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Racial Differences in the Incidence and Impact of Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The aim of this study was to compare the incidence and prognostic significance of prosthesis-patient mismatch (PPM) after transcatheter aortic valve replacement (TAVR) according to racial groups.

BACKGROUND PPM after TAVR may be of more concern in Asian populations considering their relatively small annular and valve sizes compared with Western populations.

METHODS TP-TAVR (Transpacific TAVR Registry) was an international multicenter cohort study of patients with severe aortic stenosis who underwent TAVR in the United States and South Korea from January 2015 to November 2019. PPM was defined as moderate (0.65-0.85 cm^2/m^2) or severe ($<$0.65 cm^2/m^2) at the indexed effective orifice area. The primary outcome was a composite of death, stroke, or rehospitalization at 1 year.

RESULTS Among 1,101 eligible patients (533 Asian and 569 non-Asian), the incidence of PPM was significantly lower in the Asian population (33.6%; moderate, 26.5%; severe, 7.1%) than in the non-Asian population (54.5%; moderate, 29.8%; severe, 24.7%). The 1-year rate of the primary outcome was similar between the PPM and non-PPM groups (27.5% vs 28.1%; $P = 0.69$); this pattern was consistent between Asian (25.4% vs 25.2%; $P = 0.31$) and non-Asian (28.7% vs 32.1%; $P = 0.97$) patients. After multivariable adjustment, the risk for the primary outcome did not significantly differ between the PPM and non-PPM groups in the overall population (HR: 0.95; 95% CI: 0.74-1.21), in Asian patients (HR: 1.07; 95% CI: 0.74-1.55), and in non-Asian patients (HR: 0.86; 95% CI: 0.63-1.19).

CONCLUSIONS In this study of patients with severe aortic stenosis who underwent TAVR, the incidence of PPM was significantly lower in Asian patients than in non-Asian patients. The 1-year risk for the primary composite outcome was similar between the PPM and non-PPM groups regardless of racial group. (Transpacific TAVR Registry [TP-TAVR]; NCT03826264) (J Am Coll Cardiol Intv 2021;14:2670–2681) © 2021 by the American College of Cardiology Foundation.

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Over the past decade, transcatheter aortic valve replacement (TAVR) has been established as a safe and effective procedure for the treatment of severe symptomatic aortic stenosis (AS). Most updated U.S. guidelines recommend either surgical aortic valve replacement (SAVR) or transfemoral TAVR in adults 65 to 80 years of age after shared decision making with respect to the balance between expected patient longevity and valve durability (Class 1, Level of Evidence: A) (1).

Prosthesis-patient mismatch (PPM) is a condition in which the effective orifice area (EOA) of a normally functioning implanted valve prosthesis is small relative to the patient's body size (2). Given that the number of TAVR procedures is rapidly increasing worldwide, involving diverse racial and ethnic groups of patients, considerations concerning PPM are of particular relevance in Asian populations with unique anatomical features such as smaller annular dimensions or smaller valve implant size compared with Western populations (3,4). Until recently, several studies had shown conflicting results with regard to the clinical impact of PPM in patients undergoing TAVR (5-9). However, it is still unknown whether there are interracial differences in the incidence and prognostic relevance of PPM following TAVR. We therefore performed a direct comparison of the overall incidence, important predictors, and prognostic significance of PPM after TAVR according to different racial groups (Asian vs non-Asian) using the international, multiracial TP-TAVR (Trans-Pacific TAVR Registry).

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METHODS

STUDY POPULATION, DATABASE, AND PROCEDURES. TP-TAVR was an international, multicenter, observational cohort study that included all consecutive patients with symptomatic severe AS who underwent TAVR at 2 academic medical centers in the United States (Stanford University School of Medicine and Northwestern University Feinberg School of Medicine) from June 2016 to November 2019 and at 1 academic medical center in South Korea (Asan Medical Center) from January 2015 to November 2019 (NCT03826264). This registry was initiated in February 2019, and we collected data retrospectively for cases performed before initiation and prospectively thereafter.

All 3 databases were standardized according to the common database model and merged in accordance with the policy of data use agreed upon among the participating centers; patient demographics, surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality score), functional status, clinical risk factors or comorbidities, anatomical or hemodynamic parameters by cardiac computed tomography or echocardiography, procedural details, and in-hospital and follow-up outcomes were collected in the common database. Each center's Institutional Review Board or ethics committee approved the protocol for the registry. TP-TAVR was partly funded by the CardioVascular Research Foundation and was supported by a grant (2020IF0016) from Asan Institute for Life Sciences and Corporate Relations of Asan Medical Center. The sponsor had no role in the study design or in the collection, analysis, or interpretation of data.

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

BMI = body mass index

BSA = body surface area

EOA = effective orifice area

LVEF = left ventricular ejection fraction

PPM = prosthesis-patient mismatch

SAVR = surgical aortic valve replacement

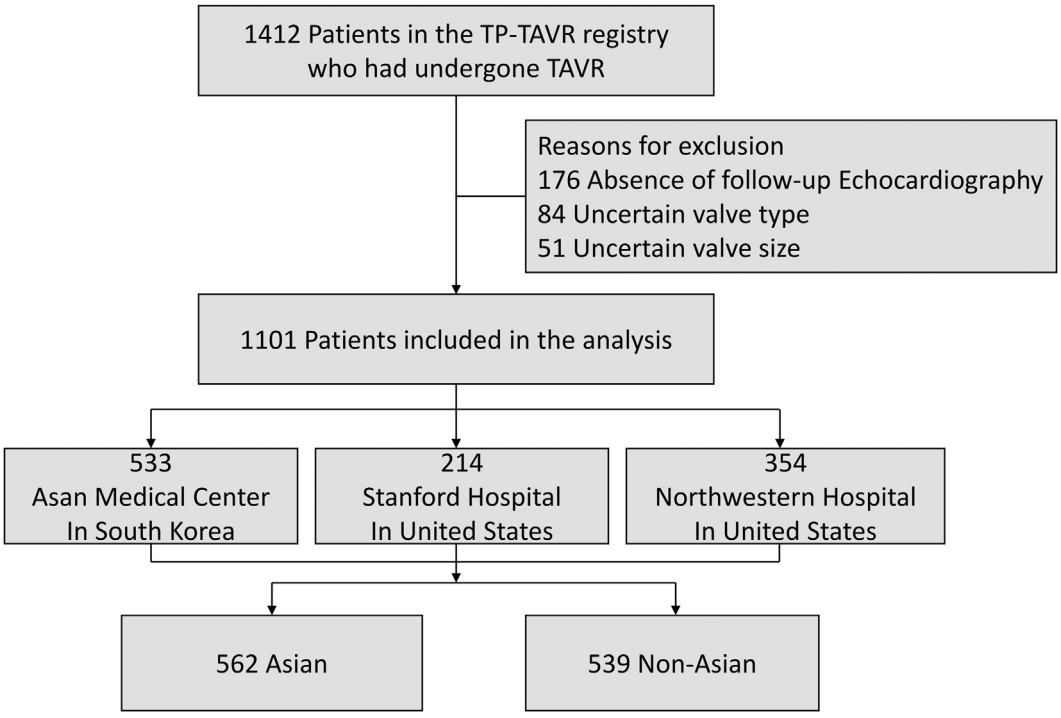
TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

At each participating center, a multidisciplinary heart team evaluated each patient's candidacy for TAVR or SAVR on the basis of age, underlying comorbidities, surgical risk, frailty status, anatomical characteristics, and preference. All TAVR procedures were conducted in accordance with local guidelines using standard techniques and were performed using commercially approved TAVR devices. Procedural planning, including the type (ie, balloon or self-expandable) and size of TAVR valve, access site, and use of preimplantation balloon aortic valvuloplasty, were also determined on the basis of the review of multimodality imaging by the local multidisciplinary heart team.

