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STRUCTURAL

# Incidence, Predictors, and Clinical Impact of Prosthesis–Patient Mismatch Following Transcatheter Aortic Valve Replacement in Asian Patients

## The OCEAN-TAVI Registry

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## ABSTRACT

**OBJECTIVES** The authors sought to investigate the prevalence, risk factors, and mid-term mortality in Asian patients with prosthesis-patient mismatch (PPM) after transcatheter aortic valve replacement (TAVR).

**BACKGROUND** Little information is available on PPM after TAVR in Asian patients.

**METHODS** The authors included 1,558 patients enrolled in the OCEAN-TAVI (Optimized transCathEter vAlvular iNtervention) Japanese multicenter registry from October 2013 to July 2016 after excluding patients who died following TAVR before discharge. PPM was defined as moderate if $\geqq 0.65$ but $\leqq 0.85$ cm$^2$/m$^2$, or severe if $<0.65$ cm$^2$/m$^2$ at the indexed effective orifice area by post-procedural echocardiography.

**RESULTS** Of the 1,546 patients, moderate and severe PPM were observed in 138 (8.9%) and 11 (0.7%) patients, respectively. These 149 patients were included in the PPM group. The median age and body surface area were 85 years (interquartile range [IQR]: 81 to 88 years) and 1.41 m$^2$ (IQR: 1.30 to 1.53 m$^2$), respectively. In our multivariate analysis, younger age, larger body surface area, smaller aortic valve area, smaller annulus area, no balloon post-dilatation, and use of Edwards Sapien 3 (Edwards Lifesciences, Irvine, California) were identified as independent predictors of PPM. The estimated cumulative all-cause mortality at 1 year using the Kaplan-Meier method was similar between the PPM and non-PPM groups (10.2% vs. 8.3%; log-rank; $p = 0.41$).

**CONCLUSIONS** The low prevalence of PPM and mortality at 1 year in patients with PPM after TAVR in this Japanese cohort implies that PPM is not a risk factor for mid-term mortality in Asian patients who have undergone TAVR.
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**ABBREVIATIONS AND ACRONYMS**

**AR** = aortic valve regurgitation

**AVA** = aortic valve area

**BMI** = body mass index

**BSA** = body surface area

**CO** = cardiac output

**IQR** = interquartile range

**PPM** = prosthesis-patient mismatch

**SAVR** = surgical aortic valve replacement

**TAVR** = transcatheter aortic valve replacement

**THV** = transcatheter heart valve

**VARC** = Valve Academic Research Consortium

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area of a normally functioning implanted valve prosthesis is small in relation to the patient's body size. It has been reported that the incidence of PPM after surgical aortic valve replacement (SAVR) ranges from 20% to 70% (1-6). Previous studies have demonstrated that severe PPM impairs long-term survival, and that moderate PPM may be associated with worse long-term survival (1-6).

Transcatheter aortic valve replacement (TAVR) is an alternative treatment to SAVR in patients with severe symptomatic aortic stenosis deemed to be intermediate or high risk for surgery (7-12). PPM has also been observed in a considerable number of patients after TAVR despite a lower incidence of PPM in patients after TAVR and better survival in patients with PPM after TAVR than in those with PPM after SAVR (5,6,13-17). A report from the PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial) demonstrated that the incidence of PPM was 46.4%, and that PPM had a negative impact on LV mass regression and mortality at 1 year in the patient subset with no post-procedural aortic valve regurgitation (AR) (6). PPM after TAVR remains an important concern.

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The major determinants of PPM after SAVR are smaller prosthetic device and larger body surface area (BSA) (13,18-20). Similarly, it has been reported that BSA is one of the most powerful predictors of PPM after TAVR (5). Although body size is correlated with aortic annulus size, the ratio of annulus size to BSA differs between Asian and Western cohorts (6,21,22); these facts raise the possibility of disparate incidence and prognosis of PPM after TAVR between Asian and Caucasian cohorts. Nevertheless, the incidence, risk factors, and clinical impact of PPM after TAVR remain unknown in Asian populations.

Thus, the aim of this study was to investigate the incidence, predictors, and mid-term mortality in patients with PPM after TAVR in an Asian cohort using data from a Japanese multicenter prospective registry.

## METHODS

**STUDY POPULATION AND DESIGN.** The OCEAN-TAVI (Optimized transCathEter vAlvular iNtervention) registry is a multicenter prospective registry affiliated with 14 high-volume centers in Japan. This registry was established to monitor and record the procedural results and post-procedural clinical outcomes of TAVR. This trial is registered with the University Hospital Medical Information Network (UMIN000020423). Between October 2013 and July 2016, a total of 1,613 consecutive high-risk Japanese patients with symptomatic, severe AS undergoing TAVR with the Edwards Sapien XT, Edwards Sapien 3 (Edwards Lifesciences, Irvine, California), or Medtronic CoreValve prosthesis (Medtronic, Minneapolis, Minnesota) were prospectively included in the OCEAN-TAVI registry. The inclusion criteria of this registry were previously reported (23-25). We excluded 67 patients because of the following reasons: death after TAVR before discharge (n = 49), conversion to SAVR (n = 5), absence of transcatheter heart valve (THV) as a result of delivery failure or migration of THV (n = 1), and unreliable echocardiographic data as a result of left ventricle obstruction or poor image (n = 12). The remaining 1,546 patients were included in this study.

**PROCEDURES.** Detailed TAVR procedures have been previously described (23-25). The prosthesis size was determined based on the findings from pre-procedural echocardiography and multidetector computed tomography. The devices were delivered via the transfemoral, trans-subclavian, transaortic, or transapical approaches.

