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Sex-Specific Outcomes of Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve

Insights From the PARTNER II S3 High-Risk and Intermediate-Risk Cohorts

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ABSTRACT

OBJECTIVES The purpose of this study was to identify sex-specific outcomes of intermediate risk patients undergoing transcatheter aortic valve replacement with the SAPIEN 3 valve.

BACKGROUND A survival difference has been observed in women as compared with men in inoperable and high-risk patients receiving early-generation balloon-expandable valves for transcatheter aortic valve replacement (TAVR). Whether a sex-specific outcome difference persists with newer-generation valves and in lower-risk patients is unknown.

METHODS The PARTNER (Placement of Aortic Transcatheter Valves) II S3 trial included high-risk (HR) (Society of Thoracic Surgeons risk score >8% or heart team determination) and intermediate-risk (IR) (Society of Thoracic Surgeons risk score 4% to 8% or heart team determination) patients with severe symptomatic aortic stenosis who were treated with TAVR with the SAPIEN 3 valve. Patient characteristics and clinical outcomes at 30 days and 1 year were compared by sex.

RESULTS Between October 2013 and December 2014, 1,661 patients were enrolled: 583 were HR (338 men, 245 women) and 1,078 were IR (666 men, 412 women). In both cohorts, women were more likely than men to be frail (22% vs. 13%; $p < 0.001$), but less likely to have comorbid conditions of renal insufficiency, coronary artery disease, atrial fibrillation, or chronic obstructive pulmonary disease. Women were more likely to receive ≤23-mm valves (74.1% vs. 11.1%; $p < 0.001$) and were less likely to receive 29-mm valves (1.4% vs. 35.1%; $p < 0.001$). In the combined cohorts, there was no difference in mortality for women compared with men at 30 days (2.0% vs. 1.2%; $p = 0.20$) or 1 year (9.3% vs. 10.2%; $p = 0.59$). There were no differences in disabling stroke or any stroke at 30 days or 1 year; however, women had an increased rate of minor stroke at 30 days (2.1% vs. 0.7%; $p = 0.01$). Female sex was associated with increased major vascular complications (7.9% vs. 4.4%; $p = 0.003$), but not with moderate or severe paravalvular regurgitation. Notably, similar outcomes regarding sex-specific outcomes were obtained within stratified analyses of the HR and IR cohorts.

CONCLUSIONS The study found no apparent sex-specific differences in survival or stroke in this trial of TAVR. This may reflect the changing demographic of patients enrolled, use of newer-generation valves with more sizes available, and more accurate valve sizing techniques. (J Am Coll Cardiol Intv 2018;11:13–20) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

MDCT = multidetector computed tomography

PVL = paravalvular leak

S3 = SAPIEN 3

S3HR = SAPIEN 3 valve in high risk or inoperable

S3i = SAPIEN 3 valve in intermediate risk

SAVR = surgical aortic valve replacement

STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality

TA = transapical

TAo = transaortic

TAVR = transcatheter aortic valve replacement

TF = transfemoral

Over the previous decade, transcatheter aortic valve replacement (TAVR) has become the therapy of choice for patients with severe aortic stenosis who are not candidates for surgery (1,2) or who are at high risk for morbidity or mortality due to surgery (3,4). More recently, TAVR with early-generation balloon-expandable valves has been shown to have comparable outcomes to surgical aortic valve replacement (SAVR) for patients at intermediate risk (5). When using third-generation balloon-expandable valves, TAVR may have superior results as compared with SAVR in intermediate-risk patients (6).

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Female sex has been demonstrated as an independent risk factor for adverse outcomes after SAVR (7–11). A comprehensive analysis of sex-specific differences among inoperable and high-risk patients undergoing TAVR within the clinical trial structure of the PARTNER (Placement of Aortic Transcatheter Valves) trial, which used the balloon-expandable SAPIEN transcatheter valve (Edwards Lifesciences, Irvine, California), clearly demonstrated that women had lower mortality than men did at 1 year following TAVR despite a higher incidence of vascular and bleeding complications (12). Similarly, an analysis of intermediate-risk patients randomized to TAVR in the PARTNER IIA trial, which used the second-generation SAPIEN XT transcatheter valve (Edwards Lifesciences), demonstrated a trend toward lower 2-year mortality in women as compared with men despite a higher incidence of vascular complications in women (13). Recently, an analysis of the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) registry confirmed a mortality difference for women undergoing TAVR in a large, "real-world" cohort of patients with an earlier-generation SAPIEN valve (14). The mortality difference in these studies was felt in part to be due to the comorbid differences between women and men.