DEFINITION OF PPM. Echocardiographic evaluation was performed at baseline (before TAVR) and postprocedure (at discharge or within 1 month). EOA was assessed using the continuity equation and indexed to body surface area (BSA). PPM was assessed on postprocedural echocardiography according to the Valve Academic Research Consortium (VARC)-2 criteria (10). PPM was defined as: 1) moderate if indexed EOA was 0.85 to 0.65 cm^2/m^2 and severe if indexed EOA was <0.65 cm^2/m^2 in patients with body mass index (BMI) <30 kg/m^2; or 2) moderate if indexed EOA was 0.70 to 0.60 cm^2/m^2 and severe if indexed EOA was <0.60 cm^2/m^2 in patients with BMI ≥ 30 kg/m^2. In addition, as proposed in the Japanese cohort study (9), we also assessed the presence and severity of PPM according to more recent recommendations for imaging assessment from Lancellotti et al (11): for BMI ≥ 30 kg/m^2, not significant at >0.70 cm^2/m^2, moderate at 0.70 to 0.56 cm^2/m^2, and severe at ≤ 0.55 cm^2/m^2, and for BMI <30 kg/m^2, the same criteria as VARC-2. This criterion is the same as recommended by VARC-3 (12).

FIGURE 1 Study Flow Diagram of Patients



TAVR = transcatheter aortic valve replacement; TP-TAVR = Trans-Pacific TAVR Registry.

OUTCOMES AND DEFINITIONS. The primary outcome of the present study was a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure. Secondary outcomes included each component of the primary outcome, procedural complications, and in-hospital events including moderate to severe paravalvular leak, device success, conversion to open heart surgery, life-threatening or disabling bleeding, major vascular complication, new requirement for dialysis, new permanent pacemaker, myocardial infarction, new-onset atrial fibrillation, major or disabling stroke, or in-hospital death. All adverse outcomes were defined using the VARC-2 definitions (10). 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 (13). All components of the primary and secondary clinical outcomes were adjudicated by an independent group of clinicians who were unaware of the participating centers, race, or device type.

STATISTICAL ANALYSIS. The principal purpose of the present study was to determine whether there are race-based (Asian vs non-Asian) differences in the incidence and prognostic impact of PPM on clinical outcomes at 1 year. Continuous variables, which are presented as mean ± SD or median (IQR), were compared using Student's *t*-test or the Wilcoxon rank sum test depending on their distribution. Categorical and ordinal variables, which are presented as frequencies and percentages, were compared using the chi-square or Fisher exact test as appropriate. Kaplan-Meier survival curves were used to describe the overall 1-year adverse event rates by PPM existence within race groups, and the survival curves were compared using log-rank tests.

Independent predictors of PPM occurrence in patients undergoing TAVR were determined using multivariable logistic regression models, separately for the overall cohort and each cohort of Asians and non-Asians. As potential predictors, the logistic regression models included the following clinical, anatomical, and procedural variables: age (<80 or ≥80 years), BMI, BSA, prior bypass surgery, atrial fibrillation or flutter, chronic kidney disease, aortic valve area, mean aortic valve pressure gradient, bicuspid aortic valve, left ventricular ejection fraction (LVEF; ≤40% or >40%), moderate to severe tricuspid

regurgitation at baseline, valve perimeter, valve area, TAVR valve type (balloon vs self-expandable), and performance of postdilation.

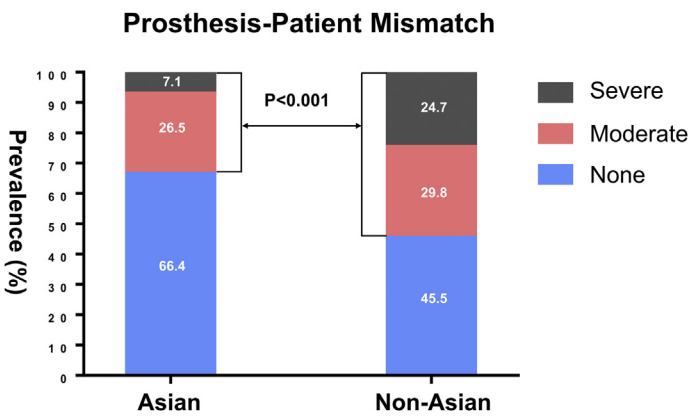
To assess whether racial differences modified the associations of PPM with the primary composite outcome and its individual components, marginal and interaction analyses were performed. In the marginal analyses, Cox regression models were used with the marginal effects of race (Asian vs non-Asian) and the presence or absence of PPM. In the interaction analyses, the interaction between race and PPM was further included. Race-specific HRs were estimated from the interaction models, while HRs for overall race and PPM effects were estimated from the marginal models. In the adjusted models, the following relevant covariates were included: age, BMI, Society of Thoracic Surgeons Predicted Risk of Mortality score, atrial fibrillation or flutter, chronic kidney disease, aortic valve area, mean pressure gradient, LVEF, and perimeter of the aortic valve at baseline. The proportional hazards assumptions were evaluated on the basis of Schoenfeld residuals, and there were no concerning violations. Sensitivity analysis was performed to assess the consistency of interracial differences in primary and secondary outcomes with the severity of PPM (none [referent] vs moderate vs severe) and with alternative criteria of Lancellotti et al (11) and VARC-3 (12). Finally, we evaluated the prognostic effect of PPM among key clinical subgroups stratified age group (>80 or ≤80 years), sex (male or female), obesity (BMI ≥30 kg/m^2 or BMI <30 kg/m^2), and left ventricular function (LVEF ≥50% or LVEF <50%).

