JACC: ASIA VOL. 4, NO. 4, 2024

ORIGINAL RESEARCH

Sex-Specific Disparities in Clinical Outcomes After Transcatheter Aortic Valve Replacement Among Different Racial Populations

Mijin Kim, MD,[a] Do-Yoon Kang, MD,[a] Jung-Min Ahn, MD,[a] Juyong Brian Kim, MD,[b] Alan C. Yeung, MD,[b] Takeshi Nishi, MD,[b] William F. Fearon, MD,[b] Eric P. Cantey, MD,[c] James D. Flaherty, MD,[c] Charles J. Davidson, MD,[c] S. Christopher Malaisrie, MD,[c] Hwa Jung Kim, MSc,[d] Jinho Lee, MD,[a] Jinsun Park, MD,[a] Hoyun Kim, MD,[a] Suji Cho, MD,[a] Yeonwoo Choi, MD,[a] Seung-Jung Park, MD,[a] Duk-Woo Park, MD[a]

ABSTRACT

BACKGROUND Sex-related disparities in clinical outcomes following transcatheter aortic valve replacement (TAVR) and the impact of sex on clinical outcomes after TAVR among different racial groups are undetermined.

OBJECTIVES This study assessed whether sex-specific differences in baseline clinical and anatomical characteristics affect clinical outcomes after TAVR and investigated the impact of sex on clinical outcomes among different racial groups.

METHODS The TP-TAVR (Trans-Pacific TAVR) registry is a multinational cohort study of patients with severe aortic stenosis who underwent TAVR at 2 major centers in the United States and 1 major center in South Korea. The primary outcome was a composite of death from any cause, stroke, or rehospitalization after 1 year.

RESULTS The incidence of the primary composite outcome was not significantly different between sexes (27.9% in men vs 28% in women; adjusted HR: 0.97; 95% CI: 0.79-1.20). This pattern was consistent in Asian (23.5% vs 23.3%; adjusted HR: 0.99; 95% CI: 0.69-1.41) and non-Asian (30.8% vs 31.6%; adjusted HR: 0.95; 95% CI: 0.72-1.24) cohorts, without a significant interaction between sex and racial group (P for interaction = 0.74). The adjusted risk for all-cause mortality was similar between sexes, regardless of racial group. However, the adjusted risk of stroke was significantly lower in male patients than in female patients, which was more prominent in the non-Asian cohort.

CONCLUSIONS Despite significantly different baseline and procedural characteristics, there were no sex-specific differences in the adjusted 1-year rates of primary composite outcomes and all-cause mortality, regardless of different racial groups. (Transpacific TAVR registry [TP-TAVR]; NCT03826264) (JACC: Asia 2024;4:292–302) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea; [b]Department of Medicine/Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California, USA; [c]Bluhm Cardiovascular Institute Northwestern University Feinberg School of Medicine, Division of Cardiology and Cardiac Surgery, Departments of Medicine and Surgery, Chicago, Illinois, USA; and the [d]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.

Sang-Hyun Kim, MD, served as Guest Associate Editor for this paper. Nathan Wong, PhD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 6, 2023; revised manuscript received November 13, 2023, accepted November 22, 2023.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.11.016

Over the last 2 decades, based on strong clinical evidence from several randomized clinical trials,[1-11] transcatheter aortic valve replacement (TAVR) has been positioned as a valuable treatment option for patients with severe symptomatic aortic stenosis (AS) who were at inoperable, high, intermediate, and even low risk for surgical aortic valve replacement (SAVR). According to the updated U.S. and European guidelines,[12,13] TAVR is now often recommended for elderly patients aged over 65 years (United States) or 75 years (European Union) after considering individual clinical, anatomical, and procedural characteristics. With such expansion of TAVR indications, the advent of TAVR has been followed by subsequent TAVR devices and technological and patient care improvements.

Several sex-specific differences in the pathogenesis, clinical presentation, and prognosis of severe AS have been well recognized.[14,15] Also, the female sex was associated with poorer outcomes after SAVR.[16-18] However, the data in the literature regarding sex differences in clinical outcomes following TAVR are inconsistent.[19-23] Some studies have reported that women had a similar survival rate compared with men,[22,23] whereas other reports revealed that women had a higher survival rate than men.[19-21] Furthermore, it is unknown whether the impact of sex on clinical outcomes after TAVR is different according to different racial groups. Given the different clinical and anatomical characteristics of Asian patients compared with Western patients,[24] the impact of sex on the clinical outcomes of TAVR could be dissimilar between Western and Asian patients. We, therefore, sought to assess whether sex-specific differences in anatomical and baseline characteristics may affect clinical outcomes after TAVR and investigated the impact of sex on outcomes in different racial groups (Asians vs non-Asians) using the international, multicenter TP-TAVR (Trans-Pacific TAVR) registry.

METHODS

STUDY POPULATION, DATABASE, AND PROCEDURES. The TP-TAVR registry (NCT03826264) is a multinational, multicenter, observational cohort study including consecutive patients with symptomatic severe AS who underwent TAVR at 2 major centers in the United States (Stanford University School of Medicine, Stanford, California, and Northwestern University Feinberg School of Medicine, Chicago, Illinois) and 1 major center in South Korea (Asan Medical Center, Seoul).[25,26] Beginning in February 2019, data were retrospectively collected for cases performed before initiation and prospectively thereafter. All 3 databases were standardized according to the common database model and combined according to the data use agreement among participating centers. Baseline demographics, functional status, clinical risk factors or coexisting conditions, surgical risk score (STS-PROM [Society of Thoracic Surgeons Predicted Risk of Mortality] score), anatomical or hemodynamic parameters, procedural characteristics, and outcomes were systematically collected. Each center's institutional review board or ethics committee approved the registry protocol. The TP-TAVR registry was supported by the CardioVascular Research Foundation (Seoul, Korea) and the Asan Institute for Life Sciences and Corporate Relations of Asan Medical Center (Seoul, South Korea).

At each participating center, a structured collaborative heart team evaluated each patient's candidacy for TAVR or SAVR based on their age, underlying comorbidities, surgical risk, frailty status, anatomical characteristics, and preference regarding treatment. TAVR procedures were conducted according to local guidelines using standard techniques and were performed with commercially approved TAVR devices. Procedural planning, including type and size of TAVR valve, access site, and use of pre- or post-balloon aortic valvuloplasty, were determined based on a review of multimodality imaging.[25,26] Following TAVR, patients were prescribed single or dual antiplatelet therapy with aspirin and clopidogrel (for at least 6 months) or oral anticoagulants (eg, warfarin or direct oral anticoagulant agents), if clinically indicated.