As compared with the SAPIEN and SAPIEN XT valves, the newer-generation SAPIEN 3 (S3) (Edwards Lifesciences) valve has a reduced profile and an additional outer cuff to enhance paravalvular sealing (15). The PARTNER II S3 observational study was implemented to evaluate the safety and efficacy of the S3 valve in both intermediate-risk (S3i) and high-risk or inoperable (S3HR) patients (6). We sought to perform a comprehensive analysis of sex-specific differences in patients undergoing TAVR in the S3i and S3HR cohorts to determine whether the difference associated with female sex after TAVR using earlier generation valves persists. We report the baseline demographic characteristics and core laboratory-assessed echocardiographic parameters of women and men treated with S3 TAVR, as well as adjudicated 30-day and 1-year outcomes stratified by sex.

METHODS

STUDY DESIGN AND PATIENTS. The PARTNER II S3 trial incorporated 2 parallel prospective, multicenter, active treatment cohorts of patients with

consultant for Edwards Lifesciences. Dr. Williams has served as a consultant for and received research funding from Edwards Lifesciences. Dr. Hahn has had echocardiographic core lab contracts with Edwards Lifesciences (no direct compensation). Dr. Webb has served as a consultant for Edwards Lifesciences; and a member of the PARTNER trial executive committee (no direct compensation). Dr. Svensson owns equity in Cardiosolution and Valvexchange as well as intellectual property with Postthorax; has served as a member of the PARTNER trial executive committee (no direct compensation); and has served as the chairman of the PARTNER trial publications office. Dr. Kirtane has received institutional research grant support from Boston Scientific, Abbott Vascular, Medtronic, Abiomed, Eli Lilly, CathWorks, Philips, Siemens, and Spectranetics. Dr. Douglas has received institutional grant support from Edwards Lifesciences and has had echocardiographic core lab contracts with Edwards Lifesciences (no direct compensation). Dr. Cohen has received research grant support from Edwards Lifesciences, Medtronic, Abbott Vascular, and Boston Scientific; and has served as a consultant for Edwards Lifesciences and Medtronic. Ms. Alu has served as a consultant for Claret Medical. Dr. Tuzcu has served as a member of the PARTNER Trial Executive Committee (no direct compensation). Dr. Makkar has received grants from Edwards Lifesciences and has served as a consultant for Abbott Vascular, Cordis, and Medtronic. Dr. Herrmann has received institutional grant support from Edwards Lifesciences, Medtronic, St. Jude Medical, Boston Scientific, Bayer, and Abbott Vascular; and has served as a consultant for Edwards Lifesciences. Dr. Babaliaros has served as a consultant for Abbott Vascular and Edwards Lifesciences. Dr. Thourani has served as a consultant for Edwards Lifesciences. Dr. Leon has served as a member of the PARTNER trial executive committee (no direct compensation). Dr. Kodali has served as a consultant and on the steering committee for Edwards Lifesciences; has served on the scientific advisory board for Thubrikar Aortic Valve, Inc., and Dura Biotech; and owns equity in Thubrikar Aortic Valve, Inc. Dr. Mack has served as a member of the PARTNER trial executive committee (no direct compensation) and as the co-principal investigator of the Edwards Lifesciences PARTNER III trial. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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symptomatic (New York Heart Association functional class ≥II), severe aortic stenosis. Severe aortic stenosis was determined by echocardiographic criteria as follows: valve area <0.8 cm^2 or valve area index <0.5 cm^2/m^2 and mean gradient >40 mm Hg or peak velocity >4 m/s, as previously detailed (16). The S3HR cohort comprised patients who were considered to be inoperable or high-risk candidates for surgery, as defined by a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of at least 8% or by the determination of a multidisciplinary heart team that included at least 1 cardiac surgeon and 1 interventional cardiologist. The S3i cohort comprised patients who were considered to be intermediate-risk candidates for surgery, as defined by STS-PROM score between 4% and 8% or by determination of a multidisciplinary heart team. The heart team assessment could deem patients at increased risk as compared with their STS-PROM score based on risk factors not accounted for by the predictive score model (e.g., liver disease, frailty, pulmonary hypertension). All patients underwent a comprehensive frailty assessment that included 5-m walk time, grip strength, Katz activities of daily living, and serum albumin. Patients who met at least 3 of 4 criteria were deemed frail. Three-dimensional imaging of the aortic annulus (via multidetector computed tomography [MDCT] or 3-dimensional transesophageal echocardiography) was recommended before treatment for high-risk patients. All intermediate-risk patients were evaluated by a mandatory MDCT scan that was analyzed by the study core laboratory. All S3HR and S3i candidates were presented on a conference call during which a screening committee reviewed the imaging and clinical data and ultimately approved patients before enrollment. An institutional review board at each study site approved the study, and all subjects provided written informed consent before enrollment.