**DEFINITIONS OF PPM, VALVE STENOSIS, AND DEVICE-ANNULUS RATIO.** Echocardiographic evaluation was performed at baseline before the TAVR procedure and at discharge. PPM was assessed with a post-procedure echocardiogram. Patients with moderate and severe PPM were included in the PPM group in this study. According to the Valve Academic

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Research Consortium (VARC)-2 criteria (2), we defined the severity of PPM according to the indexed effective orifice area of the prosthetic valve, and classified the PPM severity as follows: none or mild when >0.85 $cm^2/m^2$; moderate when between 0.85 $cm^2/m^2$ and 0.65 $cm^2/m^2$; and severe when <0.65 $cm^2/m^2$. For obese patients (body mass index [BMI] ≥30 $kg/m^2$), lower criteria were used as follows, according to a recent guideline: none or mild when >0.70 $cm^2/m^2$; moderate when between 0.70 $cm^2/m^2$ and 0.56 $cm^2/m^2$; and severe when ≤0.55 $cm^2/m^2$ (26). Valve stenosis of the THV was determined using the integrative approach shown in the VARC-2 criteria (2). The device-annulus ratio was determined as follows: the device-annulus ratio for balloon-expandable valves was calculated as the THV nominal area/annulus area; and the device-annulus ratio for self-expanding valves was calculated as the THV nominal perimeter/annulus perimeter. The nominal areas of Sapien XT, Sapien 3, and the perimeter of CoreValve are listed in Online Table 1.

**ENDPOINTS.** The primary study endpoints were all-cause and cardiovascular mortality at 1 year, and cardiovascular death was defined according to the VARC-2 criteria (2). The secondary endpoint was rehospitalization due to congestive heart failure at 1 year.

**STATISTICAL ANALYSIS.** Quantitative variables were assessed for normal distribution using the Shapiro-Wilk test, and are expressed as the mean ± SD or as the median and interquartile range (IQR) (25% to 75%), as appropriate. In addition, qualitative variables are expressed as numeric values and percentages. Quantitative variables were compared using the unpaired Student's *t*-test or the Wilcoxon rank-sum test, depending on the distribution of the variables. The chi-square test or Fisher exact test were used to compare qualitative variables. Univariate or multivariate logistic regression analyses were performed to identify the risk factors for PPM. Cumulative survival rates were analyzed using the Kaplan-Meier method, and differences were assessed with the log-rank test. All of the analyses were considered statistically significant at a 2-tailed p value of <0.05. The data were analyzed using JMP Pro software, version 12.1.0. (SAS Institute, Cary, North Carolina).

## RESULTS

Of the 1,546 patients, 149 patients with PPM were identified. Moderate and severe PPM were observed

**TABLE 1 Baseline Characteristics in Patients With or Without PPM**

| | PPM (n = 149) | Non-PPM (n = 1,397) | p Value |
|---|---|---|---|
| Clinical characteristics | | | |
| Age, yrs | 84 (80–87) | 85 (82–88) | 0.01 |
| Female | 107 (71.8) | 986 (70.6) | 0.75 |
| Height, cm | 149.1 (145.1–158.2) | 149.0 (143.2–156.0) | 0.04 |
| Weight, kg | 51.2 (44.1–58.9) | 48.7 (42–56) | 0.01 |
| Body mass index, $kg/m^2$ | 22.6 (20.1–25.2) | 21.9 (19.5–24.3) | 0.05 |
| Body surface area, $m^2$ | 1.46 (1.34–1.56) | 1.41 (1.30–1.53) | 0.01 |
| NYHA functional class, III or IV | 74 (50.0) | 693 (49.6) | 0.99 |
| PAD | 24 (16.1) | 199 (14.2) | 0.54 |
| Prior MI | 14 (9.4) | 93 (6.7) | 0.21 |
| Prior PCI | 49 (32.9) | 359 (25.7) | 0.06 |
| Prior CVA | 19 (12.8) | 196 (14.0) | 0.67 |
| Prior CABG | 12 (8.1) | 96 (6.9) | 0.59 |
| Prior CAD | 54 (36.2) | 392 (28.1) | 0.04 |
| Dyslipidemia | 66 (44.3) | 588 (42.1) | 0.60 |
| Diabetes mellitus | 46 (30.9) | 363 (26.0) | 0.20 |
| Hypertension | 123 (82.6) | 1087 (77.8) | 0.18 |
| COPD | 29 (19.5) | 248 (17.8) | 0.60 |
| Current smoker | 4 (2.68) | 37 (2.65) | 0.98 |
| eGFR, ml/min/1.73 $m^2$ | 47.8 (37.0–60.3) | 51.0 (38.0–64.0) | 0.13 |
| Previous device implantation | | | |
| Pacemaker | 15 (10.1) | 90 (6.44) | |
| ICD | 1 (0.67) | 2 (0.14) | |
| CRT or CRTD | 0 (0.0) | 2 (0.14) | |
| No device | 133 (89.3) | 1303 (93.3) | 0.24 |
| Atrial fibrillation | 38 (25.5) | 283 (20.3) | 0.13 |
| Logistic EuroSCORE, % | 12.6 (8.5–23.0) | 12.8 (8.0–21.1) | 0.99 |
| STS score, % | 6.0 (4.2–9.2) | 6.7 (4.7–9.5) | 0.13 |
| Bicuspid aortic valve | 1 (0.7) | 17 (1.2) | 0.56 |
| Echocardiographic data | | | |
| AVA, $cm^2$ | 0.56 (0.48–0.69) | 0.63 (0.50–0.74) | 0.0001 |
| Indexed AVA, $cm^2/m^2$ | 0.40 (0.31–0.47) | 0.44 (0.37–0.52) | <0.0001 |
| Peak velocity, m/s | 4.5 (4.0–5.1) | 4.5 (4.1–5.1) | 0.31 |
| Mean gradient, mm Hg | 47.7 (37.0–63.1) | 48.0 (38.0–61.0) | 0.76 |
| LVEF, % | 61.0 (51.8–67.1) | 61.0 (50.0–67.0) | 0.70 |
| AR ≥ moderate | 19 (12.8) | 131 (9.4) | 0.19 |
| MR ≥ moderate | 19 (12.8) | 130 (9.3) | 0.18 |
| PAP, mm Hg | 33.0 (28.0–42.0) | 30.0 (25.0–37.0) | 0.0007 |
| Annulus diameter, mm | 19.1 (18.0–21.0) | 20.3 (19.0–22.0) | <0.0001 |
| Annulus diameter to BSA ratio, $mm/m^2$ | 13.4 (12.3–14.3) | 14.5 (13.4–15.6) | <0.0001 |
| Computed tomography data | | | |
| Annular area, $mm^2$ | 358.1 (328.0–410.3) | 387.9 (349.0–439.5) | <0.0001 |
| Perimeter, mm | 69.0 (65.7–73.7) | 71.6 (67.8–75.7) | <0.0001 |
| Mean annulus diameter, mm | 21.8 (20.7–23.1) | 22.3 (21.1–23.8) | 0.001 |

Values are median (interquartile range) or n (%).