All reported *P* values are 2-sided, and a *P* value <0.05 was considered to indicate statistical significance. No adjustment for multiple testing was undertaken. All statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

PATIENTS CHARACTERISTICS AND INCIDENCE OF PPM. Among 1,412 patients who were included in TP-TAVR during the study period, we excluded 176 patients without follow-up echocardiographic data, 84 without information on valve type, and 51 without information on valve size; thus, a total of 1,101 patients were included in the final analysis (**Figure 1**). Among them, 533 patients (48.4%) were enrolled in South Korea (Asan Medical Center); the remaining 568 patients (51.6%) were enrolled in the United States (214 at Stanford Hospital and 354 from Northwestern Memorial Hospital), of whom 464 (81.7%) were white, 10 (1.7%) were black, 35 (6.2%) were Hispanic, 29 (5.1%) were Asian, and 30 (5.3%) were of other race/ethnicity. Ultimately, 562 patients (51.0%) constituted the Asian population, and 539 (48.9%) constituted the non-Asian population.

FIGURE 2 Incidence and Pattern of Prosthesis-Patient Mismatch Between Asian and Non-Asian Groups According to the Valve Academic Research Consortium-2 Criteria



The occurrence of significant (moderate or severe) PPM according to racial groups (Asian vs non-Asian) is shown in **Figure 2**. The incidence of PPM was significantly lower in the Asian population (33.6% overall; moderate, 26.5%; severe, 7.1%) than in the non-Asian population (54.5% overall; moderate, 29.8%; severe, 24.7%) ($P < 0.001$). With different criteria, from Lancellotti et al (11) and VARC-3 (12), the prevalence and severity of PPM were identical in the Asian cohort, but the severe form of PPM was slightly less common in the non-Asian cohort (moderate, 32.8%; severe, 21.7%) (Supplemental Figure I).

Baseline characteristics of the patients according to race (Asian vs non-Asian) and the presence of PPM are shown in **Table 1**. There were significant interracial differences in baseline characteristics. In particular, Asian patients had lower values of BMI, BSA, and Society of Thoracic Surgeons score; had a higher prevalence of bicuspid aortic valve; had smaller aortic valve area and higher mean pressure gradient; and had smaller annular perimeter and area. Most baseline clinical and anatomical characteristics did not significantly differ between the PPM and non-PPM groups, except that the annular perimeter and area on computed tomography were smaller in the PPM group. Procedural characteristics, complications, and in-hospital events are summarized in **Table 2**. Asian patients had less frequent use of the largest prosthesis, higher uptake of conscious sedation, and a higher rate of balloon postdilation than did non-Asian

TABLE 1 Baseline Characteristics of Patients According to the Presence of PPM and Racial Group

	Asian Group				Non-Asian Group				
	Overall (N = 562)	PPM (n = 189)	No PPM (n = 373)	*P* Value	Overall (N = 539)	PPM (n = 294)	No PPM (n = 245)	*P* Value	*P* Value[a]
Demographics and clinical risk factors									
Age, y	80.1 ± 5.6	79.8 ± 5.5	80.2 ± 5.7	0.45	79.5 ± 9.5	78.8 ± 9.9	80.3 ± 8.8	0.07	0.22
Male	286 (50.9)	97 (51.3)	189 (50.7)	0.88	310 (57.5)	178 (60.5)	132 (53.9)	0.12	0.03
BMI, kg/m^2	24.0 ± 3.6	24.6 ± 3.4	23.7 ± 3.7	0.007	28.5 ± 6.6	28.5 ± 6.6	28.4 ± 6.6	0.87	<0.001
BMI ≥30 kg/m^2	28 (5.0)	4 (2.1)	24 (6.4)	0.03	174 (32.3)	81 (27.6)	93 (38.0)	0.01	<0.001
BSA, m^2	1.60 ± 0.17	1.58 ± 0.17	1.63 ± 0.16	<0.001	1.91 ± 0.29	1.93 ± 0.28	1.88 ± 0.30	0.03	<0.001
STS score, %	3.3 (2.9-4.9)	3.0 (2.1-4.6)	3.4 (2.4-5.0)	0.12	4.1 (3.0-6.8)	4.2 (3.0-6.5)	4.1 (3.0-7.0)	0.70	<0.001
NYHA functional class III or IV	199 (35.4)	65 (34.4)	134 (35.9)	0.72	294 (54.5)	156 (53.1)	138 (56.3)	0.45	<0.001
Diabetes	297 (52.8)	98 (51.9)	199 (53.4)	0.74	186 (34.5)	108 (36.7)	78 (31.8)	0.23	<0.001
Hypertension	490 (87.2)	164 (86.8)	326 (87.4)	0.83	445 (82.6)	245 (83.3)	200 (81.6)	0.60	0.03
Prior MI	46 (8.2)	18 (9.5)	28 (7.5)	0.41	14 (2.6)	7 (2.4)	7 (2.9)	0.73	<0.001
Hyperlipidemia	421 (74.9)	146 (77.2)	275 (73.7)	0.36	382 (70.9)	214 (72.8)	168 (68.6)	0.28	<0.001
Current smoker	26 (4.6)	8 (4.2)	18 (4.8)	0.75	64 (11.9)	34 (11.6)	30 (12.2)	0.81	0.132
Prior PCI	154 (27.4)	51 (27.0)	103 (27.6)	0.87	163 (30.2)	96 (32.7)	67 (27.3)	0.182	0.30
Prior CABG	28 (5.0)	13 (6.9)	15 (4.0)	0.14	94 (17.4)	59 (20.1)	35 (14.3)	0.08	<0.001
Prior stroke	76 (13.5)	26 (13.8)	50 (13.4)	0.91	56 (10.4)	29 (9.9)	27 (11.0)	0.66	0.11
Atrial fibrillation	65 (11.6)	23 (12.2)	42 (11.3)	0.75	213 (39.5)	127 (43.2)	86 (35.1)	0.06	<0.001
Peripheral artery disease	18 (3.2)	6 (3.2)	12 (3.2)	0.98	113 (21.0)	64 (21.8)	49 (20.0)	0.62	<0.001
Chronic lung disease	61 (10.9)	17 (9.0)	44 (11.8)	0.31	82 (15.2)	44 (15.0)	38 (15.5)	0.86	0.03
Chronic kidney disease[b]	421 (74.9)	133 (70.4)	288 (77.2)	0.08	158 (29.3)	92 (31.3)	66 (26.9)	0.27	<0.001
End-stage renal disease	21 (3.7)	10 (5.3)	11 (2.9)	0.17	20 (3.7)	14 (4.8)	6 (2.4)	0.16	0.98
Echocardiographic findings									
Bicuspid aortic valve	57 (10.1)	13 (6.9)	44 (11.8)	0.07	25 (4.6)	11 (3.7)	14 (5.7)	0.278	0.001
Aortic valve area, mm^2	0.60 (0.50-0.71)	0.60 (0.49-0.70)	0.60 (0.51-0.72)	0.13	0.70 (0.59-0.84)	0.70 (0.56-0.80)	0.74 (0.60-0.90)	<0.001	<0.001
Mean PG, mm Hg	57 ± 21	57 21	57 ± 21	0.82	45 ± 14	46 ± 15	44 ± 14	0.053	<0.001
LV ejection fraction, %	58 ± 11	57 ± 12	58 ± 11	0.35	58 ± 13	57 ± 13	59 ± 13	0.08	0.48
Moderate to severe AR	107 (19.0)	33 (17.5)	74 (19.8)	0.50	58 (10.8)	30 (10.2)	28 (11.4)	0.65	<0.001
Moderate to severe MR	66 (11.7)	27 (14.3)	39 (10.5)	0.18	113 (21.0)	62 (21.1)	51 (20.8)	0.94	<0.001
Moderate to severe TR	34 (6.0)	19 (10.1)	15 (4.0)	0.005	84 (15.6)	49 (16.7)	35 (14.3)	0.45	<0.001
CT findings									
Annular perimeter, mm	75.7 ± 7.5	73.9 ± 7.7	76.6 ± 7.2	<0.001	78.4 ± 8.4	77.6 ± 8.4	79.3 ± 8.2	0.03	<0.001
Annular area, mm^2	441 ± 87	420 ± 86	451 ± 86	<0.001	461 ± 95	454 ± 95	469 ± 95	0.06	<0.001