Key exclusion criteria for both cohorts included bicuspid aortic valve, severe aortic regurgitation, left ventricular ejection fraction <20%, severe renal insufficiency, stroke or transient ischemic attack within 6 months, myocardial infarction within 1 month, and estimated life expectancy of <2 years. Patients with complex coronary artery disease (CAD) (left main disease or multivessel disease with SYNTAX score ≥32) were also excluded. Patients with noncomplex, untreated CAD were enrolled if a treatment plan (medical therapy vs. revascularization) was agreed on before enrollment.

Patients in both cohorts underwent TAVR with the S3 valve through optimal valve delivery access (transfemoral [TF] vs. transapical [TA] or transaortic [TAo]) as determined by the pre-procedural peripheral vascular assessment of the heart team. The S3 valve is delivered through expandable 14-F (20-, 23-, and 26-mm S3) or 16-F (29-mm S3) TF delivery sheaths or via direct routes for TA and TAo access. Post-operative dual-antiplatelet therapy with aspirin and clopidogrel was recommended for 6 months, at heart team discretion. Warfarin was also recommended for patients with atrial fibrillation in tolerant patients. Patients were consecutively enrolled in the respective cohorts between October 2013 and December 2014.

Clinical assessments were performed at baseline, 30 days, and 1 year following TAVR. This clinical assessment also included a formal examination by a board-certified neurologist. Serial echocardiographic studies were performed immediately following implantation (intraprocedural), within 24 h of hospital discharge, at 30-day follow-up, and at 1-year follow-up. A consortium of core imaging laboratories analyzed all echocardiography data independently. Clinical events were independently adjudicated by the clinical events committee. A data safety and monitoring board was in place to review all adverse events.

ENDPOINTS. The 30-day and 1-year frequencies of all-cause mortality, cardiovascular mortality, rehospitalization, all stroke, disabling stroke, major vascular complications, major bleeding, myocardial infarction, acute kidney injury, and need for permanent pacemaker were documented according to Valve Academic Research Consortium-2 endpoint definitions (17). Pre-procedural echocardiography exams were compared with 30-day and 1-year follow-up studies with particular focus on aortic valve hemodynamics and paravalvular leak (PVL).

STATISTICAL ANALYSIS. An as-treated analysis was performed that included all patients proceeding to the operating room for TAVR in the S3HR and S3i cohorts. Patients were stratified on the basis of sex. Categorical variables were compared by chi-square or Fisher exact test, as appropriate. Continuous variables are presented as mean ± SD and compared using Student *t* test. Time-to-event variables for clinical outcomes are presented as Kaplan-Meier estimate (number of events) and compared using the log-rank test. Multivariable Cox proportional hazard models were used to assess the adjusted association between sex and all-cause mortality. The model included the same following covariates used in the previous PARTNER trials: diabetes mellitus, presence of oxygen-dependent chronic obstructive pulmonary disease, STS-PROM score, major arrhythmia, renal disease, and liver disease, as well as frailty. A 2-sided

TABLE 1 Study Population

	Women (n = 657)		Men (n = 1,004)		
	TF	TA/TAo	TF	TA/TAo	All
S3HR	214	31	277	61	583
S3i	371	41	581	85	1,078
Total	585	72	858	146	1,661

S3HR = SAPIEN 3 valve in high risk or inoperable; S3i = SAPIEN 3 valve in intermediate risk; TA = transapical; TAo = transaortic; TF = transfemoral.

significance level of 0.05 was used to indicate statistical significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

CLINICAL TRIAL REGISTRATION. The PARTNER II S3 trial was registered at ClinicalTrials.gov on March 7, 2011 (NCT01314313), as a nested observational study within the PARTNER II randomized trial.