AR = aortic valve regurgitation; AVA = aortic valve area; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CRTD = cardiac resynchronization therapy defibrillator; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral valve regurgitation; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PPM = prosthesis-patient mismatch; STS = Society of Thoracic Surgeons.

**TABLE 2 Procedural Characteristics and Complications in Patients With or Without PPM**

| | PPM (n = 149) | Non-PPM (n = 1,397) | p Value |
|---|---|---|---|
| Prosthesis | | | 0.001 |
| Sapien XT | 108 (72.5) | 1,160 (83.0) | |
| Sapien 3 | 25 (16.8) | 114 (8.2) | |
| CoreValve | 16 (10.7) | 123 (8.8) | |
| Prosthesis type | | | 0.430 |
| Balloon-expandable device | 133 (9.5) | 1,274 (90.6) | |
| Self-expandable device | 16 (11.5) | 123 (88.5) | |
| Size of Sapien XT | | | <0.0001 |
| 20 mm | 9 (8.3) | 21 (1.8) | |
| 23 mm | 74 (68.5) | 687 (59.2) | |
| 26 mm | 24 (22.2) | 403 (34.7) | |
| 29 mm | 1 (0.9) | 49 (4.2) | |
| Size of Sapien 3 | | | 0.04 |
| 20 mm | 1 (4.0) | 0 (0.0) | |
| 23 mm | 19 (76.0) | 67 (59.0) | |
| 26 mm | 5 (20.0) | 41 (36.0) | |
| 29 mm | 0 (0.0) | 6 (5.2) | |
| Size of CoreValve | | | 0.89 |
| 26 mm | 9 (56.3) | 67 (54.5) | |
| 29 mm | 7 (43.8) | 56 (45.5) | |
| Approach | | | 0.09 |
| Transfemoral | 114 (76.5) | 1,163 (83.3) | |
| Transapical | 35 (23.5) | 223 (16.0) | |
| Transaortic | 0 (0.0) | 6 (0.43) | |
| Trans-subclavian | 0 (0.0) | 5 (0.36) | |
| Device-annulus area ratio | 1.18 (1.09-1.26) | 1.18 (1.10-1.25) | 0.55 |
| Balloon pre-dilatation | 114 (76.5) | 1071 (76.7) | 0.97 |
| Balloon post-dilatation | 18 (12.1) | 317 (22.7) | 0.003 |
| Contrast volume, ml | 103 (75-138) | 116 (83-153) | 0.02 |
| Procedure time, min | 81 (59-108) | 79 (58-100) | 0.38 |
| Fluoroscopy time, min | 19.0 (13.2-27.0) | 19.9 (15.0-25.4) | 0.74 |

Values are n (%) or median (interquartile range).
AKI = acute kidney injury; other abbreviations as in Table 1.

in 138 (8.9%) and 11 (0.7%) patients, respectively. Overall, the median age and BSA of the patients were 85 years (IQR: 81 to 88 years) and 1.41 $m^2$ (IQR: 1.30 to 1.53 $m^2$), respectively. Only 12 patients (0.8%) <70 years of age were included.

The patients' baseline characteristics are listed in Table 1. Patients with PPM were younger, had higher weight and height, and a larger BSA, as well as a higher prevalence of a medical history of coronary artery disease than patients without PPM. The BMI was similar between the 2 groups. From the baseline echocardiographic data, patients with PPM had a smaller aortic valve area (AVA), smaller index AVA, higher pulmonary artery pressure, smaller annulus diameter, and smaller annulus diameter to BSA ratio than patients without PPM. Median annulus diameter to BSA ratio in the entire cohort was 14.4 mm/$m^2$ (IQR: 13.3 to 15.5 mm/$m^2$). The computed tomography data also showed that aortic annulus dimensions were significantly smaller in the PPM group than in the non-PPM group (Table 1).

The procedural characteristics are listed in Table 2. Patients with PPM had smaller valve prostheses, less contrast volume, and a lower prevalence of balloon post-dilatation. Implanted device types differed between the groups as follows: Sapien XT (n = 108), Sapien 3 (n = 25), and CoreValve (n = 16) in the PPM group; Sapien XT (n = 1,160), Sapien 3 (n = 114), and CoreValve (n = 123) in the non-PPM group.

The post-procedural echocardiographic data and clinical outcomes are listed in Table 3. Patients with PPM had a higher peak velocity and mean gradient across the THV, higher pulmonary aortic pressure, and a higher incidence of mitral regurgitation. There was no difference in the incidence of more than or of equal to moderate paravalvular AR between the 2 groups. A mean pressure gradient of more than 20 mm Hg was observed in 12 patients among the PPM patients, and in 18 among the non-PPM patients (8.1% vs. 1.3%; $p < 0.0001$). However, according to the VARC-2 criteria for valve stenosis, possible THV stenosis was observed in 3 patients in the PPM group, and in 1 patient in the non-PPM group (0.1% vs. 2.0%; $p < 0.0001$). No patient with a pressure gradient of more than 40 mm Hg was found in either group.

