Outcomes in patients undergoing transcatheter aortic valve replacement: a sex-based story of success?

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Provenance: This is a Guest Commentary commissioned by Section Editor Busheng Zhang, MD, PhD (Department of Cardiac Surgery, Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai, China).

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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Transcatheter aortic valve replacement (TAVR) has been proven to be a valuable therapeutic option in patients with severe aortic stenosis deemed at high surgical risk (1). While female patients with aortic stenosis develop a greater degree of left ventricular hypertrophy and higher relative wall thickness (2,3), the impact of these gender related pathophysiological features on outcomes after TAVR have been studied less extensively. Available data suggests that female patients are at higher risk of bleeding and vascular complications (4,5) resulting in increased rehospitalization and mortality rates as compared to male subjects (6,7). In contrast, other studies report on either improved female or gender neutral survival rates after TAVR (8-11).

The article by Chandrasekhar *et al.* published in the *J Am Coll Cardiol* Vol. 68 No. 25 presents the largest observational report on comparative outcomes in male and female patients undergoing TAVR so far. It shows data from a large registry study (n=23,652) with an appropriately equal distribution between female (49.9%) and male (51.1%) patients (12). In-hospital events derived from the Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapy Registry and one year outcomes from data of Medicare & Medicaid Services were analysed using multivariable logistic as well as Fine-Gray competing risk regression analyses. In-hospital endpoints included all-cause death, myocardial infarction (MI), stroke, major bleeding, and major vascular complications according to the Vascular Academic Research Consortium-2 definition. Major adverse cardiac events (MACE) were defined as the composite of death, MI, or stroke, whereas net adverse cardiac events (NACE) were defined as a composite of in-hospital MACE, major vascular complications, or major bleeding. On the other hand, one-year endpoints were defined through time to event occurrence of death, MI, stroke, and clinically significant bleeding.

Chandrasekhar *et al.* observed a different risk profile between male and female patients: while women undergoing TAVR were older and had a lower prevalence of coronary artery disease, atrial fibrillation, and diabetes, they also had a lower glomerular filtration rate, a higher rate of porcelain aorta, a higher rate of moderate to severe mitral regurgitation, and a higher mean STS score (9.0% *vs.* 8.0%; P<0.001). In addition, more female patients were considered to be debilitated or deconditioned by the heart team (13.7% *vs.* 9.1%, P<0.001) as well as frail when making the decision for a TAVR procedure. In female patients, nontransfemoral access, surgical cutdown, and smaller sheath sizes (median; 22 *vs.* 24 F) were more frequently used. Of note, female patients achieved a significantly higher valve cover index (≥8%; 65.7% *vs.* 53.9%, P<0.0001). Twice as many female patients conversed to open surgery (1.74% *vs.* 0.96%, P<0.0001), ventricular or annulus rupture being the most frequent underlying causes, whereas valve dislodgement into the left ventricle occurred mostly in male patients (39.47% *vs.* 11.82%). Furthermore, a higher incidence of adjusted

in-hospital vascular complications (8.3% *vs.* 4.4%, P<0.001) and bleeding events (8.01% *vs.* 5.96%, P=0.06) as well as NACE (19.0% *vs.* 13.8%, P=0.06) occurred in the female cohort with no significant differences of death, MI, stroke, or MACE during the in-hospital period. Reaffirming data of the PARTNER A trial (13), women showed increased survival rates at one year after TAVR (78.7% *vs.* 75.5%, P<0.001).

Although the study's results are not surprising and align with other previous studies (8,14,15), they illustrate the importance of gender variability in TAVR cohorts including a significant number of patients. While female gender has generally worse clinical outcomes as men in trials on percutaneous coronary interventions (PCI), coronary artery bypass graft surgery (CABG), and surgical aortic valve replacement (SAVR), it is of interest, that like in various other studies, female gender beats male gender in terms of an improved one year survival rate which this study underlines. This can be due to a different risk profile at baseline but also due to the fact that female patients are generally underrepresented in clinical trials on PCI, CABG, and SAVR.

By interpreting the results of Chandrasekhar *et al.* one needs to keep in mind that TAVR was used as a therapeutic option not only for severe aortic stenosis, but in >5% also for significant aortic regurgitation and bicuspid valves. The authors additionally underline the different cardiac risk profile between men and women. While arterial hypertension is known to have gender based differences in clinical outcomes (16), it unfortunately has not been separately listed and adjusted for. In terms of cardiac risk profile, the article sheds light on two frequently discussed assessment tools: first, the STS-score to determine the 30-day mortality and morbidity risk, which significantly differed between male and female patients in this study. However, this score was initially designed to predict surgical and not TAVR risk and moreover, attributes a higher risk to female sex. Thus, it should be used with caution when interpreting gender based differences in TAVR patients (17). Secondly, the frailty assessment, which—in the clinical context—is frequently carried out subjectively. Available tools to detect frailty showed no sex differences in TAVR patients so far (18,19). Nevertheless, frailty assessment should be handled with more care using these formal tools as early procedural risks may be overestimated resulting in a potential underutilization of valve replacement. As acknowledged by the authors, one limitation of the study is that no adjustment was performed for device types. With evolving technologies of valves, deployment and sheath systems, closure devices, as well as pending data on optimal anticoagulation therapy, gender based findings may change in the future.

In conclusion, this study adds to the existing body of literature finding explanations for gender-based differences in in-hospital as well as in one-year clinical outcomes after TAVR. Being able to understand which factors significantly contribute to an improved assessment and treatment strategy before, during, and after TAVR, further studies with a longer follow-up period are needed to fully understand the impact of gender. Moreover, this claim is underlined through the fact that unlike in PCIs, approximately 50% of patients undergoing TAVR are women (20). Within this framework, the importance of individualized patient assessments within a Heart Team cannot be overstated. Amongst others, it is here where good or bad outcomes are being decided.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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