ROLE OF THE FUNDING SOURCE. The trial was funded by the study sponsor (Edwards Lifesciences). The sponsor and members of the executive steering committee collaboratively developed the study protocol. The sponsor funded the study, participated in site selection and management, and monitored data. The coprincipal investigators had unrestricted access to the data after the database was locked. M.S. had access to all of the data used in this study, and she with her coauthors prepared all drafts of the manuscript and made the decision to submit the manuscript. Independent statisticians at the Cardiovascular Research Foundation performed all data analyses. The sponsor played no role in data analysis, writing of the manuscript, or decision to publish.

All patients received informed consent at their entry into the PARTNER trial and the study was approved by each site's investigational review board.

TABLE 2 Baseline Characteristics of Combined S3HR and S3i Cohorts

	Women (n = 657)	Men (n = 1,004)	p Value
Age, yrs	82.5 ± 7.2	82.0 ± 7.1	0.20
STS-PROM score, %	6.8 ± 3.0	6.3 ± 2.8	0.003
Mean EuroSCORE	5.5 ± 4.7	7.2 ± 6.3	<0.0001
Body surface area, m^2	1.8 ± 0.2	2.0 ± 0.2	<0.0001
Frail, %	145 (22.1)	127 (12.6)	<0.0001
Diabetes type II, %	205 (31.2)	353 (35.2)	0.10
Hyperlipidemia, %	498 (75.8)	834 (83.1)	0.0003
Hypertension, %	609 (92.7)	935 (93.1)	0.74
Smoking, %	238 (36.2)	621 (61.9)	<0.0001
O_2 dependent chronic obstructive pulmonary disease, %	57 (8.7)	57 (6.5)	0.003
Severe pulmonary hypertension, %	18 (2.7)	37 (3.7)	0.29
Renal insufficiency, %*	43 (6.5)	109 (10.9)	0.003
Coronary artery disease, %	387 (58.9)	808 (80.5)	<0.0001
Prior myocardial infarction, %	69 (10.5)	220 (21.9)	<0.0001
Prior percutaneous coronary intervention, %	162 (24.7)	383 (38.0)	<0.0001
Prior coronary artery bypass grafting, %	65 (9.9)	429 (42.7)	<0.0001
Cerebrovascular disease, %	108 (16.4)	185 (18.4)	0.30
Peripheral vascular disease, %	141 (21.5)	368 (36.7)	<0.0001
Cardiomyopathy, %	35 (5.3)	108 (10.8)	0.0001
Permanent pacemaker, %	73 (11.1)	165 (16.4)	0.002
Mean echocardiographic findings			
Aortic valve area, cm^2	0.64 ± 0.16	0.72 ± 0.17	<0.0001
Aortic valve index, cm^2/m^2	0.37 ± 0.09	0.36 ± 0.08	0.12
Aortic valve mean gradient, mm Hg	47.8 ± 13.8	44.6 ± 12.8	<0.0001
Annular dimension, cm	2.1 ± 0.2	2.3 ± 0.2	<0.0001
Left ventricular ejection fraction	0.62 ± 0.12	0.55 ± 0.14	<0.0001
Stroke volume (Teichholz), ml/beat	60.7 ± 17.2	66.5 ± 19.0	<0.0001

Values are mean ± SD or n (%). *Creatinine level ≥2.0 mg/dl.

EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; other abbreviations as in Table 1.

RESULTS

BASELINE CHARACTERISTICS. A total of 1,661 patients received S3 TAVR and were analyzed on the basis of their sex (Table 1). The S3HR cohort included 583 patients (n = 338 [58%] men, n = 245 [42%] women). The S3i cohort included 1,078 patients (n = 666 [62%] men, n = 412 [38%] women).

