Review

Interventional Cardiology

Sex-related differences in transcatheter aortic valve replacement outcomes: what do interventionalists need to know?

Rebecca T Hahn
[1]Columbia University Medical Center/ New York Presbyterian Hospital, NY 10032, USA
Tel.: +1 212 342 0444
Fax: +1 212 342 3660
rth2@columbia.edu

Females exhibit differences in morphologic, hemodynamic and ventricular response to progressive aortic stenosis (AS), with better overall survival rates compared with males. In addition, females and males differ in baseline characteristics at the time of intervention for symptomatic severe AS. Females have a higher risk of death with surgical aortic valve replacement compared with males. Despite higher incidences of vascular complications, major bleeding and possibly strokes with transcatheter aortic valve replacement, females had better intermediate and long-term mortality compared with males. This review will summarize the data on sex differences in AS and transcatheter aortic valve replacement outcomes.

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Transcatheter aortic valve replacement (TAVR) has emerged as an alternative to surgical aortic valve replacement (SAVR) for select groups of patients with severe aortic stenosis (AS), such as those at high operative risk [1,2]. Notably, unlike trials in most other cardiovascular disease states, females represent a significant proportion of enrolled patients in TAVR studies. Recent work has demonstrated female sex to be a potentially favorable characteristic for patients undergoing TAVR [3–7]. Prior analyses have demonstrated differences between males and females in pre-existing comorbidities as well as the left ventricular (LV) response to severe AS potentially explaining improved clinical outcomes for females [4,5,7,8]. However, not all studies are in agreement that TAVR may be more beneficial in females, with some demonstrating no difference in outcomes or increased adverse events in females undergoing TAVR [9–14]. This review will summarize the data on sex differences in AS and TAVR outcomes.

Sex differences in response to aortic stenosis

Multiple previous studies have shown a significant sex difference in patients with AS [15–19]. For similar valve area indices, females had higher peak and mean gradients, higher relative wall thickness, smaller ventricular volumes and better indices of systolic function such as fractional shortening, ejection fraction, maximum positive dP/dT and cardiac index. Females have lower aortic valve calcium score on multislice computed tomography scans for the same severity of AS [20,21]. Males had higher LV mass for a given valve area and higher mass:volume ratios suggesting less compensatory increase in LV mass in females [18,22]. Females have more concentric hypertrophy compared with males [17,23] and end-systolic wall stress may be lower in females, particularly in the setting of high relative wall thickness [15,19]. Whether females have more [24] or less [23] fibrosis is still debated.

In addition to these differences in ventricular and hemodynamic responses to AS, there

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are sex differences in presentation and progression of disease. The Simvastatin Ezetimibe in Aortic Stenosis study prospectively followed initially asymptomatic, mild-moderate AS patients (without known coronary artery disease, peripheral vascular disease, cerebrovascular disease, diabetes mellitus or any condition requiring lipid-lowering medications) [25]. Females with asymptomatic AS were older, had a lower prevalence of comorbidities such as hypertension, renal dysfunction and coronary artery disease, compared with males [26]. Females in this study had a smaller aortic valve area at initial presentation however the 4-year rate of progression of AS did not differ by sex [27]. Females had a 50% lower rate of both stroke and coronary artery disease requiring concomitant bypass grafting at the time of aortic valve replacement, and a 31% lower all-cause mortality rate, independent of covariates such as differences in age, prevalence of hypertension, AS severity, LV geometry and LV systolic function.

Sex differences in outcomes for surgical aortic valve replacement

How sex affects outcomes in SAVR for severe AS is also poorly understood. Some studies suggest worse outcomes in females [28,29] but not after adjusting for confounders. Other studies suggest females have better long-term survival compared with males [30,31] particularly if a bioprosthesis was implanted [31]. Females may responded differently to SAVR showing a greater improvement in EF following intervention [28] with more rapid reversal of myocardial hypertrophy following SAVR [32]. Persistent LV hypertrophy after SAVR is however associated with a worse prognosis in females [33]. Females with 'adaptive' (concentrically hypertrophied) geometry may have better outcomes following SAVR compared with maladaptive geometry [23].

A number of studies now have compared the results of SAVR to TAVR [1,12,34]. Although the initial findings of the Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated similar mortality in SAVR and TAVR [1], a subsequent analysis by Williams *et al.* [7] showed a modest difference in procedural mortality favoring TAVR in females which continued to increase over time. At 6 months and 2 years of follow-up, SAVR mortality was significantly higher than TAVR mortality for females. On the other hand, there was no mortality difference between TAVR and SAVR among males. This study was the first to report a higher incidence of stroke in females. A more comprehensive look at 30-day and 1-year outcomes in the entire PARTNER 1 database including 1987 patients in the nonrandomized continued access registry, and 557 patients from the randomized, controlled trials, was presented by Kirtane on behalf of the PARTNER investigators [35]. This study showed that females were younger, with lower body surface area, and were less likely to have a number of other co-morbidities (specifically history of smoking, hypertension, hyperlipidemia, diabetes and renal disease, coronary artery disease, peripheral vascular disease, cardiomyopathy and permanent pacemakers). Female patients had larger indexed calculated aortic valve areas as well as ejection fractions. Among females, late mortality was dramatically lower with transfemoral TAVR as compared with SAVR (23.4 vs 36.9%; $p = 0.02$) whereas among females who underwent transapical TAVR, 2-year mortality was similar with TAVR and SAVR (37.3 vs 41.7%; $p = 0.62$).

