Comparison of Baseline Characteristics and Outcomes in Men Versus Women With Aortic Stenosis Undergoing Transcatheter Aortic Valve Implantation

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Female gender has been linked to increased risk of adverse events after surgical aortic valve replacement; however, the evidence regarding the role of gender differences on clinical outcomes in patients who underwent transcatheter aortic valve implantation (TAVI) is still debated. This retrospective study included 910 consecutive patients with severe, symptomatic aortic stenosis who underwent TAVI in 2 institutions from January 2012 to July 2016. The primary end point was all-cause mortality at 1 year after TAVI in women versus men. Women had a higher incidence of in-hospital vascular complications (7.8% vs 4.1%) and major or life-threatening bleeding (4.0% vs 1.6%) than men. At 1 year, women showed a lower mortality rate than men (7.0% vs 12.7%, adjusted hazard ratio [HR] 0.42, 95% confidence interval [CI] [0.23 to 0.76], p = 0.004). When stratifying by specific subgroups of interest, the survival benefit in women persisted in (1) patients with a Society of Thoracic Surgery risk score ≤ 8 (adjusted HR 0.35, 95% CI [0.14 to 0.88], p = 0.026); (2) patients treated with first-generation devices (adjusted HR 0.46, 95% CI [0.24 to 0.86], p = 0.016); and (3) patients treated with balloon-expandable valves (adjusted HR 0.40, 95% CI [0.19 to 0.86], p = 0.019). In conclusion, in this large patient cohort, women had lower 1-year mortality after TAVI than men, particularly with an STS score ≤ 8, or treated with first-generation and balloon-expandable devices. **(Am J Cardiol 2018;■■:■■–■■)**

Transcatheter aortic valve implantation (TAVI) is the new standard of care for patients with symptomatic aortic stenosis (AS), who are deemed at intermediate or greater risk of surgical aortic valve replacement (SAVR). Female gender has been shown to be associated with increased risk of adverse events after SAVR[1–5]; however, the evidence regarding the role of gender differences on clinical outcomes in patients who underwent TAVI are conflicting.[6–11] Some studies suggest that TAVI is more beneficial in women, yet others report no difference in outcomes or increased adverse events in women.[12–15] A meta-analysis published in 2015 concluded that women have improved late survival after TAVI.[16] This benefit seemed to occur despite higher periprocedural vascular and bleeding complication rates. The exact reasons for a survival benefit in women compared with men after TAVI, especially when women are known to have a higher risk of mortality after SAVR, have yet to be determined. Moreover, the disparity in the results of the published studies might be due to patient selection (inoperable patients vs high-risk patients vs intermediate-risk patients), generation of the device used (early-generation devices vs second-generation devices), and type of device used (balloon-expandable devices vs self-expandable devices). Given the conflicting data in the literature, we sought to perform a comprehensive analysis of gender-based differences in patients having TAVI in our hospital system.

Methods

Data were collected on consecutive patients with severe, symptomatic AS who underwent TAVI at Baylor Heart and Vascular Hospital (Dallas, Texas) (n = 348) and The Heart Hospital Baylor Plano (Plano, Texas) (n = 562) from January 2012 to July 2016. Baseline demographics, echocardiographic and procedural data, discharge therapy, and clinical outcomes were retrospectively collected and analyzed. For the purpose of the current analysis, data from both medical centers were pooled, and a joint database was created. The study was approved by the Baylor Institutional Review Board. In both centers, patient screening was based on echocardiographic and computed tomography scan images, integrated with laboratory work and clinical evaluation by the heart team, which is composed of clinical and interventional cardiologists, heart surgeons, and experts in cardiac imaging. The following definitions were used in accordance with the Valve Academic Research Consortium-2 standardized end point definitions for TAVI consensus document: acute kidney injury; vascular complication; minor, major, and life-threatening bleedings; stroke; re-intervention; permanent pacemaker implantation; new-onset atrial fibrillation; immediate postoperative mortality (within 72 hours of the procedure); 30-day cardiovascular mortality; and all-cause mortality and 1-year all-cause mortality.[17] Cardiovascular mortality at 1 year was not available in all