Values are mean ± SD, n (%), or median (IQR). [a]*P* values for comparison between the Asian group and the non-Asian group. [b]Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2.

AR = aortic regurgitation; AS = aortic stenosis; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; CT = computed tomographic; LV = left ventricular; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PG = pressure gradient; PPM = prosthesis-patient mismatch; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation.

patients. Asian patients had a high incidence of major bleeding and vascular complication, whereas implantation of permanent pacemakers was more common in non-Asian patients. Patients with PPM had a higher proportion of valve-in-valve procedures, a smaller size of prosthesis, and a lower rate of postdilation compared with those without PPM. Postprocedural echocardiographic findings are shown in Table 3. Compared with non-Asian patients, Asian patients had higher peak transaortic velocity and mean pressure gradient but had a larger indexed EOA.

INDEPENDENT PREDICTORS OF PPM. By multivariable analysis in the overall population, the odds of having PPM were higher for non-Asian race, greater BMI, greater BSA, history of prior bypass surgery, smaller aortic valve area at baseline, and no balloon postdilatation (Table 4). In the Asian population, greater BMI, greater BSA, and the presence of moderate to severe tricuspid regurgitation at baseline were confirmed as significant predictors of PPM occurrence. In the non-Asian population, younger age (<80 years), greater BSA, and smaller aortic valve area at baseline were independent predictors of PPM occurrence.

CLINICAL OUTCOMES. The cumulative incidences of the primary composite outcome and its individual component according to the presence of PPM and race (Asian vs non-Asian) during a median follow-up duration of 14.7 months (IQR: 11.0-25.8 months) are shown in Figure 3 and Supplemental Table I. At 1 year, the incidence of the primary composite outcome of

TABLE 2 Procedural Characteristics and In-Hospital Outcomes According to the Presence of PPM and Racial Group

	Asian Group				Non-Asian Group				
	Overall (N = 562)	PPM (n = 189)	No PPM (n = 373)	*P* Value	Overall (N = 539)	PPM (n = 294)	No PPM (n = 245)	*P* Value	*P* Value[a]
Procedural characteristics									
Procedure type				<0.001				0.07	0.07
Native	545 (97.0)	175 (92.6)	370 (99.2)		511 (94.8)	274 (93.2)	237 (96.7)		
Valve-in-valve	17 (3.0)	14 (7.4)	3 (0.8)		28 (5.2)	20 (6.8)	8 (3.3)		
Access site				0.91				0.009	0.99
Transfemoral	539 (95.9)	181 (95.8)	358 (96.0)		517 (95.9)	288 (98.0)	229 (93.5)		
Nontransfemoral	23 (4.1)	8 (4.2)	15 (4.0)		22 (4.1)	6 (2.0)	16 (6.5)		
Valve type				0.55				0.27	0.12
Balloon expandable	466 (82.9)	151 (79.9)	315 (84.5)		465 (86.3)	258 (87.8)	207 (84.5)		
SAPIEN XT	43 (7.7)	11 (5.8)	32 (8.6)		0 (0.0)	0 (0.0)	0 (0.0)		
APIEN 3	423 (75.3)	140 (74.1)	283 (75.9)		465 (86.3)	258 (87.8)	207 (84.5)		
Self-expandable	96 (17.1)	38 (20.1)	58 (15.5)		74 (13.7)	36 (12.2)	38 (15.5)		
CoreValve	9 (1.6)	3 (1.6)	6 (1.6)		13 (2.4)	4 (1.4)	9 (3.7)		
Evolut R	75 (13.3)	29 (15.3)	46 (12.3)		56 (10.4)	29 (9.9)	27 (11.0)		
Evolut PRO	7 (1.2)	4 (2.1)	3 (0.8)		5 (0.9)	3 (1.0)	2 (0.8)		
Lotus	5 (0.9)	2 (1.1)	9 (0.8)		0 (0.0)	0 (0.0)	0 (0.0)		
Size of the SAPIEN series				<0.001				0.08	0.80
20 mm	8 (1.4)	5 (2.6)	3 (0.8)		17 (3.2)	13 (4.4)	4 (1.6)		
23 mm	142 (25.3)	61 (32.3)	81 (21.7)		149 (27.6)	87 (29.6)	62 (25.3)		
26 mm	233 (41.5)	67 (35.4)	166 (44.5)		194 (36.0)	104 (35.4)	90 (36.7)		
29 mm	81 (14.4)	17 (9.0)	64 (17.2)		105 (19.5)	54 (18.4)	51 (20.8)		
Size of the CoreValve series				0.18				0.06	0.02
23 mm	13 (2.3)	8 (4.2)	5 (1.3)		11 (2.0)	8 (2.7)	3 (1.2)		
26 mm	45 (8.0)	15 (7.9)	30 (8.0)		24 (4.5)	9 (3.1)	15 (6.1)		
29 mm	27 (4.8)	12 (6.3)	15 (4.0)		27 (5.0)	17 (5.8)	10 (4.1)		
≥31 mm	7 (1.2)	2 (1.0)	5 (1.3)		12 (2.2)	2 (0.7)	10 (4.1)		
Type of anesthesia				0.89				<0.001	<0.001
Conscious sedation	445 (79.2)	149 (78.8)	296 (79.4)		292 (54.2)	139 (47.3)	153 (62.4)		
General	117 (20.8)	40 (21.2)	77 (20.6)		247 (45.8)	155 (52.7)	92 (37.6)		
Postdilation performed	365 (64.9)	111 (58.7)	254 (68.1)	0.03	120 (22.3)	54 (18.4)	66 (26.9)	0.02	<0.001
Duration of hospitalization, d	4.0 (3.0-7.0)	4.0 (3.0-7.0)	4.0 (3.0-6.0)	0.12	4.0 (3.0-5.0)	3.0 (4.0-2.0)	4.0 (3.0-5.0)	0.049	<0.001
Procedure complications or in-hospital events									
Moderate to severe paravalvular leakage	20 (3.6)	4 (2.1)	16 (4.3)	0.19	1 (0.2)	0 (0.0)	1 (0.4)	0.46	<0.001
Device success[b]	474 (84.3)	143 (75.7)	331 (88.7)	<0.001	488 (90.5)	252 (85.7)	236 (96.3)	<0.001	0.002
Conversion to open heart surgery	0 (0.0)	0 (0.0)	0 (0.0)	>0.99	3 (0.6)	1 (0.3)	2 (0.8)	0.59	0.12
Life-threatening/disabling bleeding	23 (4.1)	8 (4.2)	15 (4.0)	0.91	4 (0.7)	2 (0.7)	2 (0.8)	>0.99	<0.001
Major vascular complication	24 (4.3)	9 (4.8)	15 (4.0)	0.68	8 (1.5)	2 (0.7)	6 (2.4)	0.15	0.006
New requirement for dialysis	7 (1.2)	4 (2.1)	3 (0.8)	0.23	0 (0.0)	0 (0.0)	0 (0.0)	>0.99	0.02
New permanent pacemaker	32 (5.7)	11 (5.8)	21 (5.6)	0.93	69 (12.8)	33 (11.2)	36 (14.7)	0.23	<0.001
Myocardial infarction	6 (1.1)	3 (1.6)	3 (0.8)	0.41	3 (0.6)	1 (0.3)	2 (0.8)	0.59	0.51
New-onset atrial fibrillation	11 (2.0)	3 (1.6)	8 (2.1)	0.76	19 (3.5)	13 (4.4)	6 (2.4)	0.22	0.11
Major or disabling stroke	15 (2.7)	6 (3.2)	9 (2.4)	0.60	11 (2.0)	6 (2.0)	5 (2.0)	>0.99	0.49
In-hospital death	3 (0.5)	0 (0.0)	3 (0.5)	0.55	0 (0.0)	0 (0.0)	0 (0.0)	>0.99	0.25