In the Italian Observational Multicenter Registry trial, female SAVR patients showed a worse risk profile compared with male SAVR patients, given the higher mean age, prevalence of frailty score of 2 or higher, New York Heart Association class of 3 or higher, lower body weight and preoperative hemoglobin level ($p \leq 0.02$). Female TAVR patients also had higher age and a lower body weight and preoperative hemoglobin level ($p \leq 0.005$), but with a similar New York Heart Association class, frailty score, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), a better LV ejection fraction and a lower prevalence of low LV ejection fraction (<30%), porcelain aorta, renal dysfunction, chronic obstructive pulmonary disease, arteriopathy and previous cardiovascular surgery or percutaneous coronary intervention ($p \leq 0.01$). Females showed a smaller aortic annulus than males in both populations ($p < 0.001$). Female sex was an independent predictor in the SAVR population for risk-adjusted 30-day mortality (odds ratio [OR]: 2.34; $p = 0.043$) and transfusions (OR: 1.47; $p = 0.003$). Female sex was an independent predictor in the TAVR population for risk-adjusted major vascular complications (OR: 2.92; $p = 0.018$) and transfusions (OR: 1.93; $p = 0.003$), but proved protective against moderate-to-severe postprocedural aortic regurgitation ($p = 0.018$).

This latter finding may be related to the effect of small annular size on outcomes. Rodes-Cabau *et al.* [36] studied the PARTNER I trials and divided annular size into tertiles of annular diameter; ~60% of patients with small annular diameters were women (compared with 50% with medium annular diameters, and 20% with large annular diameters). The patients undergoing TAVR with smaller annular diameters had less prosthesis-patient mismatch compared with SAVR (39 vs 63%; $p = 0.01$).

Sex differences in outcomes following TAVR

A number of meta-analyses addressing the sex differences in outcomes with TAVR have recently been published [37,38]. The meta-analysis by Conrotto *et al.* [37]

included five studies using both the balloon-expandable and self-expanding transcatheter valves, and involved 6645 patients (50% females) [4–6,35,39]. This study pooled analysis using a random-effect model and with metaregression and found significant sex differences in baseline characteristics, procedures and outcomes. Compared with males, females in the analysis had a lower logistic EuroSCORE (22.3 ± 9.1 vs 26.2 ± 13.0) due to lower prevalence of coronary artery disease (64.1 vs 82.6%) and history of previous stroke (12.9 vs 18.5%). In addition females were older (83.4 vs 82.2 years), with higher ejection fractions (0.551 vs 0.495), more severe mean pressure gradients (52.6 vs 47.0 mm Hg) and smaller valve areas (0.6 vs 0.7 cm^2). At 30 days females had a greater risk of major vascular complications (pooled analysis OR: 1.81; 95% confidence intervals [CI:], 1.29–2.55) and major life-threatening bleeding (OR: 1.55; 95% CI:, 1.02–2.34) but had lower risk of moderate-to-severe aortic regurgitation (OR: 0.5; 95% CI: 0.38–0.67). There was no significant difference in risk between sexes in 30-day mortality (OR: 0.8; 95% CI: 0.56–1.15) or stroke (OR: 1.24; 95% CI: 0.85–1.82). All-cause death at follow-up of at least 1 year was lower in females (24.0 vs 34.0%) with a significantly lower risk of death for females (OR: 0.82; 95% CI: 0.73–0.93, I^2 = 0%). Female sex continued to have a lower risk of death using a metaregression analysis including age, ejection fraction, prior cerebrovascular accident, renal insufficiency and access site.

In the second meta-analysis by O'Connor *et al.* [38] contacted the principle investigators for five studies and analyzed the individual patient-level registry data of 11,310 patients [2,5,13,40,41]. Men had higher rates of the following risk factors: diabetes, previous myocardial infarction, previous percutaneous coronary intervention, pervious coronary artery bypass graft surgery, peripheral vascular disease, poor LV systolic function (<30%), 3-vessel coronary artery disease, higher log EuroSCORE and pulmonary disease. Females were older, had higher transvalvular gradients and higher pulmonary artery pressures and had smaller annular sizes. There was no sex difference in procedural success rate, valve migration or embolization, conversion to surgery or procedure-related death. There was a higher rate of major vascular complications and major life-threatening bleeding in females. Men however had a significantly higher rate of >2+ aortic regurgitation and were more likely to need pacemaker implantation postprocedurally.