**PREDICTORS OF PPM.** The logistic regression analysis for assessing associations between PPM and the clinical findings are presented in Table 4. Predictive factors for PPM after TAVR were age, BSA, AVA, aortic annulus area measured with computed tomography (annulus area), balloon post-dilatation, and the type of prosthetic device. In the logistic multivariate regression analysis, younger age, larger BSA, smaller AVA, smaller annulus area, no balloon post-dilatation, and the use of Sapien 3 were identified as independent predictors of PPM (Table 4).

**SUBGROUP ANALYSIS.** To evaluate the post-dilatation effect on PPM, we conducted subgroup analysis to assess the associations between post-dilatation and other variables potentially associated with PPM (Figure 1). Subgroups based on AVA, annulus area, and device-annulus ratio were divided into 2 groups using the median value of each variable. Among patients with an AVA of <0.62, the incidence of PPM in patients with post-dilatation was significantly lower than that in patients without post-dilatation (7.0% vs. 14.1%; $p = 0.02$), although the incidence of PPM in the patients with post-dilatation was similar to that in patients without post-dilatation

among the patients with an AVA ≥0.62 (4.0% vs. 7.7%; p = 0.08) (Figure 1). Post-dilatation effectively prevented PPM in patients implanted with Sapien XT, but not in those implanted with Sapien 3 or CoreValve (Figure 1). We also conducted subgroup analysis to identify differences in the device-annulus ratio for the different types of implanted THVs (27). The device-annulus ratio in patients implanted with Sapien XT was smaller than that in patients implanted with Sapien 3 (1.17 [IQR: 1.10 to 1.26] vs. 1.10 [IQR: 1.01 to 1.18]; p < 0.0001). The device-annulus ratio in patients implanted with a balloon-expandable device, including Sapien XT and Sapien 3, was greater than that in patients implanted with CoreValve (1.17 [IQR: 1.10 to 1.25] vs. 1.20 [IQR: 1.15 to 1.23]; p = 0.04). No difference in the device-annulus ratio was observed between Sapien XT and CoreValve (1.18 [IQR: 1.10 to 1.26] vs. 1.30 [IQR: 1.15 to 1.23]; p = 0.25). To investigate the effects of BSA and annulus size on the incidence of PPM, the patients were divided into 4 subgroups based on BSA and annulus size, where the threshold value was the median of each variable. The incidence of PPM in the subset with a large BSA and small annulus area was significantly higher than that in the other subsets (Figure 2). Patients in the subset with a large BSA and small annulus area were 4.78 times more likely to develop PPM than those in the subset with a small BSA and large annulus area (odds ratio: 4.78; 95% confidence interval: 2.50 to 9.94; p < 0.0001). Subgroup analysis to evaluate the interaction between annulus area and device type on the incidence of PPM was conducted, but no interaction was observed (Online Figure 1). To assess the impact of low left ventricular ejection fraction and concomitant more than mild mitral regurgitation on mortality, subgroup analysis was conducted (3,28,29). However, no interaction between these factors and PPM on mortality was observed (Online Figure 2).

**TABLE 3 Post-Procedural Echocardiographic Data and Clinical Outcomes in Patients With or Without PPM**

| | PPM (n = 149) | Non-PPM (n = 1,397) | p Value |
|---|---|---|---|
| LVEF, % | 59.0 (49.1–65.0) | 60.3 (51.0–66.0) | 0.38 |
| EOA, $cm^2$ | 1.10 (1.00–1.23) | 1.70 (1.46–2.00) | <0.0001 |
| Indexed EOA, $cm^2/m^2$ | 0.79 (0.72–0.82) | 1.20 (1.03–1.39) | <0.0001 |
| Peak velocity, m/s | 2.4 (2.1–2.8) | 2.2 (1.9–2.4) | <0.0001 |
| Mean gradient, mm Hg | 12.2 (9.7–17.0) | 9.6 (7.0–12.0) | <0.0001 |
| Paravalvular AR ≥ moderate | 2 (1.3) | 13 (0.9) | 0.65 |
| MR ≥ moderate | 17 (11.4) | 81 (6.0) | 0.01 |
| TR ≥ moderate | 21 (14.3) | 83 (6.3) | 0.004 |
| PAP, mm Hg | 34 (26.0–43.0) | 31.0 (25.0–38.0) | 0.001 |
| Valve stenosis | | | |
| Mean PG ≥ 20 mm Hg | 12 (8.1) | 18 (1.3) | <0.0001 |
| Mean PG ≥ 40 mm Hg | 0 (0.0) | 0 (0.0) | – |
| VARC-2 prosthetic valve stenosis | 3 (2.0) | 1 (0.1) | <0.0001 |

Values are median (interquartile range) or n (%).

EOA = effective orifice area; PAP = pulmonary artery pressure; PG = pressure gradient; TR = tricuspid regurgitation; VARC-2 = Valve Academic Research Consortium-2; other abbreviations as in Table 1.

