JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 11, NO. 1, 2018

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jcin.2017.10.028

EDITORIAL COMMENT

What Does Sex Have to Do With Transcatheter Aortic Valve Replacement?*

Brian R. Lindman, MD, MS, Robert N. Piana, MD

A rapid succession of randomized trials has led to the widespread adoption of transcatheter aortic valve replacement (TAVR) for a broader spectrum of patients with calcific aortic stenosis (AS). TAVR is superior to medical therapy in prohibitive risk patients (1). TAVR is firmly established as noninferior to surgical aortic valve replacement (SAVR) in patients at intermediate and high risk for surgery (2–5). Indeed, some data suggest that TAVR is superior to SAVR in intermediate- to high-risk patients, particularly when they can undergo a transfemoral approach (5,6). In clinical practice in 2017, the high-risk patient is now almost always treated with TAVR, and the intermediate-risk patient is usually treated with TAVR. Similar clinical outcomes after a catheter-based versus a surgical procedure usually leave patient and physician opting for the less invasive approach.

SEE PAGES 1 AND 13

Over the last decade, numerous trials have been completed and registries built that facilitate investigation of factors associated with clinical outcomes after TAVR and provide insight as to whether any subgroups experience particular benefit from TAVR compared with SAVR. In this issue of *JACC: Cardiovascular Interventions*, 2 papers provide new insights on sex as it relates to TAVR. In contextualizing these findings, 2 related, but different, sets of questions are relevant. 1) Are outcomes different after TAVR based on sex? If so, why, and what can we learn to optimize outcomes for both sexes? 2) Do outcomes after treatment with TAVR versus SAVR differ based on sex? If so, then what implications are there for treatment decisions? The papers in this issue of the journal address the first set of questions, but not the second. However, the second probably has more bearing on treatment decisions.

ARE OUTCOMES DIFFERENT AFTER TAVR BASED ON SEX?

Prior studies have suggested that female sex is associated with better intermediate-term outcomes after TAVR despite increased periprocedural complications (7,8). Potential explanations for this paradox have included a more favorable comorbidity profile in women at baseline with less prior coronary intervention or coronary bypass surgery, less left ventricular dysfunction, and lower rates of hyperlipidemia, diabetes, smoking, and renal disease (7,8). Paravalvular leak also emerged as an intriguing potential explanation, given its association with increased mortality. In the PARTNER (Placement of Aortic Transcatheter Valve) trial, women were more likely to receive a 23-mm valve (85.8%), whereas men were more likely to receive a 26-mm valve (78.1%). Despite larger valve sizing, men had a more than 3-fold higher incidence of moderate-to-severe paravalvular leak compared with women (10.3% vs. 3%) (9). Other potential explanations include less regression of left ventricular hypertrophy in men than women after TAVR (10).

With these prior observations as backdrop, Szerlip et al. (11) provide results from PARTNER 2 high and intermediate risk S3 cohorts that contrast with prior findings. Men had more comorbidities, had a higher EuroSCORE, and more commonly underwent a

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Vanderbilt Heart and Vascular Institute, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee. Dr. Lindman has received research grants from Edwards Lifesciences and Roche Diagnostics; served on scientific advisory boards for Roche Diagnostics; and has been a consultant for Roche Diagnostics and Medtronic. Dr. Piana has served on data safety monitoring boards for Abbott Vascular, Baim Institute for Clinical Research, and W.L. Gore & Associates.

transapical approach. Women were more commonly frail and had a higher STS score. Although women experienced more vascular complications, 30-day and 1-year rates of mortality, stroke, rehospitalization, and other clinical endpoints were similar between men and women. Adjusted models for mortality confirmed these findings. Notably, compared with the original PARTNER trial secondary analysis based on sex, there was no difference in the incidence of moderate or severe paravalvular leak between men and women (7). The authors plausibly speculate that adjustments in valve sizing algorithms, the availability of larger valves, and a new outer skirt on the S3 device may have reduced rates of paravalvular leak in men, partly explaining the differences in these results.

The report from the WIN-TAVI (Women's International Transcatheter Aortic Valve Implantation) registry in this issue provides an additional profile of current real-world application of TAVR in women (12). The risk factors for a worse outcome identified among women—higher EuroSCORE, prior percutaneous coronary intervention, and pre-existing atrial fibrillation—are consistent with those observed in "mixed" registries. Providing new insights into the relationship between sex and outcomes after TAVR, the authors found that no female sex-specific factors (including prior pregnancy, use of hormone replacement therapy, or history of osteoporosis) were independently associated with outcomes after TAVR. Although it is certainly important to investigate sex-specific factors that may be associated with particularly outcomes, these questions may best be investigated within a mixed registry (i.e., sex-specific questions could be added to more general case report forms), so that outcomes in women may be compared to those for men enrolled in a similar manner from the same centers.