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patients; therefore, it was not included as an end point. Events were adjudicated at each center during the regular follow-up visit. The primary end point of this study was all-cause mortality at 1 year after TAVI in women versus men. Postoperative echocardiographic measures were recorded as well to assess prosthetic valve function. Continuous variables are summarized as mean ± standard deviation and were compared using Student's *t* test or Mann-Whitney rank-sum test. Categorical variables were compared using chi-square test. Cox regression was used for multivariate analysis. For the prediction of 1-year all-cause mortality (dependent variable), baseline variables of clinical interest and/or satisfaction of the entry criterion of $p < 0.05$ in the univariable analysis were used as explanatory variables (Society of Thoracic Surgery [STS] score, gender, coronary artery disease, previous coronary artery bypass grafting/percutaneous coronary intervention, body surface area, left ventricle ejection fraction at baseline, stroke volume indexed, and presence of pacemaker at baseline). Interaction testing was performed to determine whether the effect of gender was consistent, irrespective of STS score and generation and type of device used, on the primary end point of the study. This test was performed with likelihood ratio tests of the null hypothesis that the interaction coefficient was zero. Survival curves were constructed using Cox regression analysis. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analyses were performed using SPSS (version 19) statistical software (SPSS, Inc., Chicago, Illinois).[18]

Results

During the study period from January 2012 to July 2016, a total of 910 patients underwent TAVI, including 423 women (46.5%) and 487 men (53.5%). Table 1 displays the baseline characteristics for the study population. Female patients were somewhat older than male patients, with a smaller body surface area, a higher STS score, a higher prevalence of hypertension, a lower prevalence of previous percutaneous or surgical coronary revascularization, a lower prevalence of coronary artery disease, and a lower prevalence of permanent pacemaker. Women had a higher mean left ventricular ejection fraction (LVEF) than men, higher aortic valve gradients but a greater prevalence of moderate or severe aortic valve regurgitation. Moreover, women had a higher mean gradient across mitral valve, along with a higher prevalence of mitral annular calcium.

No differences in the type of device or in the approach used to deliver the device were observed between women and men in our population. However, implanted valve sizes were smaller in women than in men (Table 1).

No significant differences in the use of aspirin, $P2Y_{12}$ inhibitors, and dual antiplatelet therapy were observed across gender, which is consistent with the standard discharge therapy after TAVI in our centers. Consistent with a similar prevalence of atrial fibrillation in women and men, the use of anticoagulants alone or in combination with antiplatelet drugs was not different between genders (Table 1).

Similar to baseline, women had a higher LVEF, higher aortic valve and mitral valve gradients, and larger left atrial volume after TAVI (Table 2). LVEF was persistently and significantly higher in women than in men during follow-up (Figure 1). No differences in the incidence of postoperative aortic and mitral regurgitation were observed between women and men (Table 2).

Women had a higher incidence of in-hospital vascular complications (7.8% vs 4.1%) and major or life-threatening bleeding (4.0% vs 1.6%) than men; however, when these results were adjusted by potential confounders, female gender was no longer associated with these events (Table 3). Body surface area, instead of gender, emerged as a significant predictor of vascular complication (hazard ration [HR] 0.21 for each 1 unit increase, $p = 0.04$, data not shown). Nonetheless, at 1 year, women showed a lower mortality rate than men (7.0% vs 12.7%, adjusted HR 0.42, 95% confidence

