Transcatheter Aortic Valve Replacement in Female Patients—Present Scenario

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Indian J Cardiovasc Dis Women-WINCARS 2017;2:7–13.

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Abstract

Since the publication of the pivotal PARTNER study, the transcatheter aortic valve replacement (TAVR) procedure has been established as a noninferior alternative to the traditional aortic valve replacement surgery in severe aortic stenosis (AS) patients with high-surgical risk. Approximately 50% of patients undergoing TAVR are females, and cumulative findings from various worldwide cohorts have shown sex-related differences in short- and long-term morbidity and mortality. Notably, most data indicate improved long-term mortality in female patients. These differences are partly the results of distinct anatomical and physiologic characteristics in female patients, compared with male patients. Nevertheless, recent data from intermediate-surgical risk cohorts have demonstrated that sex-related mortality differences are less apparent. Here, we review the latest literature on the influence of patient's sex on TAVR morbidity and mortality and discuss possible explanations for the outcomes presented.

Keywords
- aortic stenosis
- PARTNER trial
- surgical aortic valve replacement
- transcatheter aortic valve replacement

As the prevalence of severe symptomatic aortic stenosis (AS) increases with age, the use of transcatheter aortic valve replacement (TAVR) is expanding as an acceptable alternative to the traditional surgical aortic valve replacement (SAVR) in intermediate- and high-surgical risk patients.[1–4] Based on several worldwide registries, approximately 50% of patients undergoing TAVR are females,[5–7] and compared with male patients, they carry distinct anatomical and physiologic characteristics and subject to different short- and long-term morbidity and mortality.

Female patients with severe AS are referred to SAVR less frequently than male patients,[8] though they present with more clinically advanced valve disease[3,9–11] and worse valve hemodynamics[5,9–18] (►**Tables 1**, **2**). There are several possible reasons for these findings. First, ventricular adaptation to a stenotic aortic valve is different in female patients, compared with male patients, with predominant concentric left ventricular (LV) hypertrophy rather than LV dilation. This may be the result of different hormonal, mostly estrogen, effects.[19–22] Second, female patients with AS generally have better LV systolic function.[3,5,9,10,13–16,18,23,24] Third, female patients have lower prevalence of cardiovascular comorbidities (such as coronary artery disease[5,13,15,16,18,23–25]) and as such are less likely to be referred to a routine echocardiogram, which otherwise may allow for an earlier diagnosis of aortic valve pathology, possibly while still asymptomatic. Moreover, studies examining aortic valve disease management have shown referral delays both when measuring time to diagnosis and time to surgery in female patients compared with male patients.[8,26,27]

Another important consideration of the heart team when determining on patient's appropriate valve management is the estimated surgical risk. Several studies have shown sex-related differences in outcome after cardiac surgery,[28–30] though mainly focusing on coronary artery surgery. As a result, female sex has been considered an independent risk factor for perioperative mortality.[31] Moreover, it has been shown that female patients with severe AS have a distinctive risk profile compared with male patients (►**Table 1**). A female patient with severe AS is more likely to be older[3,5,11,13,14,18,23,32] and with lower body surface area[3,5,13,16,24] compared with male patients. Also, the diagnosis of frailty and porcelain aorta were

DOI https://doi.org/10.1055/s-0037-1607211.