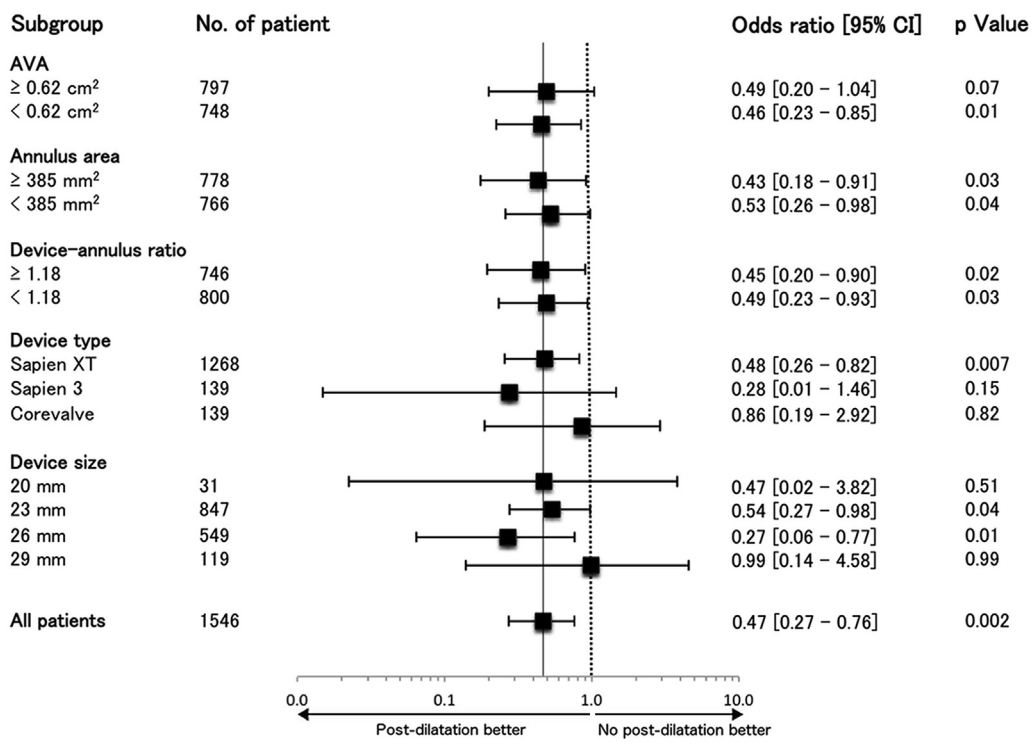
**CUMULATIVE MORTALITY AND PPM.** At a median follow-up of 306 days (IQR: 123 to 482 days), a total of 124 patients died. Of these, 11 and 113 patients were in the PPM and non-PPM groups, respectively. All patients who died in the PPM group were patients with moderate PPM. No patients with severe PPM died during this follow-up period. Kaplan-Meier estimates of cumulative all-cause and cardiovascular mortality in the 2 groups on the basis of the existence of PPM are shown in Figures 3A and 3C, respectively. Kaplan-Meier estimates of cumulative all-cause and cardiovascular mortality in the 3 groups on the basis of the severity of PPM are shown in Figures 3B and 3D, respectively. The estimated cumulative all-cause and cardiovascular mortality at 1 year were 10.2% and 3.9% in the PPM group and 8.3% and 2.3% in the non-PPM group, respectively. There was no difference in

**TABLE 4 Multivariate Logistic Regression Analysis for the Predictive Factors of PPM**

| | Univariate | | Multivariate (Model 1) | | Multivariate (Model 2) | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | p Value | OR (95% CI) | p Value | OR (95% CI) | p Value |
| Age, yrs | 0.95 (0.92–0.99) | 0.004 | 0.96 (0.93–0.99) | 0.01 | 0.96 (0.93–0.99) | 0.01 |
| Body surface area (per 0.1 $m^2$ increase) | 1.14 (1.04–1.26) | 0.01 | 1.46 (1.29–1.66) | <0.0001 | 1.47 (1.29–1.67) | <0.0001 |
| AVA (per 0.1 $cm^2$ increase) | 0.83 (0.74–0.92) | 0.0004 | 0.75 (0.67–0.85) | <0.0001 | 0.76 (0.67–0.85) | <0.0001 |
| Annular area (per 10 $cm^2$ increase) | 0.94 (0.91–0.97) | <0.0001 | 0.90 (0.87–0.93) | <0.0001 | 0.90 (0.87–0.93) | <0.0001 |
| Balloon post-dilatation | 0.47 (0.27–0.76) | 0.0015 | 1.90 (1.16–3.31) | 0.01 | 0.53 (0.30–0.87) | 0.01 |
| Device type | | | | | | |
| Sapien 3 vs. non-Sapien 3 | 2.27 (1.39–3.58) | 0.0014 | 2.73 (1.63–4.45) | 0.0002 | - | - |
| CoreValve vs. Sapien XT | 1.40 (0.77–2.37) | 0.25 | - | - | 1.58 (0.85–2.76) | 0.14 |
| Sapien 3 vs. Sapien XT | 2.36 (1.44–3.74) | 0.0009 | - | - | 2.88 (1.71–4.73) | 0.0001 |

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

**FIGURE 1 Forest Plot Showing the Odds Ratios, p Values, and Direction of Association Between Balloon Post-Dilatation and PPM**




A **dotted line** shows no effect, and a **bold line** shows an overall post-dilatation effect. AVA = aortic valve area; CI = confidence interval; PPM = prosthesis-patient mismatch.

the probability of cumulative mortality over the entire follow-up period after TAVR between the 2 groups (all-cause mortality: log-rank, p = 0.41; and cardiovascular mortality: log-rank, p = 0.21), or among the 3 groups on the basis of the severity of PPM (all-cause mortality: log-rank; p = 0.69; and cardiovascular mortality: log-rank; p = 0.44).

**REHOSPITALIZATION DUE TO CONGESTIVE HEART FAILURE AT 1 YEAR.** The PPM group had significantly higher incidence of rehospitalization due to congestive heart failure at 1 year than that in the non-PPM group (15% [23.1%] vs. 67% [10.3%]; p = 0.002). Multivariate logistic regression analysis was conducted to adjust the confounding factors of rehospitalization due to congestive heart failure at 1 year. Significant and clinically relevant variables from univariate analysis were introduced into multivariate models (30,31). The result revealed that PPM was not an independent predictor of rehospitalization due to congestive heart failure at 1 year (Online Table 2).

