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Transcatheter Aortic Valve Replacement in Women

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When transcatheter aortic valve replacement (TAVR) emerged as an alternative to surgical aortic valve replacement (SAVR) in high-risk patients with aortic stenosis, differential outcomes in various patient subgroups became a topic of interest. The PARTNER Trial investigators first shed light on this issue with their publication of one-year outcomes, including subgroup analysis that showed improved survival rates in women after TAVR.[1] Subsequently, multiple investigators have sought to define gender disparities in patients undergoing TAVR (Table I).[2-7]

Early studies were predominantly single-center, real-world observational studies with relatively small sample sizes; nonetheless, some similar findings emerged. In terms of preoperative characteristics, female patients tended to have smaller body surface areas, smaller aortic annular diameters, and higher left ventricular ejection fractions (LVEF) (Table II).[2-5] On the other hand, the prevalence of diabetes mellitus, coronary artery disease and prior revascularization, smoking, and peripheral vascular disease was higher in men. Procedural differences were most notable for smaller valve sizes in women (Table III).[2-6] In regard to outcomes, the investigators consistently identified a trend toward higher rates of vascular sequelae and bleeding among women who underwent TAVR (Table IV).[2-6] In the largest of these institutional experiences, Humphries and colleagues[5] reported significantly lower mortality rates in women than in men (median follow-up duration, 302 d; estimated 2-yr survival rate, 38.3% vs 27.9%; P=0.007).

Subsequently, the PARTNER Trial investigators[6] published more robust insights related to the impact of female sex in patients undergoing TAVR versus SAVR. The PARTNER 1A investigators randomized 699 patients to TAVR or SAVR and included female sex as one of several predefined subgroups. Among enrolled patients, men were more likely to have coronary artery disease, peripheral vascular disease, a current or prior smoking history, diabetes mellitus, and chronic kidney disease. Women, however, were older and more likely to have a lower Society of Thoracic Surgeons score, a smaller body surface area, and chronic obstructive pulmonary disease. Men had higher cardiac output and greater left ventricular mass, whereas women had higher LVEF, higher mean gradients, and smaller aortic annular diameters. Women more

TABLE I. Studies of Transcatheter Aortic Valve Replacement in Women

Reference	Study Design	Site	No. of Patients	Women (%)	Follow-Up Duration
Buchanan GL, et al.[2] (2011)	Observational	Single center (Italy)	305	47.5	30 d
Stangl V, et al.[3] (2012)	Observational	Single center (Germany)	100	58	90 d
Hayashida K, et al.[4] (2012)	Observational	Single center (France)	260	50.4	217 d
Humphries KH, et al.[5] (2012)	Observational	Dual centers (Canada)	641	51.3	302 d; survival est. 2 yr
Williams M, et al.[6] (2014)	Retrospective analysis of RCT	Multicenter	699	42.9	2 yr
Chandrasekhar J, et al.[7] (2016)	Observational	Multicenter registry	11,808	49.9	1 yr

est. = estimate; RCT = randomized controlled trial

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TABLE II. Demographic Characteristics in the TAVR Studies

	Age (yr)*		**Body Surface Area** (m^2)		**STS Score** (%)		**Comorbidities** (P <0.05)		**Anatomic Features** (P <0.05)	
Reference	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Buchanan GL, et al.[2] (2011)	78.8	80.1	1.84	1.7	8.2	9.1	CKD, COPD, DM, and prior MI or CABG	NYHA III/IV	—	Smaller annular diameter
Stangl V, et al.[3] (2012)	77	80	2	1.7	22.1**	18.4**	CAD, DM, prior MI, and revascularization	COPD	Larger CFA diameter and higher cardiac output	Smaller AV area, higher LVEF, and smaller annular diameter
Hayashida K, et al.[4] (2012)	82.4	83.8	1.85	1.65	26.2**	22.3**	CAD, DM, hyperlipidemia, peripheral vascular disease, and prior MI or revascularization		Smaller indexed AV area and pulmonary hypertension	Higher mean gradient, higher LVEF, and smaller annular diameter
Humphries KH, et al.[5] (2012)	82	83	1.9	1.6	7.5	7.5	CAD, COPD, prior MI or revascularization, and smoking	Frailty, lower eGFR, and porcelain aorta	—	Smaller AV area, higher LVEF, higher mean gradient, MR grade 3/4, and AR grade 3/4
Williams M, et al.[6] (2014)	82.9	84.5	1.93	1.69	11.62	11.93	CAD, CKD, DM, prior MI or revascularization, and smoking	COPD	Higher cardiac output and larger LV mass	Higher mean gradient, smaller annular diameter, higher LVEF, and pulmonary hypertension
Chandrasekhar J, et al.[7] (2016)	81.67	82.28	1.9	1.7	8	9	Atrial fibrillation, bilateral carotid stenosis, CAD with prior PCI or CABG, COPD, DM, peripheral artery disease, prior AV procedure, prior stroke, and smoking	Frailty, lower eGFR, NYHA III/IV, and porcelain aorta	Severe aortic incompetence (3.1%) and bicuspid aortic stenosis (2%)	Higher LVEF, moderate-to-severe MR, and moderate-to-severe TR

AR = aortic regurgitation; AV = aortic valve; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CFA = common femoral artery; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association functional class; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation

*P <0.05 in all studies, except for that of Chandrasekhar J, et al.[7]
**EuroSCORE

Values are presented as mean unless otherwise stated.