Table 1 Preprocedural patient characteristics

Author (year, reference)	Total number of patients	Valve type (%)	F/M *n* (%)	Age (mean) F/M	BSA (m^2) F/M	"Porcelain" aorta (%) F/M	CAD (%) F/M	NYHA FC III/IV (%) F/M	Logistic EuroSCORE (%) F/M	STS score (%) F/M
Chandrasekhar (2016)[3]	23,652	Balloon-expandable (87%) Self-expandable (13%)	11,808/ 11,844 (50/50)	82.3 ± 9/81.7 ± 9[a]	1.7/1.9[a]	7.7/6.0[a]	29.5/41.9[a]	82.4/80.3[a]	NR	9 ± 6/8 ± 6[a]
Kodali (2016)[17]	2,559	Sapien	1,220/1,339 (48/52	84.9/84.1	1.7/1.9	NR	67.1/87.4[a]	NR	25.1/27.7[a]	11.9/11.1
Bière (2015)[12]	3972	Sapien (67) CoreValve (31)	1,967/2,005 (50/50)	84 ± 7/81.6 ± 8[a]	NR	NR	47.9/69[a]	NR	21.4 ± 13/22.2 ± 15	NR
Forrest (2016)[33]	3,687	CoreValve	1,708/1,979 (46/54)	84 ± 8/82.7 ± 8	NR	NR	67.6/88.7[a]	88.2/86.5	20.7 ± 15/23.4 ± 17[a]	9.6 ± 5/8.3 ± 5[a]
Al-Lamee (2014)[32]	1,627	Sapien (50) Corevalve (50)	756/871 (47/53)	82.6 ± 7/80.8 ± 8[a]	1.7 ± 0.2/ 1.9 ± 0.2[a]	NR	NR	15.1/17.3[b]	21.0 ± 13/21.8 ± 14	NR
Sherif (2014)[18]	1,432	Sapien (18) Corevalve (82)	827/605 (58/42)	82.8 ± 6/80.2 ± 6[a]	NR	NR	51.6/71.1[a]	90.7/85[a]	21 ± 13/20 ± 14	NR
Katz (2016)[11]	819	Sapien (22) Corecalve (73) Inovare (3)	418/401 (51/49)	82.4 ± 7/80.6 ± 8[a]	NR	NR	NR	85/78[a]	20.4 ± 15/20.9 ± 16	15.4 ± 13/11.4 ± 10[a]
Gaglia (2016)[23]	755	Sapien (75) Corevalve (25)	383/372 (51/49)	83.5 ± 8/82.4 ± 8[a]	NR	NR	NR	NR	NR	9.8 ± 5/8 ± 4[a]
Humphries (2012)[16]	641	Sapien (97) Corevalve (3)	306/278 (52/48)	83/82	1.6/1.9[a]	29.2/12[a]	64.1/82.6[a]	87.2/85.6	NR	7.5/7.5
Buja (2013)[13]	659	CoreValve	368/291 (56/44)	82 ± 5/80 ± 7[a]	1.7/1.8[a]	11/11	43/68[a]	74/68	NR	23 ± 14/23 ± 14
Hayashida (2012)[15]	260	Sapien (85) Corevalve (15)	131/129 (50/50)	83.8 ± 6/82.4 ± 7[a]	1.7 ± 0.2/ 1.9 ± 0.2[a]	NR	48.9/79.1	86.3/82.9	22.3 ± 9/26.2 ± 13[a]	NR

Abbreviations: BSA, body surface area; CAD, coronary artery disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; F, female FC, functional class; M, male; NR, not reported; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.
Values presented as mean ± SD or *n* (%).
[a] $p \leq 0.05$.
[b] *p* value not reported.