CLINICAL OUTCOMES. The primary outcome of the study was a composite of death from any cause, stroke, or rehospitalization 1 year after the procedure. Secondary outcomes included the individual components of the primary composite outcome after 1 year, the primary composite outcome and its components after 30 days, and post-procedural, major in-hospital events including death, stroke, myocardial infarction (MI), life-threatening or disabling bleeding, major vascular complication, new permanent pacemaker insertion, or new-onset atrial fibrillation. All adverse events were defined using the Valve Academic Research Consortium (VARC) criteria.[27,28] All stroke events were confirmed by a trained neurologist or stroke specialist. Rehospitalization was defined as any hospitalization related to the procedure, the valve, or heart failure. All components of the primary and secondary clinical outcomes were adjudicated by an independent group of clinicians who were

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

LVEF = left ventricular ejection fraction

MI = myocardial infarction

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TABLE 1 Baseline Demographic and Clinical Characteristics Stratified by Gender and Race

	Overall Patients (N = 1,412)			Asian Patients (n = 581)			Non-Asian Patients (n = 831)		
	Male (n = 755)	Female (n = 657)	*P* Value	Male (n = 294)	Female (n = 287)	*P* Value	Male (n = 461)	Female (n = 370)	*P* Value
Demographics									
Age, y	80 ± 8	81 ± 8	0.04	80 ± 6	80 ± 5	0.20	80 ± 9	81 ± 9	0.06
Body mass index, kg/m^2[a]	26.8 ± 5.9	26.4 ± 6.4	0.11	23.7 ± 3.3	24.3 ± 3.9	0.04	28.7 ± 6.3	28.0 ± 7.4	0.02
STS score[b]	4.7 ± 3.4	5.4 ± 3.5	<0.001	3.8 ± 2.7	4.5 ± 3.4	<0.001	5.3 ± 3.7	6.1 ± 3.5	<0.001
NYHA functional class III/IV heart failure[c]	317 (41.7)	295 (44.9)	0.20	90 (30.6)	116 (40.4)	0.01	225 (48.8)	179 (48.4)	>0.99
Comorbidities									
Diabetes mellitus	337 (44.6)	253 (38.5)	0.02	169 (57.5)	137 (47.7)	0.02	168 (36.4)	116 (31.4)	0.12
Hypertension	642 (85)	574 (87.4)	0.20	257 (87.4)	251 (87.5)	>0.99	385 (83.5)	323 (87.3)	0.13
Current smoking	55 (7.3)	14 (2.1)	<0.001	38 (12.9)	9 (3.1)	<0.001	17 (3.7)	5 (1.4)	0.04
Hyperlipidemia	579 (76.7)	467 (71.1)	0.02	226 (76.9)	211 (73.5)	0.30	353 (76.6)	256 (69.2)	0.02
Prior MI	108 (14.3)	52 (7.9)	<0.001	15 (5.1)	17 (5.9)	0.70	9.3 (20.2)	35 (9.5)	<0.001
Prior PCI	264 (35)	141 (21.5)	<0.001	98 (33.3)	63 (22)	0.002	166 (36)	78 (21.1)	<0.001
Prior CABG	185 (19.6)	30 (4.6)	<0.001	21 (7.1)	10 (3.5)	0.05	127 (27.5)	20 (5.4)	<0.001
Prior stroke	89 (11.8)	71 (10.8)	0.60	44 (15)	33 (11.5)	0.29	45 (9.8)	38 (10.3)	0.80
History of atrial fibrillation or flutter	242 (32.1)	161 (24.5)	0.002	44 (15)	28 (9.8)	0.06	198 (43.0)	133 (35.9)	0.04
Peripheral vascular disease	143 (18.9)	84 (12.8)	0.002	12 (4.1)	10 (3.5)	0.70	131 (28.4)	74 (20.0)	0.01
Chronic lung disease	104 (13.8)	73 (11.1)	0.13	37 (12.6)	24 (8.4)	0.10	67 (14.5)	49 (13.2)	0.60
Current dialysis	32 (4.2)	21 (3.2)	0.30	12 (4.1)	11 (3.8)	0.90	20 (4.3)	10 (2.7)	0.20
Baseline electrocardiography									
Left bundle branch block	56 (7.4)	47 (7.2)	0.93	6 (2.0)	9 (3.1)	0.57	50 (10.8)	38 (10.3)	0.88
Right bundle branch block	129 (17.1)	53 (8.1)	<0.001	43 (14.6)	18 (6.3)	0.002	86 (18.7)	35 (9.5)	<0.001
Echocardiographic or CT findings									
Aortic-valve area, cm^2	0.71 ± 0.21	0.64 ± 0.18	<0.001	0.64 ± 0.17	0.59 ± 0.16	<0.001	0.75 ± 0.22	0.67 ± 0.19	<0.001
Aortic valve mean gradient, mm Hg	47.5 ± 17.4	52.8 ± 20.0	<0.001	54.0 ± 18.9	59.4 ± 23.3	0.02	43.3 ± 14.9	47.6 ± 15.1	<0.001
Bicuspid aortic valve	54 (7.2)	36 (5.5)	0.20	38 (12.9)	20 (7.0)	0.02	16 (3.5)	16 (4.3)	0.50
Left ventricular ejection fraction, %	54.6 ± 13.6	59.9 ± 11.3	<0.001	56.2 ± 12.0	59.5 ± 10.9	<0.001	53.6 ± 14.5	60.2 ± 11.6	<0.001
Mitral insufficiency, moderate/severe	126 (16.7)	91 (14.8)	0.30	42 (14.3)	28 (9.8)	0.09	84 (18.2)	69 (18.6)	0.90
Tricuspid insufficiency, moderate/severe	83 (11.0)	82 (12.5)	0.40	22 (7.5)	17 (5.9)	0.50	61 (13.2)	65 (17.6)	0.08
Systolic annular perimeter on CT, mm	81.2 ± 7.3	72.0 ± 6.3	<0.001	79.8 ± 6.4	71.21 ± 6.4	<0.001	82.2 ± 7.8	72.6 ± 6.2	<0.001
Systolic annular area on CT, mm^2	499.9 ± 84.8	393.0 ± 69.1	<0.001	488.6 ± 77.7	389.7 ± 70.4	<0.001	507.3 ± 88.5	394.9 ± 68.0	<0.001

Values are mean ± SD or n (%). [a]The body mass index is the weight in kilograms divided by the square of the height in meters. [b]Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores range from 0% to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure. STS-PROM uses an algorithm that is based on the presence of coexisting illnesses to predict 30-day operative mortality. The STS-PROM score equals the predicted mortality expressed as a percentage. [c]Categorizes patients based on how much they are limited during physical activity (I, no limitation; IV, symptoms at rest).

