Review Article

Gender differences in aortic valve replacement: is surgical aortic valve replacement riskier and transcatheter aortic valve replacement safer in women than in men?

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Abstract: Aortic stenosis (AS) is a progressive and degenerative disease that necessitates valve replacement through either surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR). Various studies have shown that, unlike for TAVR, SAVR is associated with an elevated risk for women as compared to men. The aim of this review is to better understand the risks and their possible causes, associated with the use of both TAVR and SAVR in female patients. Our systematic review included studies published between 2012 and 2020, identified through specific searches of PubMed. Compatibility of publications, determined by the use of pre-defined inclusion/exclusion criteria, resulted in 15 articles being used in our review. Overall, more men than women undergo SAVR, but our findings confirmed that SAVR is associated with worse outcomes in women in the short-term. Reasons for a higher 30-day mortality post-SAVR in women include an increased age, higher in-hospital mortality and, possibly baseline comorbidities and anatomical differences. There was no difference observed in 30-day mortality between men and women undergoing TAVR. Female patients appear to have a better longer-term survival post-TAVR than their male counterparts. Understanding the reasons why women have worse outcomes post-SAVR is essential for ensuring appropriate treatment selection for patients with AS, as well as for achieving the best possible long-term and safety outcomes for these patients.

Keywords: Transcatheter aortic valve replacement (TAVR); surgical aortic valve replacement (SAVR); women; gender disparities

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Introduction

Aortic stenosis (AS) is the most common form of valvular abnormality in the developed world and accounts for >40% of patients with native valvular disease with an approximately equal prevalence in males and females (1). AS is both a progressive and degenerative disease that necessitates valve replacement to prevent irreversible haemodynamic changes and damage to the heart (2). Interventions for AS, which are usually chosen according to physician expertise and patient characteristics, include surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR), which can be carried

out via various access routes including the transfemoral (TF), transapical (TA), transaortic (TAo), transcarotid, transsubclavian and transcaval access routes (3-6).

A number of studies have suggested that the SAVR procedure might represent a greater risk for women than for men, while the TAVR procedure presents a lower risk in women (1,7-9). Generally, these sex disparities have not been the focus of studies and in cardiovascular (CV) device trials, the sex distribution of participants is largely skewed by disease prevalence, with men constituting 70–80% of study participants, resulting in small sample sizes of women and low statistical power for identifying meaningful sex-related outcomes (10). Furthermore, the last two major studies were not designed to address the impact of sex on valve replacement (11,12). As a result, the majority of relevant differences in sex-specific outcomes are uncovered through *post-hoc* analyses, calling into question the reliability of the evidence (10). Fortunately, cardiac/valvular device implantation trials in patients with AS do not show gender bias due to a comparable prevalence of disease in male and female patients (13,14). As a result, we sought to determine whether there are significant differences between women and men with regards to the safety and effectiveness of both SAVR and TAVR.

Methods

A search was conducted of the PubMed database for articles, with no language restrictions, published since 2012 and up until April 03 2020. The search terms included "(sex OR gender) AND (differences OR comparison) AND aortic stenosis AND (transcatheter OR surgical) AND (implantation OR replacement) AND valve". Filters applied were: Clinical Study, Clinical Trial, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Meta-Analysis, Multicenter Study, Observational Study, Randomized Controlled Trial. Overall, this search criteria yielded 117 initial articles where we screened the abstract for relevancy.

The inclusion criteria for the articles in our analysis were: (I) the inclusion of patients with severe aortic valve stenosis undergoing AVR; (II) studies regarding a single-group cohort or a controlled comparison between TAVR and SAVR through random or non-random allocation and (III) available data on at least short-term (30-day or in-hospital) or 1-year all-cause mortality (*Figure 1*).

Additional studies were included by searching the bibliographies of the articles and meta-analyses identified above. Studies were included if they examined the clinical outcome in patients with AS who underwent TAVR or SAVR and if they reported clinical outcomes of interest in women or in women versus men in agreement with the above selection criteria. Again, no language restrictions were applied to these articles. An overview of the included articles, their study designs and principle findings are provided in *Tables 1*,*2*,*3*.