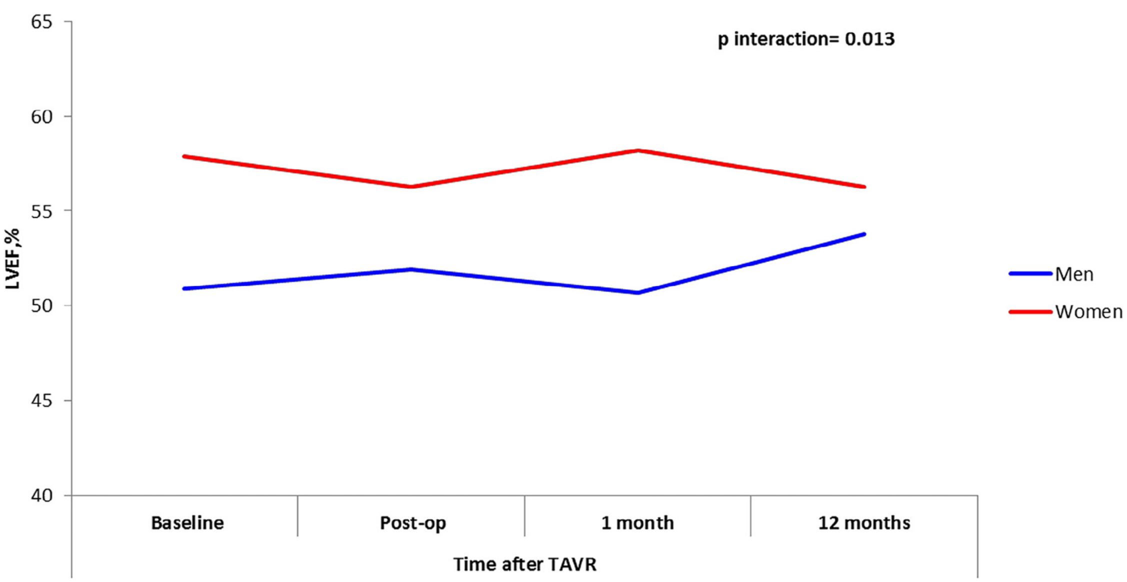

Figure 1. Left ventricular ejection fraction (LVEF) over time. Trends of LVEF during 1-year follow-up in women and men. TAVR = transcatheter aortic valve replacement.

Table 1
Characteristics of the study population

	Women (n = 423)	Men (n = 487)	p
Baseline characteristics			
Age (years)	82.0 ± 7.6	80.9 ± 8.4	0.051
Body Mass Index (Kg/m^2)	28.7 ± 16.2	27.5 ± 5.8	0.115
Body Surface Area (m^2)	1.75 ± 0.22	2.02 ± 0.21	**<0.0001**
Society of Thoracic Surgery Risk Score (%)	7.9 ± 3.7	7.1 ± 4.0	**0.007**
Hypertension	367 (88.0%)	401 (82.9%)	**0.030**
Hyperlipidemia	301 (72.7%)	359 (74.8%)	0.479
Diabetes mellitus	151 (37.7%)	194 (42.0%)	0.195
Chronic kidney disease	188 (45.0%)	229 (47.6%)	0.430
End stage renal disease	10 (2.6%)	16 (3.6%)	0.376
Coronary artery disease	263 (63.1%)	360 (74.7%)	**<0.0001**
Peripheral artery disease	118 (29.4%)	163 (35.3%)	0.067
Chronic obstructive pulmonary disease	85 (21.9%)	98 (21.9%)	0.993
Atrial fibrillation	115 (27.2%)	155 (31.8%)	0.259
Previous coronary bypass/percutaneous coronary intervention	147 (36.8%)	265 (56.9%)	**<0.0001**
Previous cerebrovascular accident	81 (20.7%)	88 (19.8%)	0.749
Permanent pacemaker	69 (16.4%)	103 (21.6%)	0.050
Echocardiographic findings			
Left ventricle ejection fraction <40%	56 (13.3%)	96 (20.0%)	**0.008**
Left ventricle ejection fraction (%)	57.1 ± 12.8	52.3 ± 13.1	**<0.0001**
Stroke Volume Indexed (ml/beat/m^2)	39.5 ± 11.3	36.2 ± 12.3	**<0.0001**
Aortic valve mean gradient (mmHg)	46.4 ± 14.4	43.2 ± 13.2	**0.001**
Aortic valve area (cm^2)	0.65 ± 0.18	0.71 ± 0.19	**<0.0001**
Aortic peak velocity (m/sec)	4.4 ± 0.62	4.3 ± 0.62	**0.001**