CABG = coronary artery bypass graft; CT = computed tomography; MI = myocardial infarction; PCI = percutaneous coronary intervention.

unaware of participating centers or the race of the patients.[25,26]

STATISTICAL ANALYSIS. The principal purpose of the study was to assess whether sex-specific differences in anatomical and baseline characteristics may affect clinical outcomes after TAVR and whether an interaction exists between sex (male vs female) and racial group (Asians vs non-Asians) that affects clinical outcomes. Continuous variables, presented as mean ± SD, were compared using Student's *t*-test or Wilcoxon rank-sum test depending on their distribution. Categorical and ordinal variables, presented as frequencies and percentages, were compared using chi-square or the Fisher exact test, as appropriate. The cumulative incidences of clinical events were based on Kaplan-Meier estimates and compared using a log-rank test.

To investigate the relative risk associated with different sex groups (male vs female) in the overall population and each cohort of Asians vs non-Asians, Cox proportional hazards models were used. The results were described by the estimated HR and their 95% CIs. After unadjusted analyses were initially performed, multivariable Cox regression analyses were conducted. In the adjusted models, the following clinically relevant covariates were adjusted: age, body mass index, STS score, diabetes mellitus, previous MI, previous stroke, atrial fibrillation, left ventricular ejection fraction (LVEF), and bicuspid aortic valve. Finally, the interaction

TABLE 2 Procedural Characteristics and In-Hospital Outcomes Stratified by Male vs Female

	Overall Patients (N = 1,412)			Asian Patients (n = 581)			Non-Asian Patients (n = 831)		
	Male (n = 755)	Female (n = 657)	*P* Value	Male (n = 294)	Female (n = 287)	*P* Value	Male (n = 461)	Female (n = 370)	*P* Value
Procedural characteristics									
Procedure type			0.09			0.96			0.06
Native	709 (93.9)	630 (95.9)		284 (96.6)	277 (96.5)		425 (92.2)	353 (95.4)	
Valve-in-valve	46 (6.1)	27 (4.1)		10 (3.4)	10 (3.5)		36 (7.8)	17 (4.6)	
Access site			0.07			0.15			0.03
Transfemoral	731 (96.8)	630 (95.9)		281 (95.6)	277 (96.5)		450 (97.6)	353 (95.4)	
Transapical	12 (1.6)	11 (1.7)		12 (4.1)	7 (2.4)		0 (0)	4 (1.1)	
Transaortic	1 (0.1)	9 (1.4)		0 (0)	3 (1)		1 (0.2)	6 (1.6)	
Subclavian	1 (0.1)	0 (0)		0 (0)	0 (0)		1 (0.2)	0 (0)	
Others	10 (1.3)	7 (1.1)		1 (0)	0 (0)		9 (2.0)	7 (1.9)	
Valve type			0.001			<0.001			0.36
Balloon-expandable	651 (86.2)	523 (79.6)		259 (88.1)	217 (75.6)		392 (85.0)	306 (82.7)	
Self-expandable	104 (13.8)	134 (20.4)		35 (11.9)	70 (24.4)		69 (15.0)	64 (17.3)	
Prosthesis size, mm			<0.001			<0.001			<0.001
20	0 (0)	27 (4.1)		0 (0)	8 (2.8)		0 (0)	19 (5.1)	
23 to 25	81 (10.8)	341 (51.9)		36 (12.3)	131 (45.6)		45 (9.8)	210 (56.8)	
26 to 28	392 (51.9)	239 (36.4)		162 (55.1)	125 (43.6)		230 (49.9)	114 (30.8)	
29 or larger	282 (37.4)	50 (7.7)		96 (32.7)	23 (8.0)		186 (40.3)	27 (7.3)	
Type of anesthesia			0.43			0.65			0.49
Conscious sedation	428 (56.7)	386 (58.8)		221 (75.2)	211 (73.5)		207 (44.9)	175 (47.3)	
General anesthesia	327 (43.3)	271 (41.2)		73 (24.8)	76 (26.5)		254 (55.1)	195 (52.7)	
Concomitant PCI	39 (5.2)	18 (2.7)	0.03	18 (6.2)	11 (3.9)	0.20	21 (4.6)	7 (1.9)	0.09
Post-dilation	273 (36)	244 (37)	0.70	199(68)	171(60)	0.04	74 (16)	73 (20)	0.2
Moderate to severe paravalvular leakage	15 (2.0)	9 (1.4)	0.37	8 (2.7)	6 (2.1)	0.62	7 (1.5)	3 (0.8)	0.36
In-hospital event									
Death	13 (1.7)	9 (1.4)	0.59	5 (1.7)	2 (0.7)	0.27	8 (1.7)	7 (1.9)	0.87
Stroke	12 (1.6)	21 (3.2)	0.05	6 (2.0)	10 (3.5)	0.29	6 (1.3)	11 (3.0)	0.09
Myocardial infarction	7 (0.9)	6 (0.9)	0.14	4 (1.4)	4 (1.4)	0.97	3 (0.7)	2 (0.5)	0.84
Life-threatening or disabling bleeding	19 (7.8)	17 (8.9)	0.66	14 (4.8)	12 (4.2)	0.74	5 (1.1)	5 (1.4)	0.73
Major vascular complication	18 (2.4)	20 (3.0)	0.45	11 (3.7)	13 (4.5)	0.63	7 (1.9)	7 (1.9)	0.68
New permanent pacemaker	74 (9.8)	48 (7.3)	0.10	15 (5.1)	18 (6.3)	0.54	59 (12.8)	30 (8.1)	0.03
New-onset atrial fibrillation	16 (2.1)	24 (3.7)	0.08	6 (2.0)	5 (1.7)	0.79	10 (2.2)	19 (5.1)	0.02
Prosthesis-patient mismatch	275/596 (46.1)	208/505 (41.2)	0.11	97/286 (33.9)	92/276 (33.3)	0.96	178/310 (57.4)	116/229 (50.7)	0.14

Values are n (%) or n/N (%).
PCI = percutaneous coronary intervention.

between sex (male or female) and race (Asian vs non-Asian) concerning the primary and secondary outcomes were also tested. The assumptions of the Cox model were assessed statistically based on Schoenfeld residuals and graphically by log-log plots in the overall cohort, Asian cohort, and non-Asian cohort, respectively, and were approximately satisfied for all variables.

All reported *P* values are 2-sided; a *P* value <0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS software version 9.4 (SAS Institute) and R software version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Among the 1,412 patients enrolled in the TP-TAVR registry, 536 patients (38.0%) were enrolled from Asan Medical Center in South Korea, 478 patients (33.9%) were enrolled from Stanford Hospital in the United States, and 398 (28.2%) were enrolled from Northwestern Memorial Hospital in the United States. Of the 1,412 patients, 755 (53.5%) were male, and 657 (46.5%) were female; 581 (41.1%) patients were Asian, and 831 (58.9%) were non-Asian (of these, 87.5% were White, 1.7% were Black, 6.1% were Hispanic, and 4.7% were classed as "other").