Results

Trends in cardiovascular disease (CVD) in women

CVD continues to be the leading cause of death among women in the United States (US), accounting for one of every three female deaths (26). Despite this fact, a recent nationwide survey from the Women's Heart Alliance showed that almost half of women were unaware that CVD is the most frequent cause of death among their sex and only 39% of primary care physicians considered CVD as one of the top concerns (8). Of these CVDs, AS accounts for >40% of patients with native valvular disease and it occurs with approximately equal prevalence in males and females (1). The prevalence of severe AS that requires immediate intervention, with either SAVR or TAVR performed through various different access routes, is increasing as the size of the elderly population increases (3).

Differences in referrals for male and female patients with AS

One important factor that impacts on patient treatment is specialist referral. Data from administrative claims databases in the US shows that significantly fewer women with AS were seen by specialists and that these patients underwent fewer diagnostic tests. This resulted in approximately half the number of women being treated with SAVR compared to men (15,27). It was suggested that this lower referral rate was likely the result of women having more unfavourable pre-operative baseline characteristics (15).

Differences in risk profiles for male and female patients with AS

Studies have shown that the risk profile and baseline conditions for women and men undergoing the SAVR procedure is different (15,16). Compared with men, women are typically older and have more non-atherosclerotic comorbid conditions, such as hypertension, diabetes mellitus (DM), obstructive pulmonary disease, atrial