The baseline demographics and comorbidities varied between women and men, as summarized in Table 2. Women were less likely to have a positive smoking history, renal insufficiency, or chronic obstructive pulmonary disease. Women were less likely to have CAD, prior percutaneous coronary intervention or coronary artery bypass, prior myocardial infarction, and peripheral vascular disease. They also were less likely to have prior pacemaker and atrial fibrillation. However, women were significantly more likely to be frail and had a slightly higher mean STS-PROM score (6.8% vs. 6.3%; p < 0.0001), which may be due to the inclusion of female sex as a covariate when calculating the STS-PROM score.

Baseline echocardiographic characteristics also differed by sex (Table 2). Women tended to have smaller aortic valve areas (0.64 cm^2 vs. 0.72 cm^2), but there was no difference in indexed valve areas (0.37 cm^2/m^2 vs. 0.36 cm^2/m^2). Annular dimensions were smaller in women (2.1 cm vs. 2.3 cm). Women had higher mean left ventricular ejection fraction (62% vs. 55%) but lower stroke volumes (60.7 ml/beat vs. 66.5 ml/beat).

PROCEDURAL CHARACTERISTICS AND OUTCOMES. The TF approach was used more frequently in women (89.0% TF vs. 11.0% TA/TAo) than in men (85.5% TF vs. 14.5% TA/TAo). Women were more likely to

receive 20-mm (7.9%) or 23-mm (66.2%) S3 valves, and men were more likely to receive 26-mm (53.8%) or 29-mm (35.1%) valves (Table 3).

Women were more likely to experience in-hospital major vascular complications (7.2% vs. 4.2%; p = 0.009). There were no differences in bleeding events or acute kidney injury between sexes. At 30 days and 1 year, there were no differences in rates of mild (30 days: 43.5% vs. 39.9%; p = 0.16; 1 year: 37% vs. 36%; p = 0.72) or moderate-severe (30 days: 4.2% vs. 3.0%; p = 0.25; 1 year: 2.2% vs. 1.3%; p = 0.22) PVL among women and men (Table 3). Following TAVR, women had smaller valve areas (1.49 cm^2 vs. 1.81 cm^2; p < 0.0001), and higher mean gradients (12.89 mm Hg vs. 10.43 mm Hg; p < 0.0001). After indexing for body size, the difference in valve area still persisted (0.85 cm^2/m^2 vs. 0.91 cm^2/m^2; p < 0.0001).

CLINICAL OUTCOMES AT 30 DAYS AND 1 YEAR. In unadjusted analyses, there were no differences among women and men in all-cause mortality (2.0% vs. 1.2%; p = 0.20) or the combined endpoint of death, disabling stroke, or rehospitalization (8.5% vs. 7.1%; p = 0.27) at 30 days (Table 3). There was no difference at 30 days and 1 year in all stroke in women versus men (30 days: 3.1% vs. 1.7%; p = 0.07; 1 year: 5.2% vs. 4.0%, p = 0.26). There was also no difference in disabling stroke at 30 days and 1 year (30 days: 0.9 vs. 1.0, p = 0.87; 1 year: 2.4% vs. 2.3%; p = 0.9). There were also no differences in myocardial infarction, placement of permanent pacemaker, acute kidney injury (combined and stratified by severity), or moderate-severe PVL.

At 1 year, there were no differences among women and men in all-cause mortality (9.4% vs. 10.4%; p = 0.56) or the combined endpoint of death, disabling stroke, or rehospitalization (22.4% vs. 20.9%; p = 0.40) (Table 3, Figure 1). No differences in isolated disabling stroke, minor stroke, or rehospitalization were present.

Due to nonproportional hazards in 1-year all-cause mortality between women and men (p = 0.02), we performed multivariable analysis at 180 days and then an additional landmark analysis from 180 days to 1 year. On multivariate analysis, female sex was not independently associated with all-cause mortality at 180 days (hazard ratio: 1.16; 95% confidence interval: 0.77 to 1.75; p = 0.48) or between 180 days and 1 year (hazard ratio: 0.61; 95% confidence interval: 0.35 to 1.06; p = 0.08), after adjustment for baseline comorbidities including diabetes mellitus, presence of oxygen-dependent chronic obstructive pulmonary disease, major arrhythmia, renal disease, liver disease, STS-PROM score, and frailty. Notably, similar sex-specific results were obtained following substratification within both S3HR and S3i cohorts at 30-days and 1 year.