TABLE 3 Unadjusted (Observed) Clinical Outcomes After 30 Days

	Overall Patients (N = 1,412)				Asian Patients (n = 581)				Non-Asian Patients (n = 831)			
	Male (n = 755)	Female (n = 657)	HR (95% CI)	*P* Value	Male (n = 294)	Female (n = 287)	HR (95% CI)	*P* Value	Male (n = 461)	Female (n = 370)	HR (95% CI)	*P* Value
Primary composite outcome	79 (10.5)	82 (12.5)	0.83 (0.61-1.12)	0.225	28 (9.5)	27 (9.4)	1.02 (0.60-1.73)	0.944	51 (11.1)	55 (14.9)	0.72 (0.49-1.06)	0.090
Secondary outcome												
Death from any cause	13 (1.7)	12 (1.8)	0.94 (0.43-2.07)	0.885	6 (2.0)	1 (0.3)	5.96 (1.35-26.22)	0.098	7 (1.5)	11 (3.0)	0.51 (0.20-1.28)	0.159
Cardiac death	4 (0.5)	8 (1.2)	0.44 (0.13-1.45)	0.175	4 (1.4)	0 (0)	NA	0.999	0 (0)	8 (2.2)	NA	0.998
Noncardiac death	10 (1.3)	4 (0.6)	2.18 (0.68-6.94)	0.188	3 (1.0)	1 (0.3)	2.99 (0.42-21.22)	0.343	7 (1.5)	3 (0.8)	1.85 (0.53-6.46)	0.371
Stroke	11 (1.5)	23 (3.5)	0.41 (0.20-0.84)	0.015	5 (1.7)	11 (3.8)	0.44 (0.16-1.18)	0.132	6 (1.3)	12 (3.2)	0.40 (0.16-1.00)	0.063
Rehospitalization	59 (7.8)	56 (8.5)	0.92 (0.64-1.32)	0.641	19 (6.5)	20 (7.0)	0.95 (0.51-1.78)	0.874	40 (8.7)	36 (9.7)	0.87 (0.55-1.37)	0.554

Values are n (%). Percentages are calculated by the Kaplan-Meier estimates. HRs are shown for male patients compared with female patients.

The baseline characteristics of the patients stratified by different sex and racial groups are shown in Table 1. Overall, there were significant differences between male and female patients regarding demographics, comorbidities, and hemodynamic or anatomical findings. Male patients were younger and had a significantly lower STS score but a higher prevalence of diabetes, smoking, hyperlipidemia, prior history of MI, PCI or bypass surgery, atrial fibrillation, and peripheral vascular disease. Such sex-specific differences in baseline characteristics were more noticeable in the non-Asian population than in the Asian population. Regarding anatomical characteristics, female patients had smaller aortic valve areas and annular sizes, and a higher mean LVEF compared with male patients. These features were consistent in both the Asian and non-Asian populations.

PROCEDURAL CHARACTERISTICS AND IN-HOSPITAL EVENTS. Procedural characteristics and in-hospital events are summarized in Table 2. Generally, self-expandable valves and smaller TAVR valves were more frequently implanted in female patients. There were no significant sex-specific differences in the rates of in-hospital clinical events except for stroke, which was more prevalent in female than male patients. In the non-Asian cohort, the implantation of a new permanent pacemaker was more frequent among male patients, but new-onset atrial fibrillation was more frequent among female patients.

CLINICAL OUTCOMES AT 30 DAYS AND 1 YEAR. Observed short-term (30-day) rates of adverse clinical outcomes are summarized in Table 3. Overall, there were no significant sex-specific differences in 30-day rates of the primary composite outcome and its components, except that the 30-day stroke rate was significantly higher in female patients than in male patients.

The primary and secondary outcomes at 1 year according to sex in the overall population and each cohort of Asians vs non-Asians are summarized in Tables 4 and 5. The 1-year observed rate of the primary composite of death, stroke, or rehospitalization was similar between male and female patients (27.9% vs 28%, respectively; log-rank $P = 0.752$) (Figure 1). This trend was consistent in both the Asian and non-

TABLE 4 Unadjusted and Adjusted Analyses of Clinical Outcomes After 1 Year in the Overall Cohort

			Unadjusted Analysis		Adjusted Analysis[a]	
	Male	Female	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Primary composite outcome	211 (27.9)	184 (28.0)	0.99 (0.81-1.20)	0.883	0.97 (0.79-1.20)	0.80
Secondary outcome						
Death from any cause	76 (10.1)	50 (7.6)	1.46 (1.01-2.12)	0.045	1.35 (0.91-1.99)	0.133
CV death	18 (2.4)	13 (1.9)	1.24 (0.61-2.51)	0.549	1.21 (0.57-2.56)	0.625
Non-CV death	58 (7.7)	37 (5.6)	1.48 (0.97-2.28)	0.070	1.35 (0.86-2.12)	0.188
Stroke	17 (2.3)	29 (4.4)	0.49 (0.27-0.89)	0.020	0.46 (0.24-0.80)	0.014
Rehospitalization	165 (21.9)	136 (20.7)	1.03 (0.82-1.30)	0.795	1.05 (0.82-1.33)	0.696

Values are n (%). Percentages are calculated by the Kaplan-Meier estimates. HRs are shown for male patients compared with female patients. [a]HRs were adjusted for age, body mass index, STS score, diabetes mellitus, previous MI, previous stroke, atrial fibrillation, left ventricular ejection fraction, and bicuspid valve.

CV = cardiovascular; other abbreviations as in Table 1.

TABLE 5 Unadjusted and Adjusted Analyses of Clinical Outcomes After 1 Year in the Asian and Non-Asian Cohorts