Table 2 Preprocedural echocardiographic parameters

Author	Total number of patients	Female/Male *n* (%)	LV systolic EF < 30% (%)	Mean TV gradient (mm Hg)	Maximal TV gradient (mm Hg)	Aortic valve area (cm^2)	Aortic annulus diameter (mm)
Chandrasekhar (2016)[3]	23,652	11,808/11,844 (50/50)	4.3/9.6[b]	NR	NR	NR	NR
Kodali (2016)[17]	2,559	1,220/1,339 (48/52)	NR	46.1/42[a]	NR	0.61/0.68 [a]	18.3/19.9[a]
Bière (2015)[12]	3,972	1,967/2,005 (50/50)	NR	51.0 ± 18/ 45.4 ± 15[a]	NR	NR	NR
Forrest (2016)[33]	3,687	1,708/1,979 (46/54)	NR	NR	NR	NR	NR
Al-Lamee (2014)[32]	1,627	756/871 (47/53)	NR	NR	85 ± 28/ 77 ± 24	0.6 ± 0.2/ 0.7 ± 0.5	21.3 ± 2/ 23.2 ± 2
Sherif (2014)[18]	1,432	827/605 (58/42)	8.5/16.4[a]	52.1 ± 21/ 45.5 ± 16[a]	46.7 ± 41/ 41.9 ± 36[a]	0.7 ± 0.4/ 0.72 ± 0.4[a]	NR
Katz (2016)[11]	819	418/401 (51/49)	NR	52.2 ± 16/ 46.3/16[a]	NR	0.6 ± 0.2/ 0.7 ± 0.2 [a]	NR
Gaglia (2016)[23]	755	383/372 (51/49)	(EF < 40%) 16.2/30.1[a]	50.1 ± 13/ 44.9 ± 12[a]	73.7 ± 19/ 67.8 ± 14[a]	0.63 ± 0.1/ 0.70 ± 0.1[a]	NR
Humphries (2012)[16]	502	306/278 (52/48)	12/28[a]	41/40[a]	NR	0.6/0.7[a]	NR
Buja (2013)[13]	659	368/291 (56/44)	(EF < 40%) 16/27[a]	55 ± 18/ 47 ± 14[a]	88 ± 26/ 77 ± 22[a]	NR	21 ± 2/ 23 ± 2[a]
Hayashida (2012)[15]	260	131/129 (50/50)	(EF < 40%) 19.8/39.5[a]	49.7 ± 20/ 45.5 ± 16	NR	0.59 ± 0.2/ 0.61 ± 0.1	20.9 ± 1/ 22.9 ± 2[a]

Abbreviations: EF, ejection fraction; LV, left ventricular; NR, not reported; TV, transvalvular.
Values are presented as mean ± SD or *n* (%) for female/male.
[a] $p \leq 0.05$.
[b] *p* value not reported.

reported more often in female patients.[3,11,16,33] All these elements are considerable factors that contribute to a higher surgical risk assessment in female patients, thus favoring the decision to refrain from SAVR in female patients more than males.

Nevertheless, data surprisingly support better long-term survival for female patients compared with male patients after SAVR,[9,34,35] suggesting lack of SAVR-specific risk assessment tools and raising the question of a possible selection bias between sexes. One possible limitation in the evaluation of female patients for SAVR is the calculated surgical risk scores. Studies comparing surgical risk scores between sexes have shown conflicting results,[5,13,16,17,24,25,33] highlighting the need for valve surgery–specific scores. Another limitation is the frailty assessment. In most reports frailty was defined upon “eyeballing,” which is influenced by personal biases. Advanced age, female sex, and lower body mass index are commonly used in the subjective “eyeball” evaluation of frailty but were not associated with a higher frailty score when comprehensively evaluated;[36] hence there is the need for using objective tools in the evaluation of frailty.[25,36–38] One way or another, as the PARTNER trial was published and TAVR emerged as a noninferior alternative for SAVR,[1,39] many female patients with severe AS, previously managed conservatively, were increasingly referred to TAVR.

Could TAVR be a better solution for a female patient with severe symptomatic AS?

In a retrospective subanalysis of high-risk patients in the pivotal PARTNER trial, female patients had lower late mortality with TAVR versus SAVR.[40] Nevertheless, TAVR carries other possible complications with distinct procedure-related characteristics and outcomes in female patients compared with male patients (►**Table 3**). Periprocedural, female patients suffer from significantly higher rates of vascular[3,5,6,11,12,16,17,32,33] and bleeding[5,7,11,12,16,17,33] complications compared with male patients. As for device success, stroke risk, and 30-day mortality, studies have not shown uniform results, but most available data indicate similar outcome for both sexes.[3,5,13,16,17,24] Importantly, female patients present with lower long-term mortality rate following TAVR compared with male patients.[5–7,40]