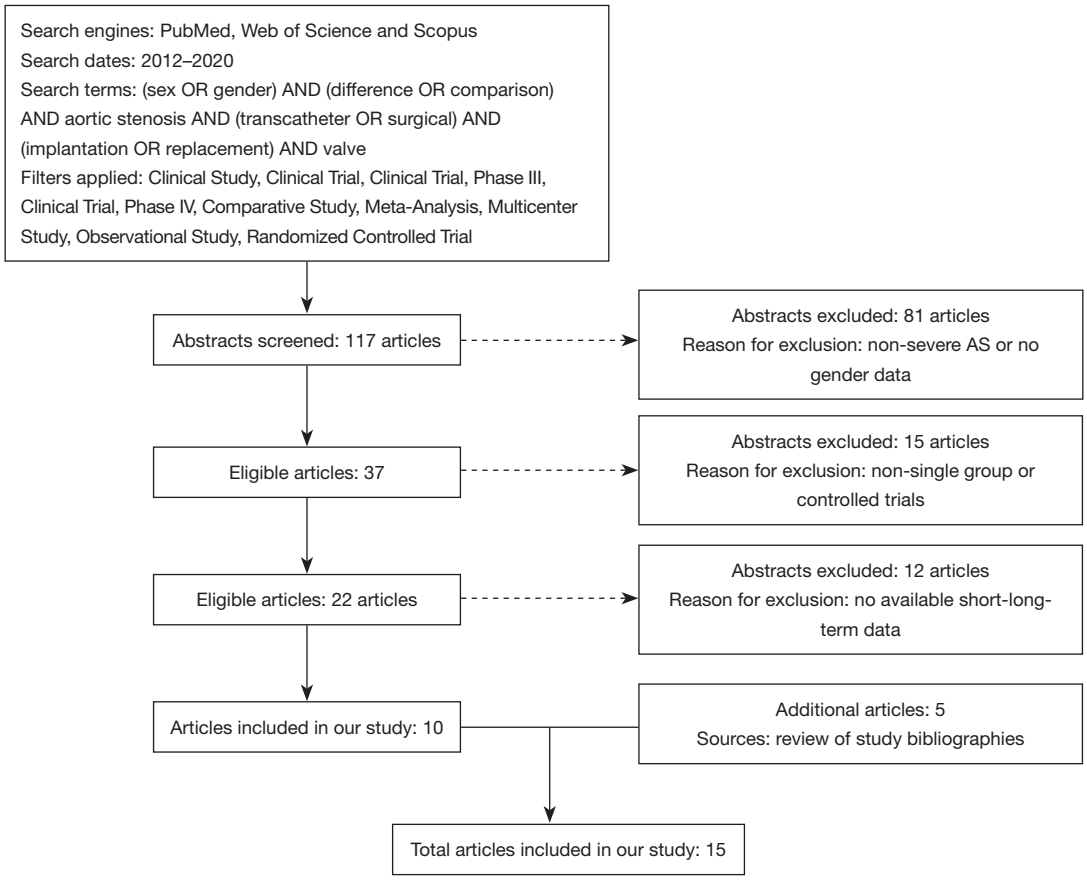

Figure 1 Overview of methodology for identifying publications included in this study.

fibrillation/flutter (AF) and anaemia, but a lower prevalence of coronary and peripheral arterial disease (PAD), renal disease, cerebrovascular disease and prior sternotomies (15,16). This supports the findings of other studies that SAVR is generally used in lower risk patient groups and may explain why this procedure is more commonly used in men (28). The increased age and higher numbers of comorbidities tend to push these female patients into the higher risk groups.

Anatomical differences in men and women with AS and their impact on treatments

One of the largest registries to date—the Italian Observational Multicentre Registry—found, that lower bodyweight and serum albumin levels in women, and parallel cardiac structures that are smaller than those in men, could result in more technically demanding SAVR procedures in women. These differences in physiology, disease pathology, presentation and management may contribute to gender-specific differences in clinical outcomes following valve surgery (8).

Women with AS demonstrate specific clinical, anatomical and pathophysiological features in myocardial adaptation to AS both before and after valve replacement. Women exhibit more concentric remodelling and subsequent concentric LV hypertrophy (LVH), with higher relative wall thickness and smaller end-diastolic diameter than seen in men, who are frequently found to have a higher prevalence of eccentric hypertrophy in this setting (13).

Furthermore, sex hormones and oestrogen receptors and their signalling pathways, which can remain active even after menopause, may also play a role in sex-specific LV remodelling, because studies in animal models have shown that oestrogen binding can modulate growth-factor signalling, modulating myocyte necrosis and apoptosis (29).

While these gender-specific differences may impact on gender-specific mortality associated with SAVR, further

Table 1 SAVR only studies

Authors	Study design	Patients number (women)	Outcomes	Principal findings
Chaker *et al.*, 2017 (15)	National Registry (2003 to 2014)	28,237 (n=14,118)	In-hospital mortality higher in women (3.3% *vs.* 2.9%; P<0.001)	Women have worse in-hospital mortality after AVR compared to men
Lopéz de Andres *et al.*, 2019 (16)	National Registry (2001 to 2015)	86,578	In-hospital mortality higher in women for both mechanical (8.94% *vs.* 6.79%; P<0.001) and bioprosthetic (6.51 *vs.* 5.42%; P=0.001) SAVR	Women have higher in-hospital mortality after mechanical and bioprosthetic SAVR than men
Elhmidi *et al.*, 2014 (17)	Single centre, retrospective	2,197 (n=907)	30-day mortality: 4.4% females, 1.6% males (P<0.001); 1-year mortality: 13% women, 9.6% men (P=0.04)	Short-term and long-term mortality worse in women
Wong *et al.*, 2018 (18)*	National Registry (2003 to 2014)	24,637	In-hospital MACCE higher in women (9.4% *vs.* 8.3%; OR 1.14, 95% CI: 1.07–1.21, P=0.0001); all-cause mortality (5.2% *vs.* 4.3%; OR 1.33, 95% CI: 1.12–1.33, P=0.0001)	Women higher in-hospital MACCE and overall all-cause mortality

*, study also included patients with concomitant mitral valve surgery. SAVR, surgical aortic valve replacement; AVR, aortic valve replacement; CI, confidence interval; MACCE, major adverse cardiovascular and cerebrovascular events; OR, odds ratio.