	Asian Cohort						Non-Asian Cohort						
			Unadjusted Analysis		Adjusted Analysis[a]				Unadjusted Analysis		Adjusted Analysis[a]		*P* Value for Interaction[b]
	Male	Female	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	Male	Female	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	
Primary composite outcome	69 (23.5)	67 (23.3)	1.01 (0.72-1.42)	0.954	0.99 (0.69-1.41)	0.945	142 (30.8)	117 (31.6)	0.94 (0.73-1.21)	0.637	0.95 (0.72-1.24)	0.686	0.735
Secondary outcome													
Death from any cause	22 (7.5)	15 (5.2)	1.52 (0.78-2.97)	0.221	1.78 (0.87-3.67)	0.116	54 (11.7)	35 (9.5)	1.38 (0.88-2.16)	0.156	1.23 (0.77-1.98)	0.384	0.799
CV death	11 (3.7)	3 (1.0)	3.55 (0.99-12.73)	0.052	3.11 (0.82-11.8)	0.097	8 (1.7)	12 (3.2)	0.62 (0.24-1.57)	0.311	0.52 (0.19-1.41)	0.197	0.028
Non-CV death	12 (4.1)	13 (4.5)	0.97 (0.43-2.15)	0.934	1.25 (0.53-2.98)	0.610	46 (10.0)	24 (6.5)	1.68 (1.00-2.81)	0.050	1.5 (0.87-2.6)	0.146	0.262
Stroke	10 (3.4)	14 (4.9)	0.68 (0.3-1.53)	0.352	0.52 (0.22-1.23)	0.137	7 (1.5)	15 (4.1)	0.36 (0.15-0.88)	0.024	0.34 (0.13-0.90)	0.029	0.285
Rehospitalization	57 (19.4)	55 (19.2)	1.01 (0.7-1.47)	0.948	1.00 (0.68-1.48)	0.983	108 (23.4)	81 (21.9)	1.02 (0.76-1.37)	0.878	1.05 (0.77-1.43)	0.759	0.972

Values are n (%). Percentages are calculated by the Kaplan-Meier estimates. HRs are shown for male patients compared with female patients. [a]HRs were adjusted for age, body mass index, STS score, diabetes mellitus, previous MI, previous stroke, atrial fibrillation, left ventricular ejection fraction, and bicuspid valve. [b]*P* values for interaction are between sex and race.

Abbreviations as in Tables 1 and 4.

Asian cohorts. With regard to each component of the primary outcome, unadjusted 1-year rate of all-cause mortality was significantly higher in male patients than in female patients among the overall cohort (Figure 2). By contrast, the rate of stroke was significantly lower in male patients than in female patients. This pattern was generally consistent in each racial group. The 1-year rate of rehospitalization was similar among male and female patients, regardless of racial group.

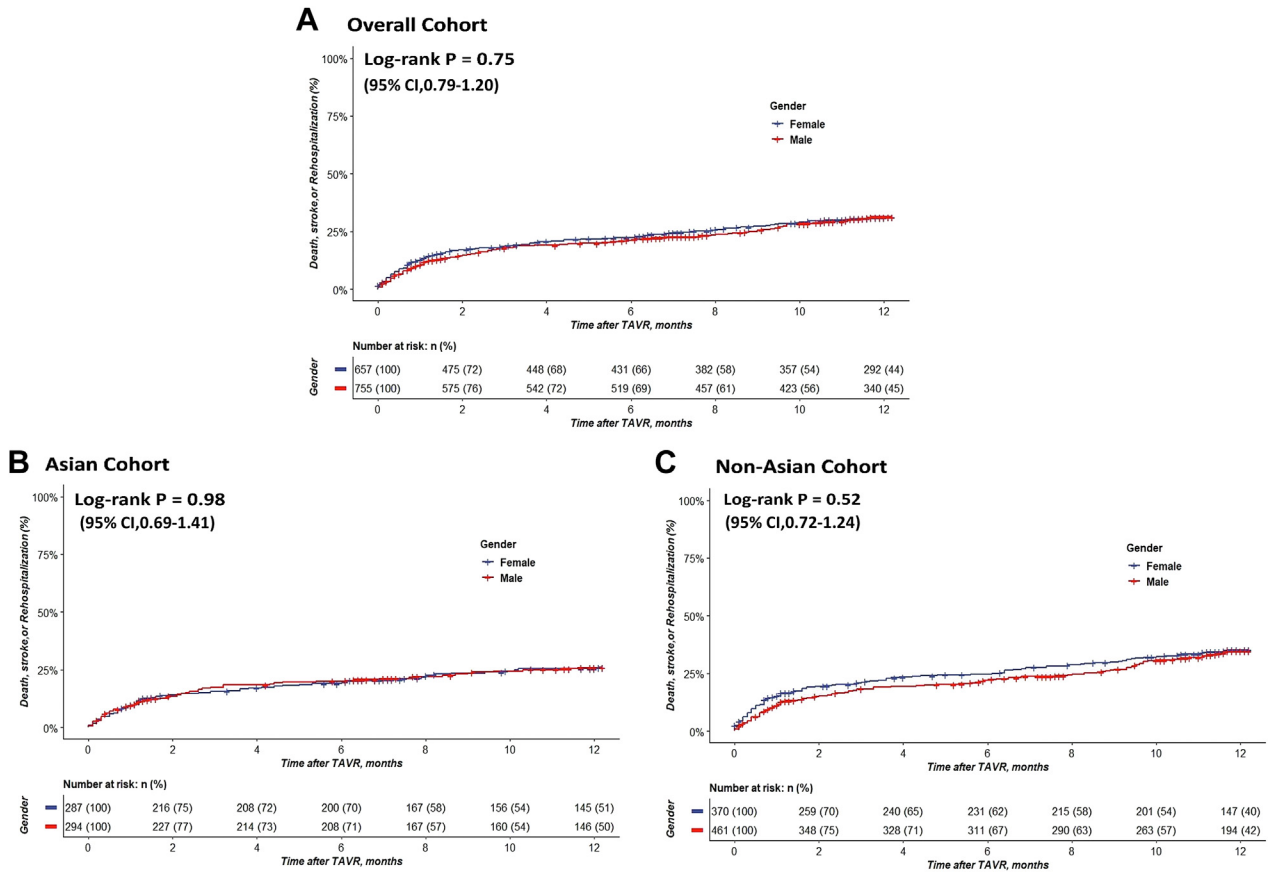
Following a multivariable adjustment of clinically relevant covariates, the adjusted risk from the primary composite outcome was not significantly different between male and female patients in the overall population (HR: 0.97; 95% CI: 0.79-1.20; $P = 0.804$) (Table 4, Central Illustration). These findings were consistent in both the Asian and non-Asian cohorts, with no significant interaction between sex and racial group (P for interaction $= 0.735$) (Table 5, Central Illustration). There were no sex-specific differences in the adjusted risks of all-cause mortality and rehospitalization in the overall cohort or each racial group. The adjusted risk for stroke was significantly lower in male patients than in female patients; this trend was similar for each racial group but statistically significant only in the non-Asian cohort. There was no significant interaction between sex and racial group with respect to each component of all-cause mortality, stroke, or rehospitalization, but not for cardiovascular death (P for interaction $= 0.028$).

DISCUSSION

The major findings of our study can be summarized as follows: first, there were considerable differences in baseline clinical, anatomical, and procedural characteristics between male and female patients, which were similar in each Asian or non-Asian cohort; second, following a multivariable adjustment of clinically relevant covariates, the 1-year rates of the primary composite outcome of death, stroke, or rehospitalization and all-cause mortality was similar between male and female patients, and this was consistent in both the Asian and non-Asian cohorts, without a significant interaction between sex and racial group; third, the adjusted risk for stroke was significantly lower in male patients than in female patients, and this trend was more notable in the non-Asian cohort.