TABLE 3 Procedural, 30-Day, and 1-Year Outcomes for the Combined S3HR and S3i Cohorts

	Women (n = 657)	Men (n = 1,004)	Comparison	p Value
Procedural outcomes (in hospital)*				
Approach				
Transfemoral, %	585 (89.0)	858 (85.5)	3.6 (0.3 to 6.8)	0.03
Transapical, %	38 (5.8)	100 (10.0)	−4.2 (−6.7 to −1.6)	0.003
Transaortic, %	34 (5.2)	46 (4.6)	0.6 (−1.5 to 2.7)	0.58
Valve size				
20 mm, %	52 (7.9)	1 (0.1)	7.8 (5.7 to 9.9)	<0.001
23 mm, %	435 (66.2)	110 (11.0)	55.2 (51.1 to 59.3)	<0.001
26 mm, %	161 (24.5)	537 (53.8)	−29.2 (−33.8 to −24.7)	<0.001
29 mm, %	9 (1.4)	351 (35.1)	−33.8 (−36.9 to −30.7)	<0.001
Major vascular complication, %	47 (7.2)	42 (4.2)	3.0 (0.6 to 5.3)	0.009
Major or disabling bleeding event, %	110 (16.7)	147 (14.6)	2.1 (−1.5 to 5.7)	0.25
Acute kidney injury, %	45 (6.8)	61 (6.1)	0.8 (−1.7 to 3.2)	0.53
30-day outcomes†				
All-cause mortality, %	13 (2.0)	12 (1.2)	1.67 (0.76 to 3.65)	0.20
Cardiac mortality, %	9 (1.4)	9 (0.9)	1.54 (0.61 to 3.87)	0.36
Rehospitalization, %	43 (6.6)	52 (5.2)	1.28 (0.86 to 1.92)	0.23
Disabling stroke, %	6 (0.9)	10 (1.0)	0.92 (0.33 to 2.53)	0.87
Combined endpoint, %‡	56 (8.5)	71 (7.1)	1.22 (0.86 to 1.73)	0.27
Myocardial infarction, %	4 (0.6)	2 (0.2)	3.07 (0.56 to 16.75)	0.17
Permanent pacemaker, %	63 (9.7)	123 (12.3)	0.78 (0.57 to 1.05)	0.10
Moderate/severe paravalvular leak, %	25 (4.2)	28 (3.0)	1.36 (0.80 to 2.31)	0.25
1-year outcomes†				
All-cause mortality, %	61 (9.4)	103 (10.4)	§	0.56
Cardiac mortality, %	43 (6.7)	53 (5.3)	1.27 (0.85 to 1.90)	0.24
Rehospitalization, %	98 (15.5)	131 (13.5)	1.17 (0.90 to 1.52)	0.25
Disabling stroke, %	15 (2.4)	22 (2.3)	1.04 (0.54 to 2.01)	0.90
Combined endpoint, %‡	146 (22.4)	208 (20.9)	1.09 (0.89 to 1.35)	0.40
Moderate/severe paravalvular leak, %	11 (2.2)	10 (1.3)	1.70 (0.73 to 3.97)	0.22