Table 2 Studies comparing TAVR and SAVR

Authors	Study design	Patients number (women)	Outcomes	Principal findings
Williams *et al.*, 2014 (7)	Multicentre, prospective	699 (n=300)	2-year mortality: women: 28.2% TAVR *vs.* 38.2% SAVR (P=0.049); men: 37.7% TAVR *vs.* 32.3% SAVR (P=0.42)	Women specific long-term survival benefit with TAVR
Onorati *et al.*, 2014 (8)	Observational Multicentre Registry	2,108 (n=1,043)	Women SAVR: 30-day mortality (OR 2.34; P=0.043) and transfusions (OR 1.47; P=0.003); women TAVR: major vascular complications (OR 2.92; P=0.018) and transfusions (OR 1.93; P=0.003); protective against moderate to severe post-procedural aortic insufficiency (P=0.018)	Being a woman is a risk factor for mortality after aortic valve replacement, for major vascular complications after TAVR, and for transfusions after both approaches
Skelding *et al.*, 2016 (9)	Single centre	353 only women (183 TAVI and 170 SAVR)	TAVR 1-year survival higher than in SAVR patients (12.7% *vs.* 21.8%; P=0.03); all-cause mortality or major stroke rate also favoured TAVR (14.9% *vs.* 24.2%; P=0.04)	Lower 1-year mortality in women for TAVR procedure; lower 1-year all-cause mortality or major stroke in women undergoing SAVR
Panoulas *et al.*, 2018 (1)	Meta-analysis	3,758 (n=1,706)	TAVR lower mortality than SAVR recipients; 1 year (OR 0.68; 95% CI: 0.50–0.94); 2 years (OR 0.74; 95% CI: 0.58–0.95); no difference in men	TAVR has a 26–31% lower mortality odds than SAVR

TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

Table 3 Women TAVR studies

Authors	Study design	Patients number (women)	Outcomes	Principal findings
Hayashida *et al.*, 2012 (19)	Single centre, prospective	260 (n=131)	30-day mortality: 12.2% women, 17.8% men (P=0.207); 1-year mortality: HR 1.62, 95% CI: 1.03–2.53, P=0.037	Similar short-term but better 1-year mortality in women
Humphries *et al.*, 2012 (20)	Multicentre, retrospective	641 (n=329)	30-day mortality: 6.5% women, 11.2% men (P=0.05)	Better short-term mortality in women
O'Connor *et al.*, 2015 (21)	Meta-analysis	11,310	Procedural mortality: 2.6 % women, 2.2% men (P=0.24); 30-day mortality: 6.5% *vs.* 6.5% (P=0.93); women improved survival at median follow-up of 387 days	Women have an increased chance for long-term survival after TAVR
Saad *et al.*, 2018 (22)	Meta-analysis	47,188 (n=23,303)	Women lower all-cause mortality at 1 year (risk ratio: 0.85; 95% CI: 0.79–0.91; P<0.001) and longest-available follow-up (mean 3.28±1.04 years; risk ratio: 0.86; 95% CI: 0.81–0.92; P<0.001)	Women higher risk of complications, but better long-term survival after TAVR
Chandrasekhar *et al.*, 2016 (23)	National Registry	23,652 (n=11,808)	1-year mortality: 21.3% women, 24.5% men (adjusted HR: 0.73; 95% CI: 0.63–0.85; P<0.001)	Long-term survival better in women than men after TAVR
Chieffo *et al.*, 2016 (24)	WIN-TAVI registry	1,019 only women	30-day VARC-2 composite safety endpoint* 14.0%	Low incidence of mortality and stroke
Chieffo *et al.*, 2018 (25)	WIN-TAVI registry	1,019 only women	1-year VARC-2 composite efficacy endpoint** 16.5%	Low incidence of mortality and stroke

*, composite of mortality, stroke, major vascular complication, life-threatening bleeding, stage 2 or 3 acute kidney injury, coronary artery obstruction, or repeat procedure for valve-related dysfunction; **, composite of mortality, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure or valve-related dysfunction beyond 30 days. TAVR, transcatheter aortic valve replacement; CI, confidence interval; HR, hazard ratio; OR, odds ratio; SAVR, surgical aortic valve replacement.

research is needed to better understand the exact cause behind this.