TAVR has been established as a safe and effective therapy for patients with severe AS and has been increasingly performed over the last few decades.[29] The female sex has been traditionally associated with an increased risk for adverse events after SAVR.[16-18] However, sex-specific differences in clinical outcomes following TAVR have not been confirmed.[22,30-34] Contrary to observed findings in SAVR patients, previous studies have suggested a significantly better survival rate for women than for men. The most common reason for this finding was that female patients tended to have fewer comorbidities and better LVEF before TAVR.[30-32] However, some studies have reported that there were no observable sex-specific differences concerning survival or stroke following TAVR.[22,33,34] Furthermore, as most of the prior studies focused on Western populations, sex-specific disparities in clinical outcomes after TAVR in different racial groups, particularly in Asian populations with different clinical and anatomical characteristics, are still lacking. In this clinical

FIGURE 1 **Time-to-Event Curves for the Primary Composite Outcome After 1 Year**



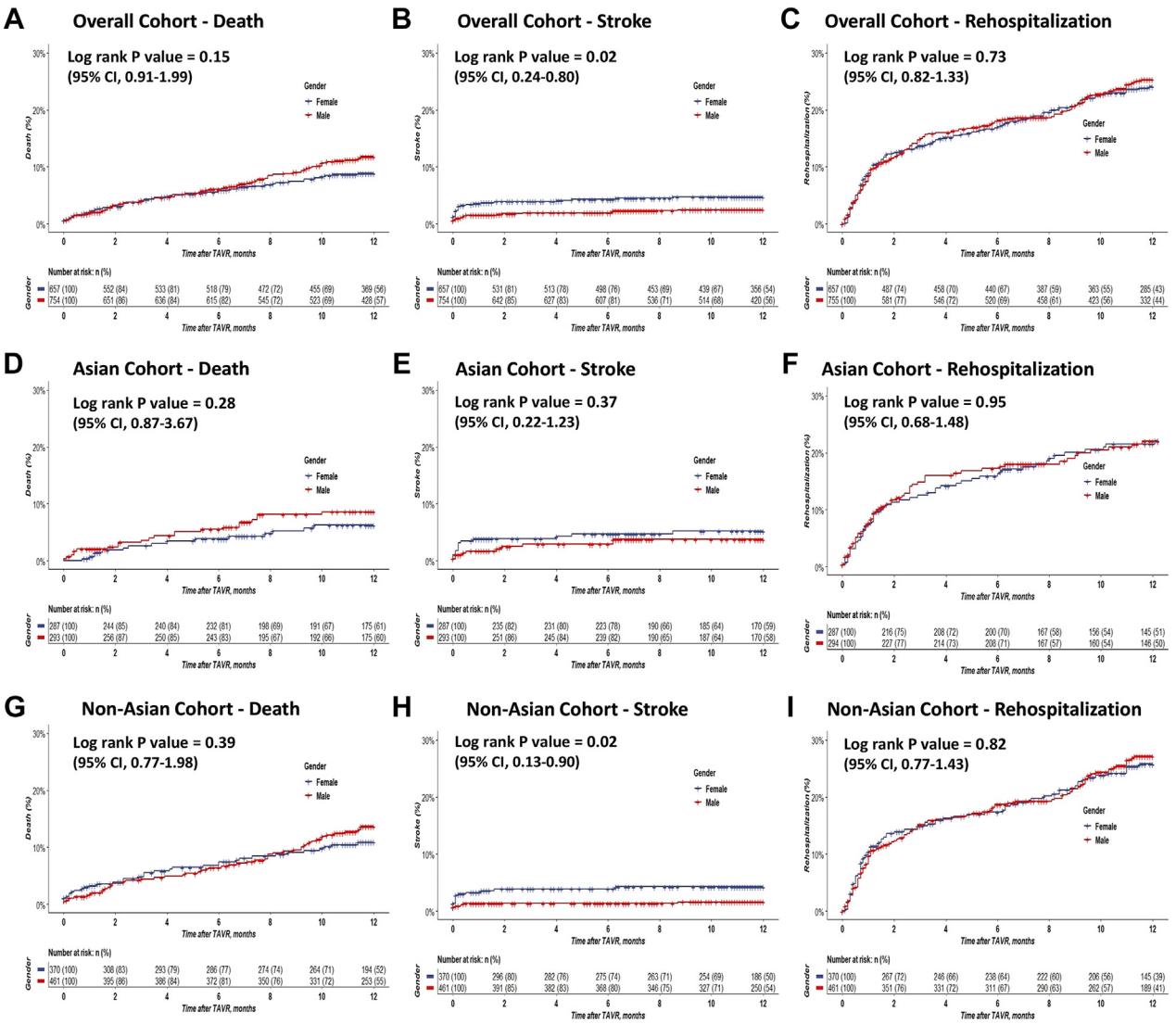
Kaplan-Meier estimates of the rate of the primary composite outcome at 1 year according to sex in the overall cohort (A), Asian cohort (B), and non-Asian cohort (C). TAVR = transcatheter aortic valve replacement.

context, our study may be the first direct comparative analysis investigating sex-specific disparities in patient characteristics and clinical outcomes in different ethnic populations.

In the current study, there were no significant differences in the observed and adjusted rates of the primary composite of death, stroke, or rehospitalization outcomes after 1 year between male and female patients following TAVR; this result was consistent in both the Asian and non-Asian cohorts. Additionally, there were no sex-specific differences in all-cause mortality, regardless of racial group. Similar to prior studies showing better survival rates among women after TAVR,[20,32-34] we found that there was a lower prevalence of comorbidities and better LVEF function at baseline among female patients. By contrast, female patients in our study were older and had a higher STS score than male patients. Thus, inconsistent findings between the current study and previous reports might be explained in part by differences in clinical or anatomical characteristics, TAVR practices, or racial or ethnic groups between our patient population and those enrolled in earlier studies.