## DISCUSSION

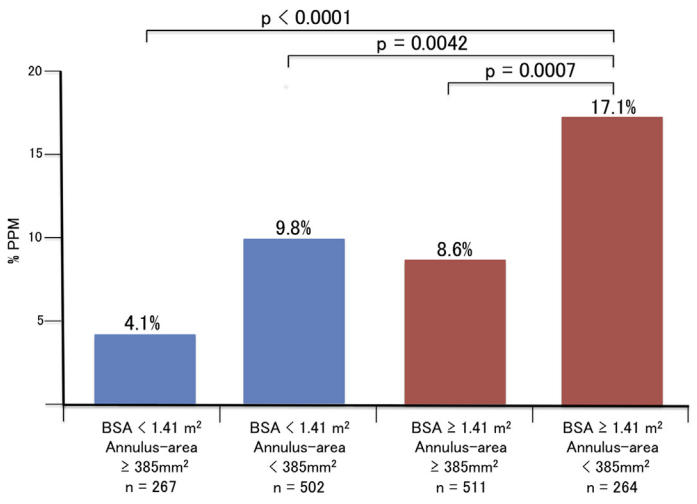
In this study, we made 3 important clinical observations. First, the incidence of moderate and of severe PPM after TAVR in this Japanese cohort was 8.9% and 0.7%, respectively. Second, the cumulative all-cause and cardiovascular mortality at 1 year in the PPM group were similar to those in the non-PPM group. Third, predictors of PPM were identified as younger age, larger BSA, no balloon post-dilatation, smaller AVA, use of Sapien 3, and smaller annulus area.

The results in the current study demonstrated a lower incidence of PPM than previous studies (5,6,13–15,17), with a similar mortality at 1 year in the PPM and non-PPM groups. Considering small body size in this cohort, it is possible to assume that BSA plays an important role in a lower incidence of PPM and lower mortality in patients with PPM. The incidence of PPM in this study was 9.8%; however, previous studies on Caucasian cohorts reported incidence of PPM after TAVR ranging from 18.2% to 60.0% (5,6,13–15,17,32). The mean BSA in this cohort

was 1.43 $m^2$, whereas the mean BSA in Caucasian populations is reportedly between 1.75 and 1.91 $m^2$ (6,17). It should be noted that the annulus size to BSA ratio might be smaller in Caucasian than that in Asian populations. For example, the annulus size to BSA ratio (mean annulus diameter divided by mean BSA) was 11.0 to 13.0 in Caucasian cohort (6,21), whereas it was 14.5 in Asian cohort (21) and 14.4 in this study. The lower incidence of PPM in this study is possibly attributable to the larger annulus size to BSA. Further, the all-cause and cardiovascular mortality at 1 year in the PPM group were similar to those in the non-PPM group. These results are consistent with those of previous studies showing that PPM after TAVR is not associated with long-term survival (6,13,17,32), unlike PPM after SAVR (6,13). The differences in BMI and the prevalence of paravalvular AR between patients undergoing SAVR and TAVR are considered to be possible confounding factors that mask the negative effect of PPM on long-term mortality (6,33). However, BMI and the incidence of paravalvular AR did not differ between the PPM and non-PPM groups in this study. Regarding the mortality of patients with PPM, Moon et al. (29) reported that PPM after SAVR is not associated with increased mortality in patients with a BSA of <1.70 $m^2$, whereas PPM is associated with a higher mortality in patients with a BSA of more than 1.70 $m^2$. These results indicate that a smaller BSA is associated with better survival in patients with PPM in this study. The reasons behind the better survival in patients with PPM with a small BSA are currently unknown. However, it should be taken into account that the relationship between cardiac output (CO) and BSA is not linear, but rather follows an allometric relationship characterized by its power (exponent) (34). de Simone et al. (34) reported that the relationship between CO and BSA can be expressed by the following equation: $CO = 2{,}421 \times BSA^{1.15}$. In other words, patients with a smaller body may demand less CO than estimated CO using an equation showing proportional connection such as $CO = A \times BSA$, where A is a constant. Similarly, the index effective orifice area by which the severity of PPM is categorized may be overestimated when assessing implanted valve performance in patients with a small BSA. The low prevalence of PPM and mortality at 1 year in patients with PPM after TAVR in this Japanese cohort implies that PPM does not impair survival in Asian patients who have undergone TAVR. To clarify this issue, further study investigating the allometric relationship between CO and BSA in patients with aortic stenosis or PPM is warranted.