Several computed tomography (CT) studies suggest that differences between sexes regarding acute and long-term outcome potentially relate to anatomic vasculature variations, especially those concerning the aortic root and the peripheral vessels.[41,42] Interestingly, it has been recently demonstrated that smaller aortic root dimensions reflect a sex-specific difference, which could not be fully explained by the smaller body size of female patients.[43] In contrast, peripheral vascular dimensions were not significantly different when adjusted

Table 3 Procedural and 30-day outcome

Author	Total number of patients	Female/Male *n* (%)	Device success (%)	Conversion to open surgery (%)	In-hospital (30-day mortality (%)	Major and life-threatening vascular complications (%)	Bleeding complications (%)	Pacemaker implantation (%)	Major stroke (%)
Chandrasekhar (2016)[3]	23,652	11,808/11,844 (50/50)	92.5/92.7	1.7/1.0[a]	5.6/4.28	8.3/4.4[a]	8.01/5.96	8.9/8.5	2.58/1.86[b]
Kodali (2016)[17]	2,559	1,220/1,339 (48/52	NR	NR	6.5/5.9	9.9/5.1[a]	10.5/7.7[a]	6.48/5.08	3.77/2.99
Bière (2015)[12]	3,972	1,967/2,005 (50/50)	NR	NR	9.5/9.2	4.6/1.9[a]	4.3/1.9[a]	9.3/12.8[a]	NR
Forrest (2016)[33]	3,687	1,708/1,979 (46/54)	86.9/86.1	0.2/0.1	5.9/5.8	9.7/4.9[a]	29.7/21.7[a]	18.6/23.2[a]	3.6/2.1[b]
Al-Lamee (2014)[32]	1,627	756/871 (47/53)	96.6/96.4	0.7/1	5.9/6.8	7.4/4.2[a]	24.2/21.9	16.2/15.3	3.8/3.7
Sherif (2014)[18]	1,432	827/605 (58/42)	NR	1.6/0.7	NR	4.1/2.8	NR	7/4	5/4
Katz (2016)[11]	819	418/ 401 (51/49)	NR	NR	11.5/6.5[a]	11.2/5.5[a]	18.4/10[a]	NR	NR
Gaglia (2016)[23]	755	383/372 (51/49)	NR	NR	8.4/4.3[a]	12.3/8.1	10.1/5.4[a]	7.4/10.2	4/4.1
Humphries (2012)[16]	584	306/278 (52/48)	NR	NR	6.5/11.2[a]	12.4/5.4[a]	21.6/15.8[a]	6.4/4.3	2/1.8
Buja (2013)[13]	659	368/291 (56/44)	99/98	1.1/0.3	9.4/5.4[a]	2.2/1.7	3.5/2.7	16/24[a]	1.9/3.4
Hayashida (2012)[15]	260	131/129 (50/50)	90.8/88.4	3.1/2.3	12.2/17.8	11.5/9.3	6.1/8.5	5.9/7.8	NR

Abbreviation: NR, not reported.
Values are presented as female/male.
[a] $p \leq 0.05$.
[b] p value not reported.

for body surface area. These sex-dependent anatomical differences have several implications on the TAVR procedure itself. First, due to their narrower aortic valve dimensions,[5,11,16–18,23,24] significantly smaller valves are required for implantation in female patients. Hence, more female patients, compared with male patients, received balloon-expandable valves because of their availability in smaller diameters.[3,11,12,18] Most likely related to this unequal distribution of device type, male patients are subject to more conduction abnormalities and thus to greater pacemaker insertion rates than female patients.[5,6,12,13,33] Also, the US nationwide TAVR registry (TVT registry) has reported increased conversion to open surgery in female patients (1.7% vs 1%, $p < 0.001$) due to various causes (ventricular rupture, aortic dissection, annulus rupture)—all associated with smaller anatomical geometry.[3] Second, significantly higher rate of TAVR performed via alternative access and higher rate of vascular complications[3,5–7,16,17,33] are most likely related to the smaller peripheral vascular diameters[5,23,43] that are characterized by sheath to femoral artery ratio > 1.[30,44]