Bicuspid aortic valve	44 (10.5%)	61 (12.6%)	0.325
Mitral valve mean gradient (mmHg)	4.0 ± 2.5	2.9 ± 1.8	**<0.0001**
Mitral annular calcium	394 (93.1%)	407 (83.6%)	**<0.0001**
Aortic regurgitation ≥moderate	54 (12.9%)	41 (8.5%)	**0.031**
Mitral regurgitation ≥moderate	74 (17.5%)	88 (18.1%)	0.810
Pulmonary Hypertension	240 (74.8%)	269 (75.6%)	0.811
Left atrial volume (ml)	81.8 ± 33.7	85.3 ± 29.3	0.164
Procedural characteristics			
Type of Valve			0.448
Balloon-expandable	244 (57.7%)	293 (60.2%)	
1st generation	*172 (70.5%)*	*208 (71.0%)*	
new generation	*72 (29.5%)*	*85 (29.0%)*	
Self-expandable	179 (42.3%)	194 (39.8%)	
1st generation	*106 (59.2%)*	*132 (68.0%)*	
new generation	*73 (40.8%)*	*62 (32.0%)*	
Approach			0.539
Trans-femoral	369 (87.2%)	434 (89.1%)	
Trans-apical	32 (7.6%)	37 (7.6%)	
Trans-aortic	17 (4.0%)	13 (2.0%)	
Subclavian	5 (1.2%)	3 (0.6%)	
Valve Size (mm)			
Balloon-expandable			**<0.0001**
20	12 (5.0%)	0 (0%)	
21	1 (0.4%)	0 (0%)	
23	148 (61.7%)	25 (8.7%)	
26	77 (32.0%)	152 (53.1%)	
29	2 (0.8%)	109 (38.1%)	
Self-Expandable			**<0.0001**
23	19 (10.7%)	1 (0.5%)	
25	6 (3.4%)	6 (3.2%)	
26	76 (42.9%)	11 (5.8%)	
27	2 (1.1%)	9 (4.7%)	
29	70 (39.5%)	91 (47.9%)	
31	4 (2.3%)	69 (36.3%)	
34	0 (0%)	3 (1.6%)	
Discharge Medications			
Aspirin	44 (10.4%)	50 (10.3%)	0.947
$P2Y_{12}$ inhibitor	5 (1.2%)	14 (2.9%)	0.075
Aspirin and $P2Y_{12}$ inhibitor	274 (64.7%)	294 (60.3%)	0.323
Warfarin	8 (1.9%)	8 (1.6%)	0.776
Factor Xa inhibitor	-	1 (0.2%)	0.351
Dabigatran	-	-	-
Aspirin and any anticoagulant	59 (13.9%)	78 (16.0%)	0.384
$P2Y_{12}$ inhibitor and any anticoagulant	18 (4.3%)	12 (2.5%)	0.131
Triple Therapy	15 (3.5%)	30 (6.2%)	0.070