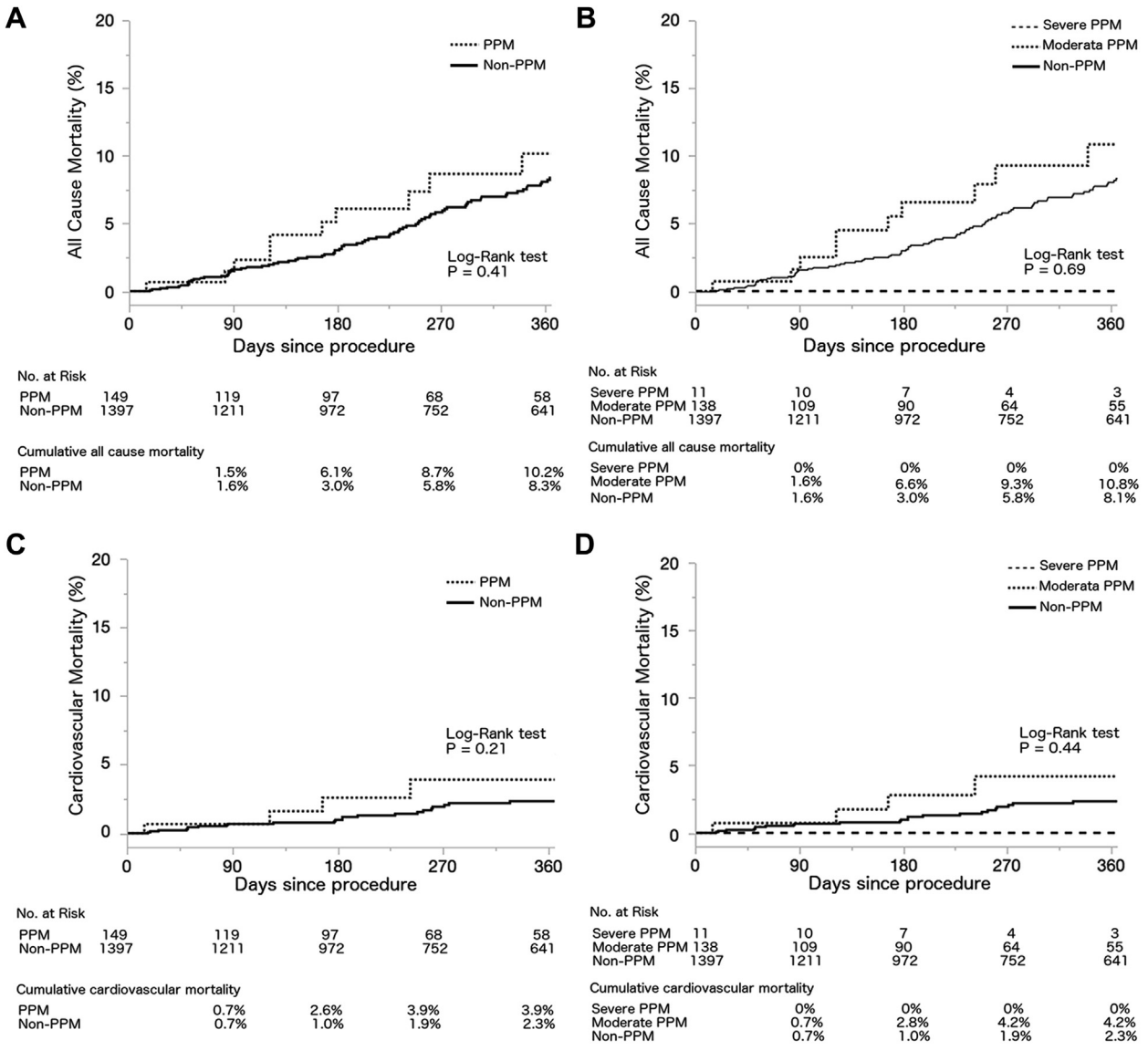
In this study, the risk factors of PPM incidence after TAVR were identified as younger age, larger BSA, no balloon post-dilatation, smaller AVA, smaller annulus area, and the use of Sapien 3. Except for smaller AVA, these factors have previously been reported as risk factors for PPM occurrence as follows: larger BSA (6,13,20,32); younger age (6,32); no post-dilatation (6); and the use of Sapien 3 compared with Sapien XT (27). BSA and aortic annulus size are particularly well-known as major risk factors for PPM, and PPM occurred 4.78 times more in patients with a large BSA and small annulus area than in those with a small BSA and large annulus area in this study (**Figure 2**). Interestingly, our results showed that balloon post-dilatation in patients whose AVA was <0.62 was associated with a lower incidence of PPM (**Figure 1**). Post-dilatation may contribute to providing sufficient expansion of the prosthetic device and prevent PPM, especially in patients with a small AVA before TAVR. The use of Sapien 3 compared with a non-Sapien 3 prosthesis was also identified as an independent predictor of PPM in this study. Theron et al. (27) reported that Sapien 3 implantation was associated with a 5-fold increased risk of PPM compared with Sapien XT implantation, and that the potential mechanism behind the higher incidence of PPM is systolic blood obstruction caused by the outer sealing cuff of the Sapien 3 and less oversizing for Sapien 3 than for Sapien XT. In the present study, the device-annulus ratio in the subset of patients implanted with Sapien XT was significantly greater than that in the subset of patients

**FIGURE 2 Incidence of PPM in Patient Subgroups Based on Their BSA and Aortic Annulus Size**




BMI = body mass index; BSA = body surface area; PPM = prosthesis-patient mismatch.

**FIGURE 3 Time-to-Event Curves for Cumulative All-Cause and Cardiovascular Mortality**




The mortality rate was calculated using the Kaplan-Meier method and compared using the log-rank test. All-cause mortality is shown for PPM and non-PPM **(A)** and for category of severity of PPM **(B)**; cardiovascular mortality is shown for PPM and non-PPM **(C)** and for category of severity of PPM **(D)**. PPM = prosthesis-patient mismatch.

implanted with Sapien 3 (1.17 [IQR: 1.10 to 1.26] vs. 1.10 [IQR: 1.01 to 1.18]; $p < 0.0001$), suggesting that the lower device-annulus ratio could have caused the higher incidence of PPM in the patients implanted with Sapien 3. However, some caution should be taken because of the limited numbers of patients implanted with Sapien 3 in this study.

It remains unclear whether the prevalence of PPM after TAVR is lower than that after SAVR in Asian cohorts; the prevalence of PPM after TAVR was reportedly lower than that after SAVR in a Caucasian cohort (5). Especially in patients with a small aortic annulus, PPM was found to occur less frequently after TAVR than after SAVR (6,18). However, the reported incidence of PPM after SAVR in an Asian cohort (8.7%) (31) was comparable with that in the present study but was much lower than that in a Caucasian cohort (20% to 70%) (1-6). Further research addressing the

difference in PPM incidence between patients undergoing SAVR and TAVR in an Asian cohort is warranted.

**STUDY LIMITATIONS.** In this study, we used the data from a multicenter registry. This study has some limitations. First, most of the patients were implanted with Sapien XT because Sapien XT was approved firstly by the Pharmaceuticals and Medical Devices Agency in Japan. Second, errors can occur when estimating the prosthetic valve effective orifice area by Doppler echocardiography as a result of the difficulty in measuring the stroke volume in the LV outflow tract (6).

## CONCLUSIONS

The prevalence of PPM after TAVR in Japanese patients with small body size was 9.8%. Mortality at 1 year in the PPM group was similar to that in the non-PPM group. These findings imply that PPM is not a risk factor for mortality in Asian patients who have undergone TAVR.

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## PERSPECTIVES

**WHAT IS KNOWN?** BSA is a major determinant of PPM, and the BSA of Asians is smaller than that of Caucasians. However, little information is available on PPM after TAVR in Asian patients.

**WHAT IS NEW?** The incidence of PPM after TAVR in a Japanese cohort was 9.8%. All-cause mortality at 1 year in the PPM group was similar to that in the non-PPM group, suggesting that PPM is not a risk factor for mortality in Asian patients who have undergone TAVR.