Values are n (%) or median (IQR). [a]*P* values for comparison between the Asian group and the non-Asian group. [b]Composite end point (successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system; correct position of the device in the proper anatomical location; intended performance of the prosthetic heart valve [aortic valve area >1.2 cm^2 and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation]; only 1 valve implanted in the proper anatomical location.

PPM = prosthesis-patient mismatch.

death, stroke, or rehospitalization was 27.5% and 28.1% in the PPM group and the non-PPM group, respectively (log-rank $P = 0.69$). There were no significant differences in the 1-year rates of all-cause death (PPM vs no PPM, 6.2% vs 7.3%; $P = 0.46$), stroke (2.8% vs 3.9%; $P = 0.34$), or rehospitalization (23.7% vs 23.6%; $P = 0.87$). This trend was also consistent in the subpopulations stratified by race.

The results of unadjusted and adjusted marginal and interaction analyses for the primary composite outcome and its individual components according to PPM and race are summarized in Table 5. After

TABLE 3 Postprocedural Echocardiographic Data and Pattern of PPM According to Racial Groups

	Asian Group				Non-Asian Group				
	Overall (N = 562)	PPM (n = 189)	No PPM (n = 373)	*P* Value	Overall (N = 539)	PPM (n = 294)	No PPM (n = 245)	*P* Value	*P* Value[a]
LV ejection fraction, %	59 ± 9	59 ± 9	60 ± 9	0.16	58 ± 12	57 ± 12	59 ± 12	0.04	0.02
EOA, cm^2	1.50 ± 0.37	1.18 ± 0.18	1.67 ± 0.33	<0.001	1.52 ± 0.49	1.22 ± 0.25	1.88 ± 0.45	<0.001	0.56
Indexed EOA, cm^2/m^2	0.94 ± 0.22	0.73 ± 0.10	1.05 ± 0.18	<0.001	0.80 ± 0.25	0.63 ± 0.12	1.01 ± 0.20	<0.001	<0.001
Moderate PPM[a]	149 (26.5)	149 (78.8)	0 (0.0)	NA	161 (29.8)	161 (54.8)	0 (0.0)	NA	NA
Severe PPM[a]	40 (7.1)	40 (21.2)	0 (0.0)	NA	144 (24.7)	133 (45.2)	0 (0.0)	NA	NA
Peak velocity, m/s	2.5 ± 0.5	2.7 ± 0.5	2.4 ± 0.4	<0.001	2.4 ± 0.5	2.5 ± 0.5	2.2 ± 0.5	<0.001	<0.001
Pressure gradient, mm Hg	13 ± 5	16 ± 6	12 ± 4	<0.001	12 ± 6	14 ± 6	10 ± 4	<0.001	<0.001
≥20	68 (12.1)	43 (22.8)	25 (6.7)	<0.001	47 (8.7)	41 (13.9)	6 (2.4)	<0.001	0.70
≥40	1 (0.2)	1 (0.5)	0 (0.0)	0.34	0 (0.0)	0 (0.0)	0 (0.0)	>0.99	0.51
Paravalvular leakage, moderate to severe	20 (3.6)	4 (2.1)	16 (4.3)	0.19	1 (0.2)	0 (0.0)	1 (0.4)	0.46	0.45
Moderate to severe MR	28 (5.0)	10 (5.3)	18 (4.8)	0.81	26 (4.8)	13 (4.4)	13 (5.3)	0.63	0.28
Moderate to severe TR	26 (4.6)	9 (4.8)	17 (4.6)	0.91	34 (6.3)	19 (6.5)	15 (6.1)	0.87	0.51

Values are mean ± SD or n (%). [a]*P* value for comparison between the Asian group and the non-Asian group.
EOA = effective orifice area; NA = not available; other abbreviations as in Table 1.

multivariable adjustment for important clinical, hemodynamic, and anatomical covariates, the risks for the primary composite of death, stroke, or rehospitalization did not significantly differ between the PPM and non-PPM groups in the overall cohort (HR: 0.95; 95% CI: 0.74-1.21; $P = 0.66$), in the Asian cohort (HR: 1.07; 95% CI: 0.74-1.55; $P = 0.71$), and in the non-Asian cohort (HR: 0.86; 95% CI: 0.63-1.19; $P = 0.37$). Moreover, these race-specific HRs were not significantly different by race (P for interaction = 0.39). Consistently, the race-specific HRs for the individual events of all-cause mortality, stroke, and rehospitalization were <1 (lower risk in patients with PPM than in those with no PPM) among non-Asians, whereas those HRs were >1 among Asians. However, none of the comparisons reached statistical significance.