DO OUTCOMES AFTER TREATMENT WITH TAVR VERSUS SAVR DIFFER BASED ON SEX?

This question is not addressed by the current analyses, but is the one that has more potential implications for treatment decisions. In other words, should one make the treatment choice of TAVR versus SAVR differently based on sex? The PARTNER I trial, which randomized high risk patients to treatment with TAVR (with the original SAPIEN valve [Edwards Lifesciences, Irvine, California]) versus SAVR, showed that there was a significant interaction between sex and treatment group with respect to 1-year mortality (interaction $p = 0.05$) (2). A follow-up analysis of the 2-year data from that trial showed that among women, there was a significant survival advantage from TAVR compared with SAVR, largely due to differences observed in the transfemoral cohort; these differences were not observed in the men (9). A separate 3-center European propensity analysis of low-, intermediate-, and high-risk patients also found an interaction between sex and procedural approach (TAVR vs. SAVR) with respect to 1-year all-cause mortality (13). Again, women tended to have better outcomes than men after TAVR.

However, these findings need to be viewed within the following context. In 3 subsequent randomized trials, including the PARTNER II trial of intermediate-risk patients and the self-expanding TAVR trials in high-risk and intermediate-risk patients, there have been no significant interactions between sex and treatment allocation (TAVR vs. SAVR) with respect to mortality or the composite primary trial endpoint (3–5). That said, the point estimate tends to consistently favor TAVR for women in comparison to men. Related to this, other significant subgroup analyses from PARTNER I based on diabetes status or prior CABG have not been confirmed in subsequent trials (14). By contrast, although there was not an interaction based on TAVR approach (transfemoral vs. transapical) in the PARTNER I trial (perhaps due to the large sheath and surgical cut-down required for the transfemoral approach), subsequent data from studies with smaller sheaths have demonstrated a benefit of TAVR compared with SAVR but only when a transfemoral approach is feasible (5,6,15).

PUTTING IT ALL TOGETHER

Men and women undergoing TAVR have different baseline characteristics and experience some procedural complications at different rates. Early data suggested that females had lower mortality after TAVR compared with males, whereas the data from the PARTNER 2 study with the SAPIEN 3 valve show that there are no differences in 1-year mortality between men and women, perhaps due to improvements in valve sizing, availability of larger valves, and less paravalvular leak in males using modern deployment techniques and enhanced valve design.

With a goal of optimizing outcomes for all patients, observations of differences in outcomes between the sexes encourage us to explore the reason for those differences to determine whether there are factors that we can modify to optimize outcomes for both men and women. In these analyses, it is helpful to try to distinguish between sex-based differences that happen to be associated with sex (e.g., differences in paravalvular leak rates) versus those that may be more rooted in sex-specific differences in

pathophysiology (e.g., patterns of hypertrophic remodeling and regression of left ventricular hypertrophy). For the former, observed differences according to sex may be due to technical advances and resolved by focusing on procedural improvements (e.g., reducing paravalvular leak with valve design or sizing improvements). For the latter, new insights into pathobiology may be gleaned that uncover novel therapeutic targets that could potentially be augmented or blocked to optimize outcomes (perhaps for both sexes).

In 2017, the inclination of patients and providers will be to treat patients with AS at extreme, high, or intermediate risk for surgery with TAVR. Beyond the tendency to prefer a less invasive approach, should female sex be a factor that more definitively favors TAVR over SAVR? Not quite. However, as multiple factors (e.g., comorbidities, anatomy, concomitant valve lesions) are considered when weighing whether to recommend a transcatheter versus surgical therapy, along with the feasibility of a transfemoral approach, female sex would provide another firm "nudge" toward TAVR. Moving forward, further investigations are warranted to better understand the relationship between sex and: 1) the pathophysiology of AS before and after unloading the heart with valve replacement; 2) particular procedural complications from valve replacement; and 3) long-term patient-centered outcomes. These studies can inform future quality improvement initiatives and point to potential adjunctive therapies or interventions that may be administered in a sex-specific manner but with the overall goal of improving quality of life and survival for both sexes.

ADDRESS FOR CORRESPONDENCE: Dr. Robert N. Piana, Vanderbilt University Medical Center, 1215 21st Avenue South, Medical Center East, 5th Floor, Nashville, Tennessee 37232-8802. E-mail: robert.piana@vanderbilt.edu.

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KEY WORDS aortic stenosis, sex, transcatheter aortic valve replacement