Table 2
Postoperative echocardiographic findings

Variable	Women (n = 423)	Men (n = 487)	p
Left ventricle ejection fraction (%)	57.5 ± 10.9	53.6 ± 12.1	**<0.0001**
Aortic valve mean gradient (mmHg)	8.9 ± 4.5	8.1 ± 3.9	**0.003**
Aortic valve area (cm^2)	1.8 ± 0.52	2.0 ± 0.60	**<0.0001**
Aortic peak velocity (m/sec)	2.05 ± 0.52	1.96 ± 0.45	0.087
Mitral valve mean gradient (mmHg)	4.1 ± 2.2	3.2 ± 1.7	**<0.0001**
Aortic regurgitation ≥moderate	69 (16.3%)	77 (15.8%)	0.837
Mitral regurgitation ≥moderate	25 (11.3%)	35 (12.4%)	0.175
Left atrial volume (ml)	81.6 ± 28.3	101.0 ± 85.8	**0.048**

Table 3
Clinical outcomes and relative adjusted hazard ratios

Variable	Women (n = 423)	Men (n = 487)	Adjusted HR, 95% [CI]	p
In-Hospital Outcomes				
Acute Kidney Injury	14 (3.3%)	17 (3.5%)	0.85 [0.24-2.98]	0.913
Vascular complication	33 (7.8%)	20 (4.1%)	1.16 [0.53-2.52]	0.708
Minor bleeding	50 (11.8%)	55 (11.3%)	0.84 [0.47-1.50]	0.553
Major or life-threatening bleeding	17 (4.0%)	8 (1.6%)	2.20 [0.63-1.69]	0.217
Stroke	13 (3.8%)	18 (4.5%)	0.63 [0.20-1.95]	0.421
Valve-in-Valve	4 (1.2%)	12 (3.0%)	0.24 [0.04-1.35]	0.106
Permanent Pacemaker Implantation	72 (17.0%)	95 (19.7%)	0.77 [0.48-1.26]	0.299
New-Onset Atrial Fibrillation	47 (11.1%)	37 (7.6%)	1.48 [0.78-2.82]	0.227
Immediate post-procedural Mortality	4 (0.9%)	3 (0.6%)	0.62 [0.05-1.01]	0.700
30-day Cardiovascular Mortality	7 (1.7%)	13 (2.7%)	0.37 [0.07-1.96]	0.242
30-day All-cause Mortality	12 (2.8%)	14 (2.9%)	0.78 [0.30-2.02]	0.602
1-year All-cause Mortality	24 (7.0%)	51 (12.7%)	**0.42 [0.23-0.76]**	**0.004**

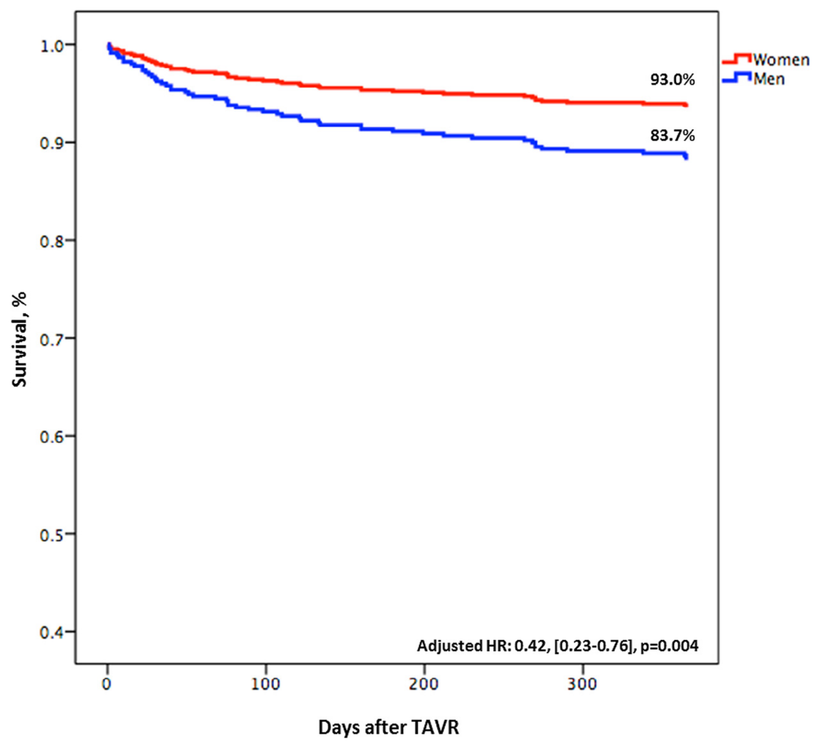

Figure 2. Survival curves after TAVR. One-year survival after TAVR in women versus men. HR = hazard ratio; TAVR = transcatheter aortic valve replacement.

interval [CI] [0.23 to 0.76], p = 0.004). No differences in any of the other clinical outcomes analyzed were observed (Table 3, Figure 2). Interestingly, when the analysis for 1-year all-cause mortality was stratified by specific subgroups of interest, the survival benefit of female gender persisted in (1) patients with an STS score ≤ 8 (low-intermediate) (adjusted HR 0.35, 95% CI [0.14 to 0.88], p = 0.026); (2) patients treated with first-generation devices (adjusted HR 0.46, 95% CI [0.24

Table 4
Subgroup analysis and adjusted hazard ratio for 1-year all-cause mortality

Variable	Women	Men	Adjusted HR, 95% [CI]	p	p for interaction
Society of Thoracic Surgery Risk Score ≤8	8 (4.9%)	26 (11.8%)	0.35, [0.14-0.88]	**0.026**	0.304
Society of Thoracic Surgery Risk Score>8	10 (8.7%)	13 (12.3%)	0.55, [0.18-1.67]	0.289	
First Generation Devices	22 (8.5%)	46 (14.8%)	0.46, [0.24-0.86]	**0.016**	**0.004**
Second Generation Devices	2 (2.4%)	5 (5.5%)	0.11, [0.01-1.16]	0.066	
Balloon-expandable valves	14 (6.6%)	35 (13.8%)	0.40, [0.19-0.86]	**0.019**	0.331
Self-expandable valves	10 (7.6%)	16 (10.8%)	0.46, [0.17-1.22]	0.117	

to 0.86], p = 0.016) although with a significant interaction (p = 0.004); and (3) patients treated with balloon-expandable valves (adjusted HR 0.40, 95% CI [0.19 to 0.86], p = 0.019) (Table 4).