The use of SAVR and TAVR for the treatment of AS in female patients

Although both SAVR and TAVR provide beneficial outcomes for patients with AS, the increased risk associated with SAVR in female patients, compared to male patients, has recently come under question (1,7-9). SAVR has been available since the 1960s and, for the majority of patients, reduces mortality, provides symptom relief and increases quality-of-life (28). Various comorbidities, however, represent a relevant increase in risk because AS usually appears at an advanced age. Surgery for AS in women is usually more technically demanding due to smaller annuli size, increased need for aortic enlargement and complications related to cardiopulmonary bypass. In addition, women tend to be older and in a more advanced stage of the disease with greater frailty at the time of surgical referral (30).

The alternative approach to SAVR is the TAVR procedure. TAVR also provides an option for patients who are deemed 'inoperable', such as those with porcelain aorta or a hostile chest from previous radiotherapy where surgery is not technically possible. As a result, TAVR provides a solution for the substantial proportion of patients who would previously have been untreated despite their poor prognosis. Procedural success with TAVR is comparable between women and men (14,31), but studies have shown that TAVR is associated with a lower risk in terms of 30-day and 1-year mortality in women than in men (1,7-9). Furthermore, the TAVR procedure is not associated with any differences in terms of post-procedural frailty or quality-of-life between women and men (14).

SAVR: sex-related differences in treatment outcomes

SAVR was the first procedure that provided definitive treatment for AS, and for decades it represented the gold standard treatment for this disease (32). However, the surgical procedure excludes a considerable portion of

the patients affected by AS—approximately one-third of elderly patients with severe, symptomatic AS are denied surgery by the attending practitioner—due to increased age, a left ventricular ejection fraction (LVEF) <50% and comorbidities (33). In addition, various studies have reported worse outcomes for women with SAVR compared to men. Conversely, however, women appear to have a better outcome with the more recently introduced TAVR approach than men, and the number of studies showing this trend is increasing (1,7-9).

SAVR: in-hospital and 30-day mortality

Chaker *et al.* reported a consistently higher unadjusted and adjusted in-hospital mortality (IHM) rate in women post-SAVR compared to men. Their study suggested that women had more vascular complications and blood transfusions than men and were more likely to be discharged to a skilled nursing facility, nursing home, or intermediate care centre (15). A higher IHM in women was also registered in the 2019 study from Lopéz-de-Andrés *et al.* where they stated that females had significantly higher IHM irrespective of all the comorbid conditions analysed (16). These results differ from some older studies that, after adjustment of the results, did not show a significant difference in IHM and suggest that there is no greater than a 2.5-fold increase in risk for females compared with males undergoing AVR. Female gender, however, may impose an increased risk for cardiac morbidity after AVR (34).

In the Elhmidi *et al.* study, the 30-day mortality endpoint showed that women exhibited a higher 30-day mortality post-SAVR when compared to male patients and that female gender was considered an independent factor for 30-day mortality after adjustment for baseline characteristics. Interestingly, after 30 days, the only independent risk factor for later mortality in their study was age (17).

TAVR: gender-specific data on treatment risk in women

Interventional cardiology has been revolutionised by TAVR, which is now established as the standard treatment for severe AS in patients at high-risk for SAVR (35). Such are the benefits of TAVR that the procedure is now being increasingly performed in intermediate- and low-risk patients with AS (36,37). Several studies have focused their attention on the growing evidence that women benefit from a better outcome with this procedure when compared to men, especially in the long-term. This is of great interest, not only because women represent 50% of the eligible patients for TAVR but also because this procedure appears to be more cost-effective in women due to their longer life expectancy (20).