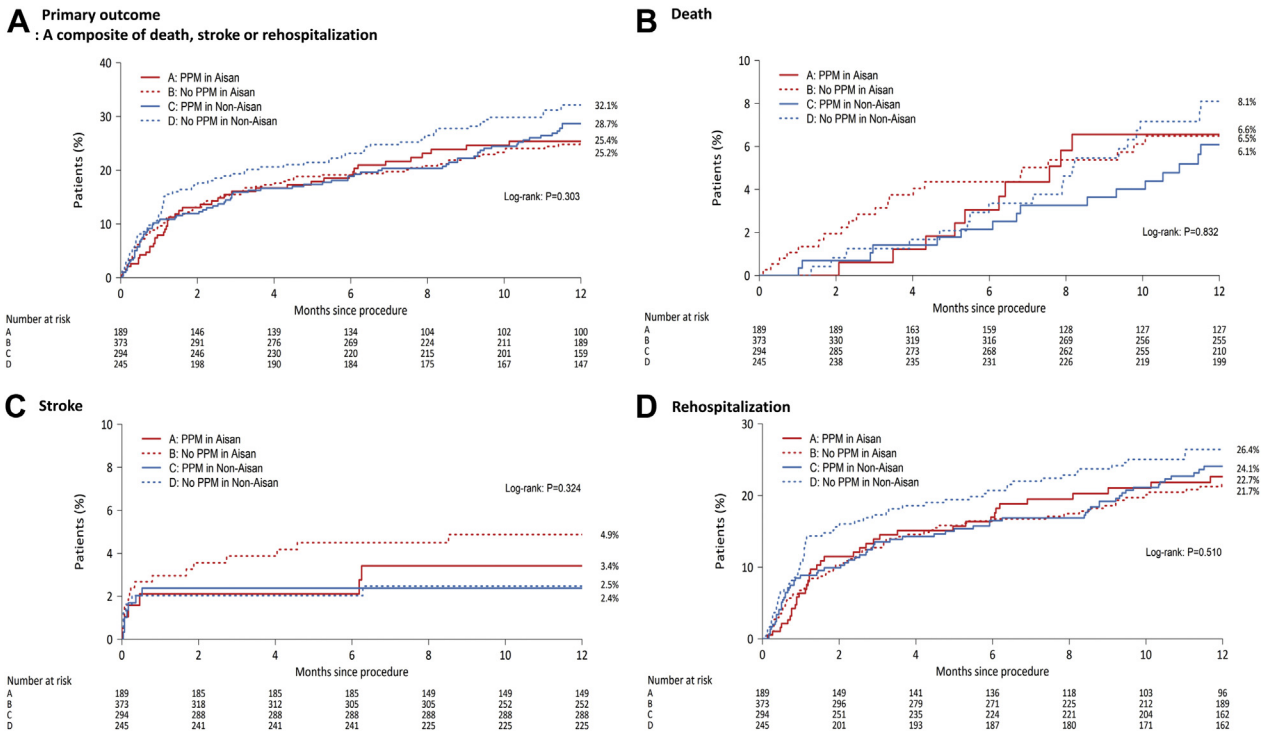
In sensitivity analysis comparing the severity of PPM (none vs moderate vs severe), we did not

TABLE 4 Multivariate Analyses for Independent Predictors of Moderate or Severe Prosthesis-Patient Mismatch

	Overall Group (N = 1,101)		Asian Group (n = 562)		Non-Asian Group (n = 539)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Race: Asian vs non-Asian (referent)	0.43 (0.31-0.60)	<0.001	–	–	–	–
Age ≥80 y	0.81 (0.61-1.06)	0.12	0.98 (0.66-1.46)	0.92	0.66 (0.45-0.98)	0.04
BMI, kg/m^2	1.03 (1.01-1.05)	0.046	1.06 (1.01-1.12)	0.03	1.00 (0.97-1.03)	0.87
BSA, per 0.1 m^2	1.43 (1.30-1.56)	<0.001	1.56 (1.36-1.79)	<0.001	1.37 (1.22-1.53)	<0.001
Prior CABG	1.52 (1.01-2.30)	0.047	1.71 (0.75-3.91)	0.21	1.44 (0.88-2.45)	0.14
Atrial fibrillation or flutter	1.26 (0.92-1.72)	0.15	0.90 (049-1.64)	0.73	1.47 (1.00-2.15)	0.05
Chronic kidney disease	0.97 (0.73-1.30)	0.85	0.74 (0.47-1.16)	0.18	1.27 (0.85-1.89)	0.24
Aortic valve area	0.27 (0.12-0.60)	0.001	0.22 (0.05-1.02)	0.053	0.29 (0.11-0.75)	0.01
Mean pressure gradient, per 10 mm Hg	0.99 (0.91-1.07)	0.79	0.94 (0.84-1.05)	0.29	1.09 (0.95-1.26)	0.23
Bicuspid aortic valve	0.67 (0.40-1.13)	0.13	0.79 (0.40-1.57)	0.50	0.63 (0.27-1.45)	0.28
LV ejection fraction ≤40%	0.76 (0.49-1.18)	0.22	0.76 (0.39-1.48)	0.43	0.80 (0.44-1.46)	0.47
Moderate to severe TR at baseline	1.29 (0.84-1.99)	0.24	2.52 (1.16-5.46)	0.02	0.97 (0.58-1.63)	0.91
Valve perimeter	0.94 (0.88-1.01)	0.10	0.97 (0.87-1.09)	0.64	0.94 (0.86-1.02)	0.11
Valve area, per 100 mm^2	1.22 (0.67-2.23)	0.52	0.81 (0.30-2.21)	0.68	1.45 (0.70-2.97)	0.31
Balloon-expandable THV	1.37 (0.94-2.02)	0.11	1.31 (0.76-2.26)	0.32	1.60 (0.92-2.78)	0.10
Postdilation performed	0.74 (0.55-0.99)	0.049	0.87 (0.58-1.33)	0.53	0.72 (0.46-1.12)	0.14

OR = odds ratio; THV = transcatheter heart valve; other abbreviations as in Table 1.

FIGURE 3 **Time-to-Event Curves for the Primary Composite Outcome and the Individual Components of the Primary Composite Outcome at 1 Year**



Shown are Kaplan-Meier estimates of the rate of the primary composite outcome **(A)** and the individual components of the primary composite outcome, which are death from any cause **(B)**, stroke **(C)**, and rehospitalization **(D)**, between Asian and non-Asian populations. The *P* values were obtained from the overall log-rank test. PPM indicates prosthesis-patient mismatch. *P* values were obtained from the overall log-rank test. PPM = prosthesis-patient mismatch.

observe any significant differences according to the severity of PPM in the overall group and in each racial group (Supplemental Table II). Using the criteria of Lancellotti et al (11) and VARC-3 (12), overall findings were consistent; the 1-year risk for the primary composite outcome and its individual components was similar according to the severity of PPM without significant interaction between racial groups and the clinical impact of PPM (Supplemental Table III). Finally, the adjusted HRs for the primary outcome among the key clinical subgroups are illustrated in Supplemental Figure II. The 1-year adjusted risks for the primary composite outcome between PPM and non-PPM were consistent across multiple subgroups in overall cohort and in each cohort of Asian and non-Asian.