On subanalysis, a number of procedural outcomes varied by both sex and implanted valve type (Table 1). Valve embolization and cardiac tamponade were more common in females for either valve type. Pacemaker implantation was significantly more common in men among the patients who received self-expandable valves (26.4 vs 19.4%; p < 0.001), but sex differences were not seen with the balloon-expandable valve (9.3 vs 8.4%; p = 0.15). Significant aortic regurgitation (grade > 2) occurred more frequently in males than in females treated with balloon-expandable valves (5.2 vs 2.8%; p < 0.001), but there was no difference between males and females treated with self-expandable valves. The rate of stroke at 30-day follow-up was higher in women who received self-expandable valves (3.2 vs 2.1%; p = 0.037), but no difference existed in patients

Table 1. Procedural and 30-day outcomes according to sex and valve type.

	Self-expanding valve			Balloon expandable valve			p-value (a) vs (c)	p-value (b) vs (d)
	(a) Females n = 1724	(b) Males n = 2038	p-value	(c) Females n = 3736	(d) Males n = 3762	p-value		
Device success	97%	97%	0.97	97.4%	96.8%	0.13	0.049	0.81
Conversion to surgery	0.6%	0.8%	0.607	1.1%	0.9%	0.36	0.074	0.85
Procedure-related death (<72 h)	2.5%	2.2%	0.604	2.6%	2.3%	0.29	0.49	0.90
Valve embolization	1.2%	1.5%	<0.001	0.8%	1.5%	0.008	0.11	0.94
Cardiac tamponade	1.9%	1%	0.032	1.0%	0.5%	0.023	0.009	0.032
Pacemaker	19.4%	26.4%	<0.001	8.4%	9.3%	0.15	<0.001	<0.001
AR >2+	2.5%	3.4%	0.16	2.8%	5.2%	<0.001	0.49	<0.001
Stroke (30 days)	3.2%	2.1%	0.037	5.0%	4.4%	0.26	0.001	<0.001
Major vascular	4.4%	2.6%	0.002	7.2%	3.8%	<0.001	<0.001	0.017
Major bleeding	7.1%	4.7%	0.026	11.6%	10%	0.058	<0.001	<0.001
Myocardial infarction	0.9%	0.8%	0.755	2.9%	3.0%	0.82	<0.001	<0.001
All-cause death (30 days)	6.0%	6.0%	0.993	6.7%	6.7%	0.97	0.29	0.40

Data from [38].

who received balloon-expandable valves. However, major vascular complications and major bleeding were consistently higher in women regardless of the type of valve implanted.

Although all-cause mortality was the same for females and males at 30 days, Kaplan–Meier survival curves with a median duration of follow-up of 387 days (interquartile range 192–730 days) showed a significant survival advantage for females (log-rank $p < 0.001$). The Cox model adjusted hazard ratio for female sex was 0.79 (95% CI: 0.73–0.86; $p < 0.001$). This survival advantage was consistent, irrespective of valve type or route of access. On multivariable analysis, the predictors of death for both sexes were: body mass index, pulmonary disease and creatinine clearance, post-TAVR aortic regurgitation (>2+) and nonfemoral approach. Age was an additional predictor of death in males only.

Conclusion

Females exhibit differences in morphologic, hemodynamic and ventricular response to progressive AS, with better overall survival rates compared with males. In addition, females and males differ in baseline characteristics at the time of intervention for symptomatic severe AS. Females have a higher risk of death with SAVR compared with males. Despite higher incidences of vascular complications, major bleeding and possibly strokes with TAVR, females had better intermediate and long-term mortality compared with males. This may be related to the lower incidence of baseline co-morbidities and lower body mass index for females undergoing TAVR, as well as the protective effect of female sex against significant post-TAVR aortic regurgitation in the setting of lower calcium burden and smaller annuli.

Future perspective

The significant overall survival advantage of female sex with AS will be better characterized in the future as we advance our understanding of the ventriculoarterial relationship and molecular and myocardial response to pressure load. In addition, as new transcatheter devices are developed reducing the risks of vascular complications as well as the incidence of significant paravalvular regurgitation, sex-related differences in TAVR procedural complications will likely be reduced. How this will affect outcomes remains to be seen.

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Executive summary

Sex differences in response to aortic stenosis

- For similar valve area indices, females had higher peak and mean gradients, higher relative wall thickness, smaller ventricular volumes and better indices of systolic function.
- Females have lower aortic valve calcium score on multislice computed tomography scans for the same severity of aortic stenosis.

Sex differences in outcomes for surgical aortic valve replacement

- Studies comparing surgical aortic valve replacement (SAVR) to transcatheter aortic valve replacement (TAVR) have shown early and intermediate mortality was significantly higher in SAVR than TAVR in females
- Females undergoing TAVR (vs SAVR) may have a higher risk of stroke and vascular complications.

Sex differences in outcomes following TAVR

- Compared with males, females undergoing TAVR had fewer baseline co-morbidities (i.e., diabetes, significant coronary artery disease, peripheral vascular disease, poor left ventricular systolic function and pulmonary disease).
- Females (vs males) undergoing TAVR had a higher risk of vascular complications and major life-threatening bleeding.
- Females (vs males) undergoing TAVR had a lower risk of moderate-to-severe aortic regurgitation.
- Females undergoing TAVR had better intermediate and long-term mortality compared with males.

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