Discussion

In this study on 910 consecutive patients, women showed a significantly lower risk of 1-year all-cause mortality after TAVI than men. This survival benefit was independently associated with female gender in 2 specific subgroups of patients: (1) low- to intermediate-risk patients and (2) patients treated with balloon-expandable valves.

Previous studies have consistently shown that women have higher risk of death after SAVR, and gender is included in the STS risk calculator.[1–5] In contrast, our data indicate that women have a survival advantage after TAVI. Previous studies on this topic have been conflicting. Data coming from large registries and meta-analysis also suggested lower mortality of women after TAVI.[16,19–21] In contrast, other studies did not find any gender-related differences in TAVI outcome.[22,23] In our patients, women experienced a 58% reduction in the risk of all-cause mortality at 1 year after TAVI, even after adjusting for potential confounders such as coronary artery disease, previous revascularization, LVEF, body surface area, the presence of permanent pacemaker at baseline, and stroke volume index, the latter being a strong predictor of outcomes after SAVR or TAVI[24] (Table 3, Figure 2). It has to be acknowledged, however, that there might be a difference in the myocardial structural changes between genders because women are known to undergo greater regression of left ventricular hypertrophy after aortic valve replacement than men. Men with AS have been shown to have more cardiac fibrosis and thus less left ventricular mass regression after aortic valve replacement.[25] However, although left ventricular reverse remodeling occurs both after TAVI and after SAVR, women do not experience better survival after surgery.

Although our findings confirm some previous reports, ours is the first study to identify subgroups of women with a survival advantage: lower STS score (meaning that in the high-risk category, the role of gender is attenuated) and those treated with balloon-expandable valves (Table 4). In our series, most patients were treated with balloon-expandable devices, which could bias the results of this subgroup analysis. All of the previous studies, however, showed a better survival for women at 1-year use of balloon-expandable than self-expandable valves.[16,19,20] Data from the Transcatheter Valve Therapy registry on 23,652 patients reported a better survival in women, and in this study, more than 88% of patients were treated with balloon-expandable devices.[20,26] O'Connor et al[16] published a patient-level meta-analysis confirming these data, and also in this case, 2/3 of the population was treated with balloon-expandable valves. In contrast, 2 studies, by Czarnecki et al[22] and Al-Lamee et al[23] where balloon-expandable and self-expandable devices were more balanced, found no differences in mortality between men and women. In this regard, self-expandable valves are generally implanted at a lower level compared with balloon-expandable valves. It has been reported that the lower implantation depth might, in some cases, interfere with the anterior mitral valve leaflet, leading to mitral stenosis.[27] In our population, women showed higher mitral gradients at baseline and it is possible that the group treated with self-expandable valves experience a worsening in mitral function, which could potentially affect survival in the long term. In this study, we were not able to specifically address this hypothesis, which deserves further investigation.

Vascular complications and bleeding have been reported to be more frequent in women.[19,20] In our patients, when the results were adjusted including potential confounders (mentioned previously), it turned out that the event rate was not different between genders (Table 3). In particular, the only predictor of vascular complication in our study was body surface area, with a progressively decreasing risk for each unit increment in body surface area. Women are generally smaller in body size than men, and this might have driven the results of other studies.

This study has several limitations, mainly due to the retrospective design of the study. Since we included TAVI patients starting in 2012, both old and new generation devices were used. Moreover, no external committee was used to adjudicate events.

In conclusion, the results of our study demonstrate that women have a lower mortality after TAVI, particularly with lower STS risk scores and balloon-expandable valves. Given that woman have a known higher risk of mortality after SAVR, these findings may influence clinical decision-making as to the choice of procedure and implanted valves in women.

Disclosures

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