DISCUSSION

In this registry-based, multicenter, international study of patients with severe AS undergoing TAVR, we examined the incidence, predictors, and prognostic impact of PPM according to racial groups (Asian vs non-Asian). The major findings were as follows (**Central Illustration**): 1) PPM on post-TAVR echocardiography was less common in the Asian group than in the non-Asian group; 2) we identified several key predictors of PPM, which were slightly different between the Asian and non-Asian groups; 3) the 1-year rates of the primary composite outcome of death, stroke, or rehospitalization were similar between the PPM and non-PPM groups, which was consistent among the Asian and non-Asian groups; and 4) after multivariable adjustment, the risk for the primary composite outcome did not significantly differ between the PPM and non-PPM groups, without a significant interaction between PPM and racial group on clinical outcomes.

Asian populations have several different anatomical and procedural characteristics compared with non-Asian populations, such as lower BMI, lower BSA, smaller aortic valve annular size, and subsequent use of smaller TAVR prostheses (14-16). In this context, the incidence and pattern of PPM might be more

TABLE 5 Marginal and Interaction Analyses for Clinical Outcomes at 1 Year According to the Presence of PPM and Racial Group[a]

	Unadjusted HR (95% CI)				Adjusted HR (95% CI)[b]			
	Marginal Analysis		Interaction Analysis		Marginal Analysis		Interaction Analysis	
	Overall	Asian	Non-Asian	*P* Value for Interaction	Overall	Asian	Non-Asian	*P* Value for Interaction
Primary composite outcome[c]				0.48				0.39
No PPM	Referent	Referent	Referent		Referent	Referent	Referent	
PPM	0.91 (0.72-1.16)	1.01 (0.70-1.46)	0.85 (0.62-1.16)		0.95 (0.74-1.21)	1.07 (0.74-1.55)	0.86 (0.63-1.19)	
P value	0.45	0.97	0.30		0.66	0.71	0.37	
Death				0.61				0.42
No PPM	Referent	Referent	Referent		Referent	Referent	Referent	
PPM	0.82 (0.50-1.36)	0.95 (0.45-2.03)	0.73 (0.38-1.42)		0.79 (0.47-1.33)	1.01 (0.47-2.16)	0.66 (0.34-1.30)	
P value	0.44	0.90	0.36		0.38	0.99	0.23	
Stroke				0.63				NA
No PPM	Referent	Referent	Referent		Referent	Referent	Referent	
PPM	0.80 (0.40-1.60)	0.69 (0.27-1.76)	0.98 (0.33-2.92)		NA	NA	NA	
P value	0.53	0.44	0.97					
Rehospitalization			0.44				0.36	
No PPM	Referent	Referent	Referent		Referent	Referent	Referent	
PPM	0.94 (0.73-1.23)	1.06 (0.72-1.57)	0.86 (0.61-1.22)		1.00 (0.76-1.30)	1.15 (0.77-1.71)	0.90 (0.63-1.27)	
P value	0.67	0.77	0.40		0.98	0.50	0.54	

[a]The marginal analyses and interaction analyses included prosthesis-patient mismatch (PPM) and race in the Cox proportional hazards regression models without and with their interaction term, respectively. HRs are for the PPM group compared with the no-PPM group. [b]Multivariable models were adjusted for age, body mass index, Society of Thoracic Surgeon risk score, atrial fibrillation or flutter, chronic kidney disease, aortic valve area, mean pressure gradient, left ventricular ejection fraction, and perimeter of aortic valve at baseline. [c]Primary composite outcome was defined as a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure.

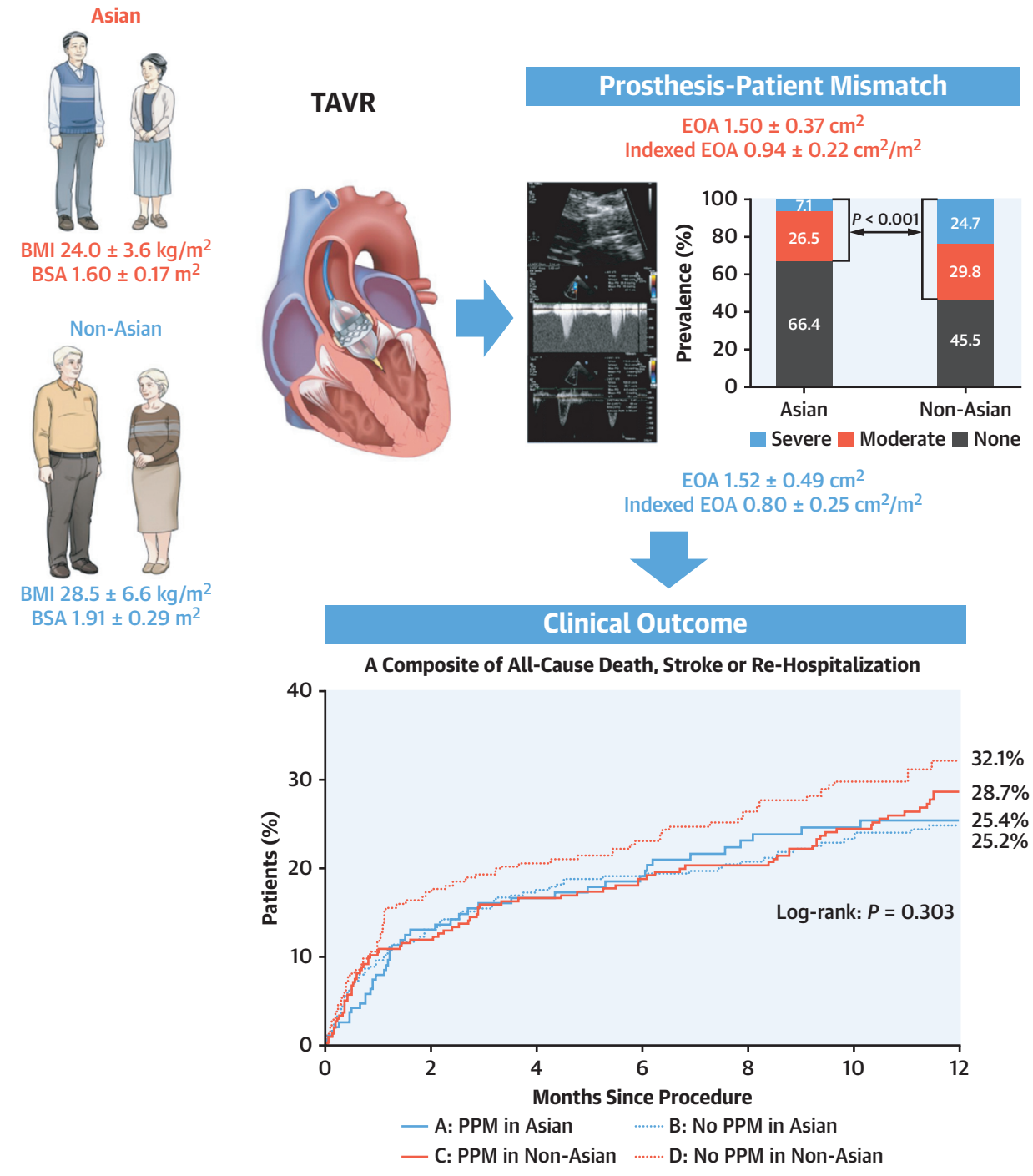
concerning but still poorly understood in Asian populations compared with Western populations. A recent report from the OCEAN-TAVI (Optimized Transcatheter Valvular Intervention) registry showed that the incidence of PPM was relatively low (overall, 9.6%; moderate, 8.9%; severe, 0.7%), and PPM was not a risk factor for mid-term mortality in a Japanese cohort of TAVR patients (9). However, until recently, there were no data directly comparing different racial groups; the present study is the first to investigate whether there is an interracial (Asian vs non-Asian) difference with regard to the incidence of PPM and its clinical impact.