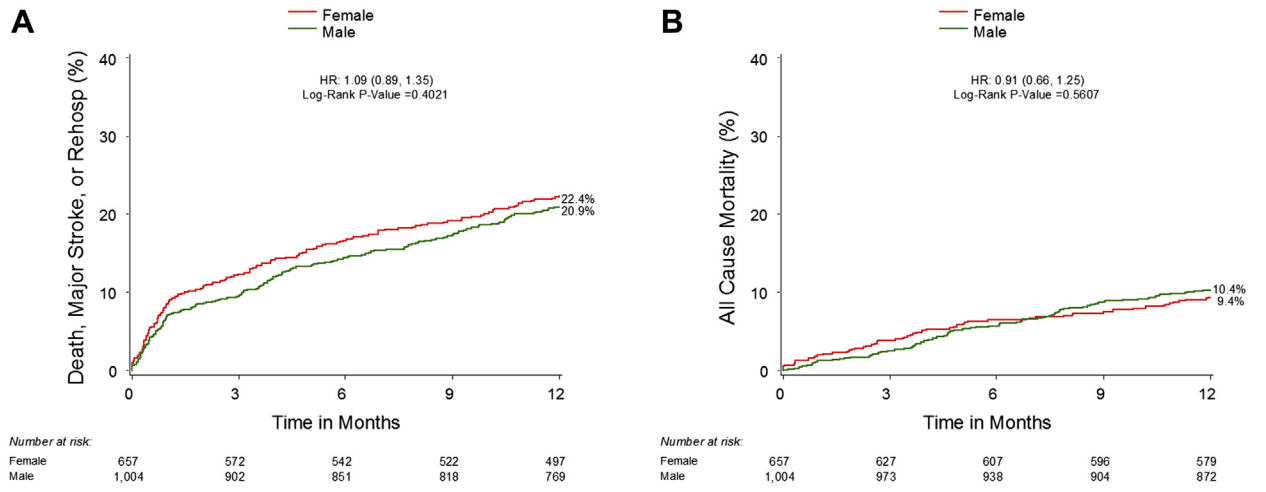
*Values are n (%). †Values are event (Kaplan-Meier %) or hazard ratio (95% CI). ‡Combined 30-day and 1-year endpoint includes all-cause mortality, rehospitalization, or disabling stroke. §Hazard ratio was not applicable due to violation of the proportional hazards assumption (p = 0.02).

Abbreviations as in Table 1.

DISCUSSION

Female sex is well established as an independent risk factor for mortality and major morbidity following SAVR (7–11), but has been associated with a relative improvement in mortality following TAVR with early generation balloon-expandable valves including the SAPIEN and SAPIEN XT (12–14). This current study represents the first analysis of sex-specific outcomes in a lower-risk population (STS-PROM score: 6.8% women vs. 6.3% men; p = 0.003) of patients with

FIGURE 1 S3 Combined Endpoint and All-Cause Mortality at 1 Year: Female Versus Male



Time-to-event curves for the **(A)** combined endpoint of death, disabling stroke, or rehospitalization and **(B)** all-cause mortality for the combined SAPIEN 3 with high risk (S3HR) and SAPIEN 3 with intermediate risk (S3i) cohorts. HR = high risk; rehosp = rehospitalization.

severe aortic stenosis who underwent TAVR with the newer-generation S3 valve. This analysis includes a total of 1,661 patients (40% women, 60% men) enrolled in the nonrandomized PARTNER II S3 trial prospective, active treatment cohorts. The main finding of this study is that women and men undergoing TAVR with the S3 valve had equivalent 1-year mortality rates, in contradistinction to previous studies.

We previously reported a 1-year mortality of TAVR in the PARTNER trial data collected from May 2007 to January 2012 of 19.0% in women versus 25.9% in men ($p < 0.001$) (12) and Chandrasekhar et al. (14) recently published data from the TVT registry reflecting the real-world experience outside of clinical trials that showed a 1-year mortality of 21.3% versus 24.5% ($p < 0.001$) in women versus men (14). In both of these studies, women had a distinct survival advantage when undergoing TAVR as compared with men. This survival difference was despite a consistently increased incidence of major vascular complications and bleeding events at 30 days in female patients. The excess periprocedural morbidity experienced by women undergoing TAVR might have been offset by the lower incidence of comorbidities compared with men. Also, women in prior investigations have tended to have smaller aortic annulus diameters and increased ejection fractions before TAVR and a lesser degree of aortic regurgitation due to PVL following TAVR, suggesting women may benefit from better preservation of cardiac function and more optimal post-operative hemodynamics as compared with men. Considered together, these differences in comorbid disease burden and echocardiographic parameters have been proposed as potential explanations of the better survival associated with female sex in prior studies (12).