TABLE III. Procedural Details in the TAVR Studies

Reference	Balloon-Expandable Device		Self-Expanding Device		Femoral Access		Use of Smaller Valves*	
	Men	Women	Men	Women	Men	Women	Men	Women
Buchanan GL, et al.[2] (2011)	81.1	66.4	18.9	33.6	81.1	82.2	NS	NS
Stangl V, et al.[3] (2012)	21	3	79	97	NS	NS	10	67
Hayashida K, et al.[4] (2012)	79.1	91.6	21.9	8.4	61.3	68.7	26.3 (mean)	23.9 (mean)
Humphries KH, et al.[5] (2012)	97% Edwards SAPIEN (NS)				62	48	11.2	30.5
Williams M, et al.[6] (2014)	100% Edwards SAPIEN				60.7	39.3	26.8	78
Chandrasekhar J, et al.[7] (2016)	85.97	88.48	13.94	11.43	65	55	11.58	65.25

NS = not specified; TAVR = transcatheter aortic valve replacement

*For example, 23-mm Edwards SAPIEN or 26-mm Medtronic CoreValve

Values are stated as percentage.

TABLE IV. Outcomes in the TAVR Studies

Reference	Vascular Sequelae		Bleeding (30 d)		Aortic Incompetence		CVA		Death (30 d)		Death (Follow-Up)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Buchanan GL, et al.[2] (2011)	11.9	19.9	22.6	29.5	4.4	4.1	1.3	0.7	3.8	5.6	—	—
Stangl V, et al.[3] (2012)	7.1	8.6	4.8	12.1	0	0	2	2	2.4	3.4	7	9
Hayashida K, et al.[4] (2012)	9.3	11.5	8.5	6.1	5.4	3.1	2.3	0.8	17.8	12.2	**36.4**	**24.4**
Humphries KH, et al.[5] (2012)	**5.4**	**12.4**	15.8	21.6	3.1	1.6	1.8	2	**11.2**	**6.5**	**38.3**	**27.9**
Williams M, et al.[6] (2014)	13.9	23.8	9.5	10.9	10.3	3	4.5	6.8	6	6.8	**37.7**	**28.2**
Chandrasekhar J, et al.[7] (2016)	**4.39**	**8.27**	5.96	8.01	3.4	3.1	3.4	4.6	4.28	5.6	**24.5**	**21.3**

CVA = cerebrovascular accident; NS = not specified; TAVR = transcatheter aortic valve replacement

Values are stated as percentage. Bold font indicates statistical significance (P <0.05).

frequently underwent nontransfemoral access and were given smaller prosthetic valves.

In terms of outcomes, women had a higher incidence of vascular sequelae and cerebrovascular accidents (CVA). The 30-day mortality rate was not significantly different between men and women. At 2 years, however, mortality rates improved among women. Of note, men assigned to SAVR had survival rates similar to those of men who underwent TAVR, and better survival rates than women who underwent SAVR. Meanwhile, women who underwent TAVR (in particular, via the transfemoral approach) had a survival benefit in comparison with those who had surgery. Although the superior long-term survival rate in women might be related to fewer baseline comorbidities, other findings are less clear. For instance, the higher incidence of CVA in women despite the lower incidence of baseline cerebrovascular disease in this group is not intuitively explainable.

Despite their important findings, the aforementioned studies are limited by confounding baseline demographic and anatomic differences. Chandrasekhar and colleagues[7] analyzed the Transcatheter Valve Therapy registry, which includes all patients who have undergone commercial TAVR in the United States. The authors reviewed data on 11,808 patients, with outcomes adjusted for various potential confounders. Table II shows the baseline demographic, clinical, and anatomic differences among men and women.[7] Women were more likely to undergo nontransfemoral access during TAVR and to need smaller valves. In-hospital vascular sequelae were significantly higher in women, who also showed a trend toward more bleeding events. Although the 30-day mortality rate was no different among men and women, women had higher survival rates at one year.

The body of evidence illustrates that men and women undergoing TAVR have unique demographic, comorbid, and anatomic characteristics that influence their procedural and long-term outcomes. The finding by the PARTNER Trial investigators that survival rates after TAVR were superior in women, despite an increased incidence of vascular sequelae and CVA, is now supported by large-registry data with statistical correction for potentially confounding factors. It is important to note that the cited studies included patients who were treated with predominantly early-generation TAVR devices. More recent advances with smaller-profile devices are likely to lower the incidence of vascular sequelae and the need for nontransfemoral access. These advances can be expected to expand the already evident advantage of TAVR over SAVR in women.

Further studies are needed to evaluate whether sex differences remain relevant in the current state of TAVR, which includes smaller-profile devices, patients typically at lower risk, broader valve indications, and an emphasis on minimally invasive approaches. In addition, the development of a preoperative risk calculator unique to female patients might lead to more accurate outcome predictions in this group.

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