

The gender paradox in TAVR

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Comment on: Chandrasekhar J, Dangas G, Yu J, *et al.* Sex-Based Differences in Outcomes with Transcatheter Aortic Valve Therapy: TVT Registry From 2011 to 2014. *J Am Coll Cardiol* 2016;68:2733-44.

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In the era prior to transcatheter aortic valve replacement (TAVR), several studies have suggested that women have been less frequently referred to surgical aortic valve replacement (SAVR) due to various reasons (1). At age younger than 65 years, gender does not seem to play a major role in referral to SAVR. However, among octogenarians and nonagenarians, women were unequally denied of SAVR (2). In the TAVR era things have changed, in most TAVR studies, female patients are equally represented (3,4).

Studies assessing the independent impact of gender on TAVR outcomes have consistently showed the paradox between lower pre-procedural risk profile of women, the surprisingly higher peri-procedural complication rates, however, superior long term outcomes in women as compared to men (5,6). To date, the reasons for these findings are not fully understood.

Given this issue in question, Chandrasekhar and colleagues evaluated the gender-based differences among patients undergoing TAVR in the U.S. National TAVR Registry, the Transcatheter Valve Therapies (TVT) (7). The primary goal of the trial was to assess whether gender has an impact on long term outcome as well as an influence on complication rates. The TVT registry includes all patients undergoing TAVR in the U.S. as it is a mandatory registry linked to procedural reimbursement. Trial participants were all elderly patients half of which were females. As anticipated, in-hospital complication rates were higher among female patients, most of which were attributed to vascular complications. However, at 1-year follow

up, female patients had significantly favorable outcome regarding major adverse cardiovascular events.

The study by Chandrasekhar *et al.* provides real-life data in a large dataset of all-comer men and women who undergo TAVR and the authors should be congratulated for this analysis. Notably, the study analyzed clinical outcomes using first generation devices (mostly a balloon expandable valve) with significantly larger delivery systems that are nowadays obsolete. Nowadays TAVR is performed mostly via a 14–16 Fr systems which have been shown to significantly decrease the risk for vascular complications and bleeding events. This may further improve the outcomes of women after TAVR. Unfortunately, the data provided in the study does not provide us with clear explanation for the gender paradox in TAVR. What may be the explanations for this paradox?

Women undergoing TAVR have fewer comorbidities such as coronary artery disease, peripheral vascular disease, diabetes and chronic obstructive pulmonary disease (8). Despite the fact that women suffer from higher rates of procedural complications, these may impact mostly on short term outcome. However, baseline comorbidities affect long term outcomes. Thus women, who have less comorbidities experience better long term outcomes after TAVR.

Furthermore, the ability of the heart to compensate in the presence of significant aortic stenosis seems to be different between genders. With similar degree of outflow tract obstruction, cardiac performance is more frequently depressed in men compared to women. In women there

is predominant hypertrophy rather than dilation and preserved systolic function (9). These differences may be related to high estrogen levels, which have protective effects on cell survival while causing downregulation in gene expression of collagen I & II and MMP-2. Accordingly, female gender was found to be an independent predictor of early improvement in systolic function after aortic valve replacement (10).

Finally, prosthesis-patient mismatch (PPM) is associated with decreased left ventricular mass regression post TAVR (11) and poor outcome after valve replacement (12). After SAVR, women suffer more frequently from PPM as compared to men (13). Women, who frequently have smaller annuli as compared to men (14) may benefit more from TAVR which is associated with significantly lower rates of PPM, especially in the subset of smaller annulus (11).

Ultimately, despite higher rates of in-hospital complications, women have excellent long term outcome after TAVR, and should not be deferred from treatment. Future studies should focus on gender differences in hemodynamic and left ventricular response to valve replacement in order to elucidate gender-specific factors allowing the physician to tailor specific therapies to each gender.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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