According to O'Connor *et al.* there is a significant difference in baseline clinical demographics of male and female patients undergoing TAVR. In particular, men had a higher number of risk factors than women [including DM, previous myocardial infarction (MI), previous percutaneous coronary intervention (PCI) and poor LV systolic function (LVEF <30%)]. Conversely, women were older, had higher transvalvular gradients and high pulmonary artery pressures, higher LVEF and smaller annular sizes (21). This depiction of the baseline conditions of patients undergoing TAVR was consistent in the other studies analysed in our systematic review.

This is also supported by the PARTNER trial, published in 2010, which showed that women who undergo TAVR are typically older and deemed to be more frail than male counterparts. Conversely, however, women tend to have a higher LVEF and reduced frequency of coronary artery disease (CAD) and prior coronary revascularisation compared to men (38).

TAVR: in-hospital and 30-day mortality

Chandrasekhar *et al.* showed a higher risk of in-hospital vascular complications in women undergoing TAVR for AS but concluded that there were no differences in IHM between the sexes (23). One of the main trial endpoints of the treatment of AS is 30-day mortality. Interestingly, although men and women show significantly different risk profiles and baseline conditions, various studies have shown a similar rate of 30-day mortality for both sexes post-TAVR. These studies include the registry study conducted by Hayashida *et al.*, where no significant difference was observed between the sexes (19); an observation that was later supported by Saad *et al.* (22). The OBSERVANT registry found no sex-related differences in 30-day mortality following TAVR, but they did identify increased rates of vascular damage and the need for blood transfusions in women. A propensity matched sub-study of this registry found comparable IHM rates in females undergoing SAVR and TAVR with a higher transfusion rate, more renal and heart failure, and higher transvalvular gradients in females following SAVR and more post-procedural aortic regurgitation, a higher stroke rate, more vascular complications, and a higher permanent pacemaker insertion

and PCI rate in women undergoing TAVR (8). While O'Connor *et al.* reported no differences in 30-day mortality between male and female patients, their study also showed that women had higher rates of major vascular, bleeding and stroke events (21). This result is partially supported by the finding of Humphries *et al.* where women showed more major/life-threatening bleeds, needed more blood transfusions and had more vascular complications, but overall women seemed to have a better survival rate at 30 days (20).

Overall, the likelihood of poor outcomes of TAVR in female patients with AS is relatively low. The first ever all-female TAVR registry was the WIN-TAVI registry (Women's INternational Transcatheter Aortic Valve Implantation). It included 1,019 patients enrolled between January 2013 and December 2015. The primary endpoint was the Valve Academic Research Consortium (VARC)-2 early safety endpoint at 30 days (composite of mortality, stroke, major vascular complication, life-threatening bleeding, stage 2 or 3 acute kidney injury, coronary artery obstruction, or repeat procedure for valve-related dysfunction). Chieffo *et al.* registered a 30-day VARC-2 composite safety endpoint approximately of 14.0% of their all-female study population, with a low incidence of early mortality and stroke (24).

TAVR: 1-year mortality

Three studies focussed on 1-year mortality post-TAVR in patients with AS as one of their study endpoints (19,22,23). Both Chandrasekhar *et al.* and Hayashida *et al.* identified a higher 1-year survival rate for women and these studies suggested that this could be explained by women's longer life expectancy and that it was also influenced by a lower rate of baseline comorbidities (19,23). Saad *et al.* reported a lower 1-year mortality for women but noted a potential increased risk of stroke (22).