Similar to prior studies from the PARTNER trial, differences between the sexes were seen, including lower prevalence of comorbidities and better left ventricular function at baseline and higher periprocedural complications. There are multiple potential explanations. First, the patients in our analysis are lower risk than has previously been reported. The average STS-PROM score in the study by Kodali et al. (12) was 11.9% women and 11.1% men. In Chandrasekhar et al. (14) the average STS-PROM score was 9% women and 8% men. Second, procedural techniques including precise positioning, smaller vascular sheaths, and high transfemoral access rates resulting in low rates of vascular injury make the procedure safer compared with earlier studies. Third, the valve design, availability of a broader range of valve sizes, and more appropriate valve size selection using MDCT used in the S3 trial as compared with previous TAVR studies resulted in very low rates of PVL for

both sexes. Specifically, a 29-mm S3 valve was available for implantation throughout the entire study duration, and preoperative MDCT imaging was available for S3HR patients and mandated for S3i patients. By contrast, a 29-mm size was not available in the first-generation SAPIEN valves, and a 29-mm SAPIEN XT was first implanted halfway through enrollment in the randomized portion of the PARTNER II trial (18). Thus, in the most comprehensive study of sex-specific outcomes in TAVR to date 13% of male patients received a 29-mm valve (SAPIEN XT or S3) (14,19).

Together, the availability of 29-mm S3 valve and MDCT imaging for valve sizing in this study appears to have disproportionately benefited men more than women. Thus, proper valve sizing might have been achieved with relatively equivalent frequency in men and women in this analysis, whereas women were more likely to receive the optimal valve size in prior studies. With improved valve sizing benefitting predominantly men as compared with women, a decreased incidence of PVL in men should be reasonably expected. Indeed, in our study there was no difference in moderate-severe PVL between women and men at 30 days (4.2% vs. 3.0%; $p = 0.25$) or 1 year (2.2% vs. 1.3%; $p = 0.22$), whereas a higher incidence of PVL at 30 days has previously been identified in men versus women (14.3% vs. 6.0% $p < 0.001$) (12).

Prosthesis-patient mismatch may also be a predictor of adverse outcomes following TAVR (20). Kodali et al. (12) reported that at 30 days women had lower valve areas (1.57 cm^2 vs. 1.83 cm^2; $p < 0.001$) and higher mean gradients (9.76 vs. 8.91; $p < 0.001$), but when indexed for body size there was no difference (0.96 cm^2 vs. 0.96 cm^2; $p = 0.80$). Chandrasekhar et al. (14) reported a statistically significantly higher aortic valve cover index in female patients of ≥8% ($p < 0.0001$). In our analysis, women had a higher mean gradient and lower valve area index (12.8 and 0.85 vs. 10.43 and 0.91, respectively; $p < 0.0001$). This would mean that men now have a better and more appropriate cover index reducing the mortality associated with prosthesis-patient mismatch. Thus, the survival difference associated with female sex identified in previous studies might have been primarily due to the unavailability of the 29-mm size in earlier generation TAVR valves and the historical lack of standardization for pre-procedural MDCT imaging, which led to increased PVL and inappropriate valve size, ultimately causing an increase in mortality in male patients.

STUDY LIMITATIONS. First, there is an overall decreased incidence of mortality in this lower-risk population as compared with the prior studies. With a lower incidence of an event occurring, the current post hoc analysis may be underpowered to show a statistical difference in 1-year survival. Second, our conclusions are specific to the S3 valve and therefore may not be generalizable to other TAVR valve systems. Finally, our multivariate analysis used the same limited number of covariates as previous PARTNER trials. However, using an expanded list of covariates not included in the STS-PROM including frailty, atrial fibrillation, mitral regurgitation, and tricuspid regurgitation did not change the results of the multivariate analysis.

CONCLUSIONS

High-risk and intermediate-risk women undergoing TAVR with the S3 valve had significant differences in both baseline characteristics and post-procedural complications, but did not have a survival difference at 1-year as compared with men. This finding is in contradistinction to previous studies and may be the result of the overall lower risk, factors affecting valve sizing to minimize PVL, and decrease in prosthesis-patient mismatch in men. These include the availability of 29-mm valves and pre-procedural MDCT imaging for valve sizing that primarily benefitted men as compared with women in this experience.

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PERSPECTIVES

WHAT IS KNOWN? In the initial studies with first- and second-generation TAVR valves in inoperable and high-surgical-risk patients, women had a lower mortality than men did at 1 and 2 years.

WHAT IS NEW? In this study of the Edwards S3 valve in high- and intermediate-risk patients there was no survival difference between women and men.

WHAT IS NEXT? Future studies evaluating all newer-generation valves in intermediate- and low-risk patients will need to determine if these results of no sex-specific survival difference are substantiated.

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