international, multicenter, prospective, observational registry of women undergoing TAVR across multiple sites, mostly in Europe. Initial analysis from WIN-TAVI noted that in intermediate to high-risk women, TAVR was associated with low risk of 1-year mortality and stroke.¹³ This registry is also unique in that reproductive history was collected as a variable, which historically has not been included in large-scale registry analyses. Further studies such as the RHEIA (Randomized Research in Women All Comers With Aortic Stenosis) trial are currently ongoing to assess TAVR compared to SAVR in symptomatic women.¹⁴ Women are not just “smaller” versions of men, and progressive research in AS interventions will continue to help guide clinicians in the care of this particular subset of patients.

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