Interestingly, in the current study, the rate of stroke was higher in female patients than in male patients, and this sex disparity concerning stroke events was more remarkable in the non-Asian cohort than in the Asian cohort. Previous studies have indicated that stroke rates are not significantly different between sex groups after TAVR.[30-33] Although the precise mechanisms for such dissimilar observations on stroke events have yet to be elucidated, it has been postulated that baseline clinical or anatomical factors, underlying comorbid conditions, procedural factors such as differences of post-dilation and

FIGURE 2 **Time-to-Event Curves for Secondary Outcome After 1 Year**

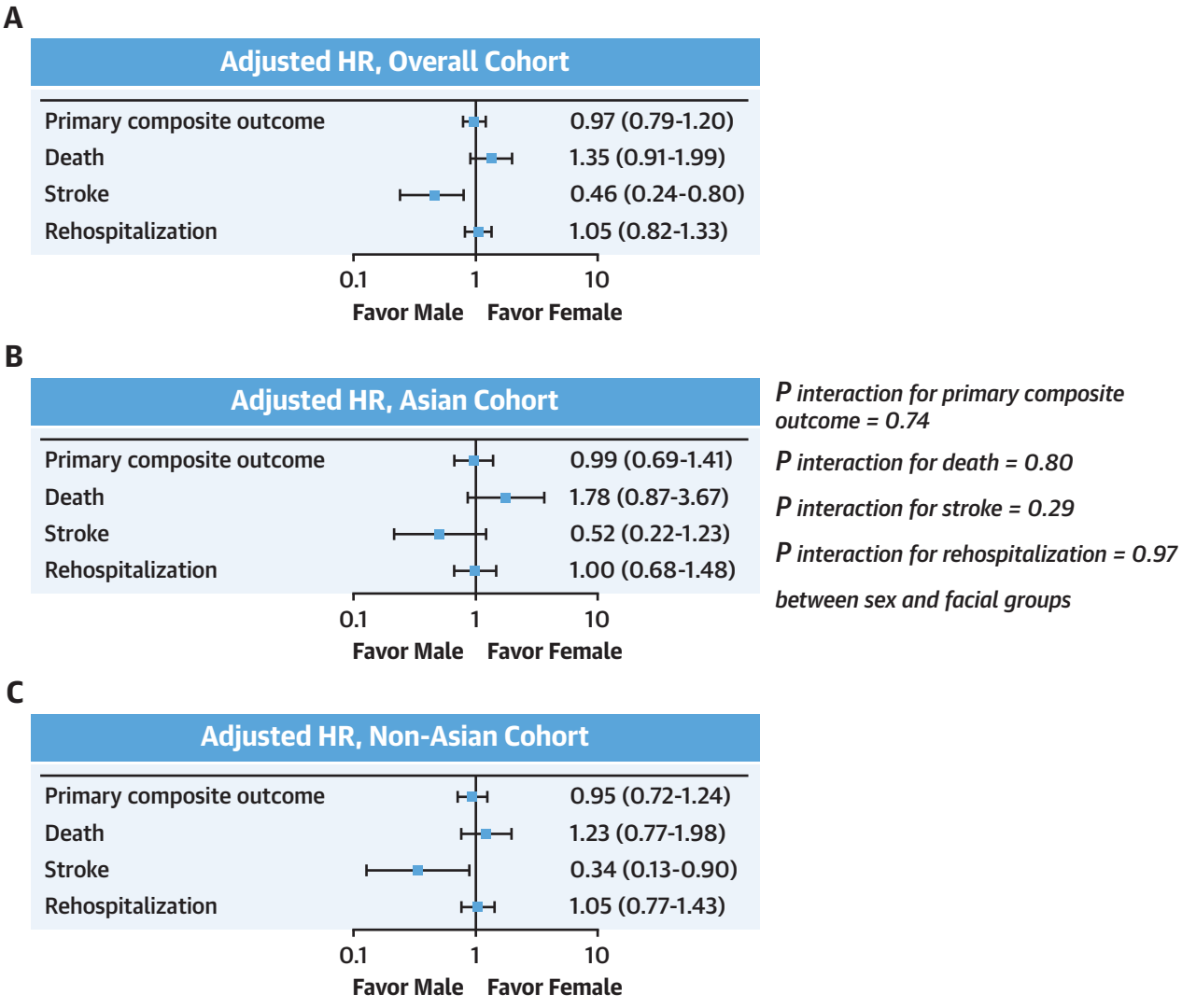


Kaplan-Meier estimates of the rate of the individual components of the primary outcome of death from any cause (A), stroke (B), and rehospitalization (C) in the overall cohort. Kaplan–Meier estimates of all-cause mortality (D), stroke (E) and rehospitalization (F) in Asian cohort and all-cause mortality (G), stroke (H) and rehospitalization (I) in non-Asian cohort. TAVR = transcatheter aortic valve replacement.

unmeasured confounders such as post-TAVR medication may contribute to this disparity. This should be further confirmed or refuted by larger-sized clinical studies with longer-term follow-up.

STUDY LIMITATIONS. First, the observational nature of this study may have affected the observed results owing to selection bias and unmeasured confounders. Therefore, the overall findings should be interpreted as exploratory and regarded as hypothesis-generating only. Second, because the TP-TAVR registry was a multicenter, multinational registry with different medical systems, intersite variability might exist and could influence observed results. Therefore, it may be still undetermined whether pooling the races together in this merged cohort was influenced by potential TAVR practice differences between the United States and Korea. Third, because our study evaluated clinical

CENTRAL ILLUSTRATION **Adjusted HRs for the Primary and Secondary Outcomes**



Kim M, et al. JACC: Asia. 2024;4(4):292–302.

Adjusted HR for the primary composite outcome and its individual components were stratified according to sex in the overall cohort (A), Asian cohort (B), and non-Asian cohort (C).

outcomes for up to 1 year, the current study might be inadequate to address the long-term prognostic impact of sex on clinical outcomes. Finally, despite a risk adjustment of a wide range of important clinical covariates, other relevant comorbidities associated with poorer outcomes post-TAVR, including frailty, socioeconomic factors, or concomitant medications, were not systematically collected in our database, and thus this limitation should be considered.

CONCLUSIONS

In this multinational, multiethnic study of TAVR patients, there were significant differences in baseline clinical and anatomical characteristics between male and female patients. However, the observed and adjusted rates of the primary composite outcome of death, stroke, or rehospitalization and all-cause mortality after 1 year were not significantly different between male and female patients following TAVR.

These findings were consistent in different racial group of Asian vs non-Asian.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was supported by a grant (2020IF0016) from the Asan Institute for Life Sciences and Corporate Relations of Asan Medical Center (Seoul, South Korea) with the NAVER Corp (Seongnam, Korea). This study was also funded in part by the CVRF (Seoul, South Korea), Edwards Lifesciences, and Medtronic. Dr Yeung has received institutional research support from Edwards Lifesciences. Dr Fearon has received institutional research support from Edwards Lifesciences. Dr Malaisrie has received institutional research support from Edwards Lifesciences, Medtronic, Cryolife, and Terumo Aortic. Dr S.-J. Park has received receiving grants from Edwards Lifesciences, Medtronic, and Abbott. Dr D.-W. Park has received research grants and consultancy and speaker fees from Edwards Lifesciences, Medtronic, Abbott, and Daiichi-Sankyo during the study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Duk-Woo Park, Division of Cardiology, Asan Medical Center, University of Ulsan College of Medicine 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea. E-mail: dwpark@amc.seoul.kr.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although female sex was associated with poorer outcomes after SAVR, sex-specific difference in clinical outcomes following TAVR are still conflicting. It is also unknown whether the impact of sex on clinical outcomes after TAVR may be different according to racial group. In this multinational multicenter registry, we found that there were considerable differences in baseline clinical, anatomical, and procedural characteristics between male and female patients. However, the observed and adjusted rates of the primary composite outcome of death, stroke, or rehospitalization and all-cause mortality at 1 year were not significantly different between male and female patients, irrespective of different racial groups of Asian or non-Asian.