The main novel finding of this study directly comparing different racial groups was that significant PPM was unexpectedly less frequent in Asian patients, who have small aortic anatomies but also small body size compared with non-Asian patients. Previous studies showed that aortic valve diameters were closely related to BSA (17). This correlation between BSA and aortic valve size might explain why Asians had smaller aortic valve size than non-Asians. Although the Asian cohort had relatively smaller BSA and smaller aortic annuli, the relation between aortic valve size and body size might be different in Asian and Western populations, which could explain the difference in PPM frequencies. Therefore, small prostheses per se might not always result in inferior hemodynamic status and a higher incidence of PPM.

The prevalence of severe PPM among the non-Asian cohort in our registry appears to be higher compared with other studies among Western populations (8). A recent study demonstrated that the prevalence of PPM after TAVR was highly variable (approximately 10%-60%) among studies (18). Although it is difficult to explain the discrepancy between the non-Asian cohort included in the present study and the other registries, it might be explained in part by differences in patient characteristics, procedural characteristics, and intersite variability for echocardiographic measurement.

Several studies have reported key determinants of PPM following TAVR; the important predictors of PPM were larger BSA and BMI, female sex, nonwhite/Hispanic race, younger age, prior coronary artery bypass graft surgery, valve-in-valve procedure, left ventricular dysfunction, atrial fibrillation or flutter, severe mitral or tricuspid regurgitation, small annular area and aortic valve area, small prosthesis size, and balloon postdilation (6,7-9,19). The major predictors of PPM in TP-TAVR were similar to those from prior studies. In a prior study, the use of self-expandable TAVR valves was associated with a lower incidence of PPM compared with balloon-expandable valves (20). In our study, the type of TAVR device was not

CENTRAL ILLUSTRATION **Occurrence and Prognostic Impact of Prosthesis-Patient Mismatch Between Asian and Non-Asian Groups**



Park, H. et al. J Am Coll Cardiol Intv. 2021;14(24):2670–2681.

BMI = body mass index; BSA = body surface area; EOA = effective orifice area; PPM = prosthesis-patient mismatch; TAVR = transcatheter aortic valve replacement.

associated with a higher incidence of PPM. However, this result should be interpreted with caution, because the participating centers used mostly balloon-expandable valves in this registry (>80%).

Numerous studies have reported that PPM after SAVR is associated with a higher risk for mortality and adverse clinical outcomes (21-24). TAVR has been shown to result in larger EOA and a lower rate of PPM compared with SAVR (25). However, the prognostic impact of PPM on clinical outcomes has been highly conflicting in a series of TAVR studies (5-9,26). Some studies showed that PPM after TAVR was associated with increased mortality and adverse cardiac events (5-8). In contrast, other studies have shown that PPM following TAVR was not associated with an increased risk for mortality and clinical outcomes (9,26). In our registry, we found that the 1-year risk for the primary composite of death, stroke, or rehospitalization was similar between the PPM and non-PPM groups regardless of race. The differential prognostic impact of PPM following TAVR might be explained in part by the varying sizes of the study populations, different characteristics of TAVR patients, differences in the practice pattern of the procedures, and different types or sizes of TAVR devices among the studies. Also, considering the limited duration of clinical follow-up in our study, further large studies with extended (at least 3-5 years) follow-up are required to delineate the true long-term prognostic effect of PPM after TAVR.

STUDY LIMITATIONS. First, this was a nonrandomized, observational study, which is subject to potential selection and ascertainment biases. Therefore, the overall findings of the present study should be interpreted as exploratory and hypothesis generating only.

Second, because of the multicenter design of the registry, intersite variability in care may also exist, such as the selection of eligible patients for TAVR, TAVR technique, and post-TAVR surveillance and care.

Third, the participating centers used mainly balloon-expandable valves and included patients who underwent TAVR at high-volume centers; thus, the results may not be generalizable to other clinical settings.

Fourth, although there was no core laboratory evaluation for echocardiographic or computed tomographic data, all results were reported from high-volume, academic medical centers. However, we cannot exclude that the difference in the incidence of PPM between Asians and non-Asians was at least in part related to intersite variability in the measurement of EOA.

Fifth, given the relatively small sample size and short-term follow-up, our study was underpowered to detect the clinically relevant differences in hard clinical endpoints in patients with and without PPM.

Last, further analyses may be clinically relevant to determine whether the presence of PPM is associated with differences in left ventricular mass regression or remodeling or soft clinical outcomes (ie, improvement in quality of life, change in symptoms, or change in frailty).

CONCLUSIONS

In this multiracial registry-based study of patients who underwent TAVR for severe AS, Asian patients had a significantly lower incidence of PPM than did non-Asian patients. Several race-specific predictors for PPM were identified. The risk for the primary composite of death, stroke, or rehospitalization and mortality at 1 year was similar between the PPM and no-PPM groups, regardless of racial group. Further large-scale clinical studies with long-term follow-up are mandatory to evaluate the true prognostic impact of PPM post-TAVR and to determine how this phenomenon is applied in decision making regarding valve choice and future risk stratification.

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PERSPECTIVES

WHAT IS KNOWN? Although several studies have shown conflicting results with regard to the incidence and clinical impact of PPM in patients undergoing TAVR, it is unknown whether there are interracial differences in pattern and prognostic value of PPM.

WHAT IS NEW? In this international registry, the incidence of PPM was significantly lower in the Asian population than in the non-Asian population. PPM compared with no PPM was not associated with a higher risk for the primary composite outcome of death, stroke, or rehospitalization at 1 year, which was consistent in Asians and non-Asians.

WHAT IS NEXT? Further long-term follow-up studies are required to define universal and clinically relevant PPM and address its long-term clinical outcomes and related racial disparity.

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APPENDIX For supplemental tables, figures, and references, please see the online version of this paper.