Overall, despite the sex-related procedural aspects and complication profile, long-term prognosis, as shown on different global registries, was consistently favorable in female TAVR patients[5–7,17,40] compared with male patients (►**Table 4**). The largest TVT registry[3] demonstrated higher survival in female patients over a 1-year follow-up. Similar trends were reported by others.[5,12,15,18,40] Moreover, recent results from the German Transcatheter Aortic Valve Interventions Registry have shown that female sex has a protective effect on 5-year mortality rate following TAVR (hazard ratio [HR] = 0.66; 95% confidence interval [CI]: 0.56–0.77).[45] This may be the outcome of several contributing factors. Physiologically, data have shown earlier remodeling and LV hypertrophy regression after SAVR in female patients.[46] These benefits may extend to female patients having TAVR.[47] Another plausible reason may be that, as already shown, female patients generally present with fewer baseline comorbidities, including LV dysfunction, compared with male patients, which may ultimately affect survival. To be noted that in a recently published post hoc analysis, the survival benefit for female patients was only observed in patients with a preprocedural left ventricular ejection fraction (LVEF) < 50%.[48] Furthermore, female patients have an overall longer life expectancy, which irrespectively may influence the overall survival advantage of female patients over male patients. As for vascular complications, it seems that long-term survival is not significantly affected by the increased rate of periprocedural vascular events in female patients. Moreover, the use of new-generation devices compatible with smaller sheaths and the growing expertise of the operators will probably diminish the risk for those complications as well.

All the aforementioned sex-related differences concerning TAVR have led to the establishment of the Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) real-world registry that was the first all-female multinational registry.[49] Interestingly, one of the investigators' novel findings was that remote pregnancy acted as a predictor of 30-day primary safety endpoint. Surely, more data are needed regarding the effect of pregnancies on long-term mortality.

Since the indication for TAVR is expanding to intermediate-risk surgical patients, it is interesting to find out whether sex-related issues still act as major modifiers. Data from the pivotal studies of intermediate-risk TAVR (SURTAVI[50] and PARTNER 2[51]) showed that female patients constitute < 50% of those studies populations, in contrast to the high-risk TAVR studies. Surprisingly, stratified analysis of this intermediate-risk cohort showed similar outcomes in both sexes (Szerlip et al. TCT 2016, Washington DC, presented as a poster,[52]). There are several plausible causes contributing to those findings. As intermediate- versus high-risk female patients are usually younger, they may "lose" their advantage in longevity. Another cause could be the increased availability of larger valve sizes, allowing male patients to progressively present with improved valve performance and better clinical outcome. To be noted that a possible future consideration in intermediate-risk female patients is the development of degenerated valve post-TAVR. The need for

Table 4 Postprocedural long-term outcome

Author	Total number of patients	Female/Male *n* (%)	Mortality at 1 year (F/M, %)
Chandrasekhar (2016)[3]	23,652	11,808/11,844 (50/50)	21.3/24.5[a]
Kodali (2016)[17]	2,559	1,220/1,339 (48/52)	19/25.9[b]
Bière (2015)[12]	3972	1,967/2,005 (50/50)	19.3/23.7[a]
Forrest (2016)[33]	3,687	1,708/1,979 (46/54)	21.3/24.1
Al-Lamee (2014)[32]	1.627	756/871 (47/53)	22.4/21.9
Sherif (2014)[18]	1,432	827/605 (58/42)	17.3/23.6[a]
Katz (2016)[11]	819	418/ 401 (51/49)	2-year mortality: 29.7/25.9
Gaglia (2016)[23]	755	383/372 (51/49)	20.6/21.5
Buja (2013)[13]	659	368/291 (56/44)	16/19

[a] $p \leq 0.05$.
[b] *p* value not reported.

valve-in-valve procedure will surely present a problem for female patients due to their already smaller aortic valve area.

In conclusion, further randomized control studies with long-term follow-up focusing on sex-related differences will allow physicians to improve the management of female patients with severe symptomatic AS and to further identify female subgroups that preferentially benefit from TAVR.

Funding
None.

Conflict of Interest
None.

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