TRANSLATIONAL OUTLOOK: Further large-sized studies are required to determine the clinical role of sex-specific differences on TAVR outcomes and risk stratification among different ethnic groups.

REFERENCES

1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198. https://doi.org/10.1056/NEJMoa1103510

2. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686–1695. https://doi.org/10.1056/NEJMoa1200384

3. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477–2484. https://doi.org/10.1016/s0140-6736(15)60308-7

4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798. https://doi.org/10.1056/NEJMoa1400590

5. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2015;66:113–121. https://doi.org/10.1016/j.jacc.2015.05.017

6. Gleason TG, Reardon MJ, Popma JJ, et al. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. *J Am Coll Cardiol*. 2018;72:2687–2696. https://doi.org/10.1016/j.jacc.2018.08.2146

7. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620. https://doi.org/10.1056/NEJMoa1514616

8. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331. https://doi.org/10.1056/NEJMoa1700456

9. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705. https://doi.org/10.1056/NEJMoa1814052

10. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–1715. https://doi.org/10.1056/NEJMoa1816885

11. Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the all-comers NOTION randomized clinical trial. *J Am Coll Cardiol*. 2015;65:2184–2194. https://doi.org/10.1016/j.jacc.2015.03.014

12. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:450–500. https://doi.org/10.1016/j.jacc.2020.11.035

13. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632. https://doi.org/10.1093/eurheartj/ehab395

14. Simard L, Côté N, Dagenais F, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? *Circ Res*. 2017;120:681–691. https://doi.org/10.1161/circresaha.116.309306

15. Toyofuku M, Taniguchi T, Morimoto T, et al. Sex differences in severe aortic stenosis- clinical presentation and mortality. *Circ J*. 2017;81:1213–1221. https://doi.org/10.1253/circj.CJ-16-1244

16. Duncan AI, Lin J, Koch CG, et al. The impact of gender on in-hospital mortality and morbidity after isolated aortic valve replacement. *Anesth Analg*. 2006;103:800–808. https://doi.org/10.1213/01.ane.0000231890.95212.12

17. Fuchs C, Mascherbauer J, Rosenhek R, et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis. *Heart*. 2010;96:539–545. https://doi.org/10.1136/hrt.2009.186650

18. Onorati F, D'Errigo P, Barbanti M, et al. Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: results of the multicenter Italian OBSERVANT Registry. *J Thorac Cardiovasc Surg*. 2014;147:1529–1539. https://doi.org/10.1016/j.jtcvs.2013.05.039

19. O'Connor SA, Morice MC, Gilard M, et al. Revisiting sex equality with transcatheter aortic valve replacement outcomes: a collaborative, patient-level meta-analysis of 11,310 patients.

J Am Coll Cardiol. 2015;66:221–228. https://doi.org/10.1016/j.jacc.2015.05.024

20. Kodali S, Williams MR, Doshi D, et al. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. *Ann Intern Med*. 2016;164:377–384. https://doi.org/10.7326/m15-0121

21. Saad M, Nairooz R, Pothineni NVK, et al. Long-term outcomes with transcatheter aortic valve replacement in women compared with men: evidence from a meta-analysis. *J Am Coll Cardiol Intv*. 2018;11:24–35. https://doi.org/10.1016/j.jcin.2017.08.015

22. Vlastra W, Chandrasekhar J, García Del Blanco B, et al. Sex differences in transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;74:2758–2767. https://doi.org/10.1016/j.jacc.2019.09.015

23. Chiam PTL, Hayashida K, Watanabe Y, et al. Sex differences in patients undergoing transcatheter aortic valve replacement in Asia. *Open Heart*. 2021;8(1):e001541. https://doi.org/10.1136/openhrt-2020-001541

24. Lee CH, Inohara T, Hayashida K, Park D-W. Transcatheter aortic valve replacement in Asia: present status and future perspectives. *JACC: Asia*. 2021;1:279–293. https://doi.org/10.1016/j.jacasi.2021.10.006

25. Park H, Ahn JM, Kang DY, et al. Racial differences in the incidence and impact of prosthesis-patient mismatch after transcatheter aortic valve replacement. *J Am Coll Cardiol Intv*. 2021;14:2670–2681. https://doi.org/10.1016/j.jcin.2021.08.038

26. Kang DY, Ahn JM, Kim JB, et al. Inter-racial differences in patients undergoing transcatheter aortic valve implantation. *Heart*. 2022;108(19):1562–1570. https://doi.org/10.1136/heartjnl-2021-320364

27. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438–1454. https://doi.org/10.1016/j.jacc.2012.09.001

28. VARC-3 Writing Committee, Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77:2717–2746. https://doi.org/10.1016/j.jacc.2021.02.038

29. Mori M, Gupta A, Wang Y, et al. Trends in transcatheter and surgical aortic valve replacement among older adults in the United States. *J Am Coll Cardiol*. 2021;78:2161–2172. https://doi.org/10.1016/j.jacc.2021.09.855

30. Stangl V, Baldenhofer G, Laule M, Baumann G, Stangl K. Influence of sex on outcome following transcatheter aortic valve implantation (TAVI): systematic review and meta-analysis. *J Interv Cardiol*. 2014;27:531–539. https://doi.org/10.1111/joic.12150

31. Azarbaijani Y, O'Callaghan K, Sanders WE, et al. Sex-specific outcomes after transcatheter aortic valve replacement: a review of the literature. *Cardiol Rev*. 2018;26:73–81. https://doi.org/10.1097/crd.0000000000000177

32. Humphries KH, Toggweiler S, Rodés-Cabau J, et al. Sex differences in mortality after transcatheter aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol*. 2012;60:882–886. https://doi.org/10.1016/j.jacc.2012.05.009

33. Szerlip M, Gualano S, Holper E, et al. 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. *J Am Coll Cardiol Intv*. 2018;11:13–20. https://doi.org/10.1016/j.jcin.2017.09.035

34. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation*. 2011;123:299–308. https://doi.org/10.1161/circulationaha.110.946533

KEY WORDS aortic valve stenosis, sex, TAVR