Skelding *et al.* conducted an evaluation of TAVR with a self-expanding valve versus SAVR in women through a randomised trial (9). The study objective was to compare outcomes in women after SAVR. Overall 353 women were treated, and 183 women received TAVR and 170 SAVR. Baseline characteristics and the predicted risk of the two groups were comparable, although the frequency of DM was lower in patients undergoing TAVR (33.3% *vs.* 45.3%; P=0.02). TAVR-treated patients experienced a statistically significant 1-year survival advantage compared with SAVR patients (12.7% *vs.* 21.8%; P=0.03). The composite all-cause mortality or major stroke rate also favoured TAVR (14.9% *vs.* 24.2%; P=0.04). The study concluded that female TAVR patients had lower 1-year mortality and lower 1-year all-cause mortality or major stroke compared with women undergoing SAVR, with both cohorts experiencing improved quality-of-life.

The 1-year outcome of the WIN-TAVI registry revealed a VARC-2 composite efficacy endpoint (composite of mortality, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure or valve-related dysfunction beyond 30 days) of 16.5% in female patients undergoing TAVR, with a low incidence of 1-year mortality and stroke (25).

TAVR: longer-term outcomes

Williams *et al.* carried out a retrospective sub-analysis of high-risk, symptomatic AS patients in the PARTNER trial and the results showed that female subjects had lower late mortality with TAVR compared with SAVR. The study outlined the differences in baseline characteristics for men and women, with women being older and having fewer important comorbidities (7). At 2-year of follow up, all-cause mortality in the female TAVR group was significantly lower than in the female SAVR group [hazard ratio (HR) 0.67], driven by a very significant reduction in women undergoing TF-TAVR, and no mortality benefit in those with a TA access route. Furthermore, there was no survival advantage in men undergoing TAVR compared with SAVR at 2 years.

Panoulas *et al.* performed a meta-analysis of the gender-specific subgroup results of randomised controlled trials that evaluated the survival of patients with severe AS treated with TAVR versus SAVR. Four randomised clinical trials met the criteria, totalling 3,758 patients (comprising 1,706 women and 2,052 men). Female TAVR recipients had a significantly lower mortality than SAVR recipients at 1-year [odds ratio (OR) 0.68; 95% CI: 0.50–0.94] and at 2-year (OR 0.74; 95% CI: 0.58–0.95). Amongst males there was no difference in mortality between TAVR and SAVR at 1-year (OR 1.09; 95% CI: 0.86–1.39) or 2-year (OR 1.05; 95% CI: 0.85–1.3). The difference in treatment effect between genders was significant at both 1-year ($P_{interaction}$=0.02) and 2-year ($P_{interaction}$=0.04). In women, TAVR has a 26–31% lower mortality odds than SAVR. In men, there is no difference in mortality between TAVR and SAVR (1). These results indicate that for women TAVR results in significantly better survival than SAVR. Interestingly, men

do not show this same pattern, and the difference between the genders is statistically significant.

Rationale for the benefit of TAVR over SAVR in women

The reasons for this possible female-sex-related survival benefit in patients with AS undergoing TAVR are still not entirely clear. Some possible reasons cited by Panoulas *et al.* include that there is a tendency in women for TAVR (in comparison to SAVR) to result in lower peri-procedural mortality, lower bleeding rates and acute kidney injury (AKI), better LV function recovery and larger post-procedural AVA, may more than counteract the higher rate of moderate paravalvular leak and vascular complications. This 'TAVR survival benefit' was not observed in males, who in general have higher comorbidity burden, including cardiovascular and respiratory disease, alongside increased paravalvular aortic regurgitation (1).

Conclusions

Our literature review suggests that SAVR is associated with an increased risk of 30-day mortality in women compared to men, which is possibly due to increased age, comorbidities and higher in-hospital mortality. Anatomical differences between women and men with AS may also play a role in the increased risk associated with SAVR, but further research is needed to confirm this. With this information, women with adverse anatomical risks for SAVR can be more readily identified and treated with TAVR to ensure optimal patient safety and outcomes. Conversely, there is no gender bias associated with TAVR in terms of procedural success or post-procedural mortality, frailty or quality-of-life.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-700). MT is an employee of Edwards Lifesciences. PB reports grants and other from Edwards Lifesciences, outside the submitted work.The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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