**WHAT IS NEXT?** Long-term mortality in patients with PPM after TAVR in Asian patients should be investigated.

## REFERENCES

**1.** Blais C, Dumesnil JG, Baillot R, Simard S, Doyle D, Pibarot P. Impact of valve prosthesis-patient mismatch on short-term mortality after aortic valve replacement. Circulation 2003;108:983–8.

**2.** Head SJ, Mokhles MM, Osnabrugge RL, et al. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J 2012;33:1518–29.

**3.** Mohty D, Dumesnil JG, Echahidi N, et al. Impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: influence of age, obesity, and left ventricular dysfunction. J Am Coll Cardiol 2009;53:39–47.

**4.** Tasca G, Mhagna Z, Perotti S, et al. Impact of prosthesis-patient mismatch on cardiac events and midterm mortality after aortic valve replacement in patients with pure aortic stenosis. Circulation 2006;113:570–6.

**5.** Hahn RT, Pibarot P, Stewart WJ, et al. Comparison of transcatheter and surgical aortic valve replacement in severe aortic stenosis: a longitudinal study of echocardiography parameters in cohort A of the PARTNER trial (Placement of Aortic Transcatheter Valves). J Am Coll Cardiol 2013;61:2514–21.

**6.** Pibarot P, Weissman NJ, Stewart WJ, et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort-A analysis. J Am Coll Cardiol 2014;64:1323–34.

**7.** Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

**8.** Shi WY, Yap CH, Hayward PA, et al. Impact of prosthesis-patient mismatch after mitral valve replacement: a multicentre analysis of early outcomes and mid-term survival. Heart 2011;97:1074–81.

**9.** Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485–91.

**10.** Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.

**11.** Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

**12.** Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321–31.

**13.** Takagi H, Umemoto T, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Prosthesis-patient mismatch after transcatheter aortic valve implantation. Ann Thorac Surg 2016;101:872–80.

**14.** Ewe SH, Muratori M, Delgado V, et al. Hemodynamic and clinical impact of prosthesis-patient mismatch after transcatheter aortic valve implantation. J Am Coll Cardiol 2011;58:1910–8.

**15.** Rodes-Cabau J, Pibarot P, Suri RM, et al. Impact of aortic annulus size on valve hemodynamics and clinical outcomes after transcatheter and surgical aortic valve replacement: insights from the PARTNER Trial. Circ Cardiovasc Interv 2014;7:701–11.

**16.** Dayan V, Vignolo G, Soca G, Paganini JJ, Brusich D, Pibarot P. Predictors and outcomes of prosthesis-patient mismatch after aortic valve replacement. J Am Coll Cardiol Img 2016;9:924–33.

**17.** Mooney J, Sellers SL, Blanke P, et al. CT-defined prosthesis-patient mismatch downgrades frequency and severity, and demonstrates no association with adverse outcomes after TAVR. J Am Coll Cardiol Intv 2017;10:1578–87.

**18.** Kalavrouziotis D, Rodes-Cabau J, Bagur R, et al. Transcatheter aortic valve implantation in patients with severe aortic stenosis and small aortic annulus. J Am Coll Cardiol 2011;58:1016–24.

**19.** Pibarot P, Dumesnil JG, Lemieux M, Cartier P, Metras J, Durand LG. Impact of prosthesis-patient mismatch on hemodynamic and symptomatic status, morbidity and mortality after aortic valve replacement with a bioprosthetic heart valve. J Heart Valve Dis 1998;7:211–8.

**20.** Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol 2000;36:1131–41.

**21.** Watanabe Y, Hayashida K, Takayama M, et al. First direct comparison of clinical outcomes

between European and Asian cohorts in transcatheter aortic valve implantation: the Massy study group vs. the PREVAIL JAPAN trial. J Cardiol 2015;65:112–6.

**22.** Yoon SH, Ohno Y, Araki M, et al. Comparison of aortic root anatomy and calcification distribution between Asian and Caucasian patients who underwent transcatheter aortic valve implantation. Am J Cardiol 2015;116:1566–73.

**23.** Watanabe Y, Kozuma K, Hioki H, et al. Comparison of results of transcatheter aortic valve implantation in patients with versus without active cancer. Am J Cardiol 2016;118:572–7.

**24.** Kano S, Yamamoto M, Shimura T, et al. Gait speed can predict advanced clinical outcomes in patients who undergo transcatheter aortic valve replacement: insights from a Japanese multicenter registry. Circ Cardiovasc Interv 2017;10:e005088.

**25.** Inohara T, Hayashida K, Watanabe Y, et al. Streamlining the learning process for TAVI: insight from a comparative analysis of the OCEAN-TAVI and the Massy registries. Catheter Cardiovasc Interv 2016;87:963–70.

**26.** Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:589–90.

**27.** Theron A, Pinto J, Grisoli D, et al. Patient-prosthesis mismatch in new generation transcatheter heart valves: a propensity score analysis. Eur Heart J Cardiovasc Imaging 2018;19:225–33.

**28.** Cortes C, Amat-Santos IJ, Nombela-Franco L, et al. Mitral regurgitation after transcatheter aortic valve replacement: prognosis, imaging predictors, and potential management. J Am Coll Cardiol Intv 2016;9:1603–14.

**29.** Moon MR, Pasque MK, Munfakh NA, et al. Prosthesis-patient mismatch after aortic valve replacement: impact of age and body size on late survival. Ann Thorac Surg 2006;81:481–8; discussion 489.

**30.** Durand E, Doutriaux M, Bettinger N, et al. Incidence, prognostic impact, and predictive factors of readmission for heart failure after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2017;10:2426–36.

**31.** Nombela-Franco L, del Trigo M, Morrison-Polo G, et al. Incidence, causes, and predictors of early (</=30 days) and late unplanned hospital readmissions after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2015;8:1748–57.

**32.** Thyregod HG, Steinbruchel DA, Ihlemann N, et al. No clinical effect of prosthesis-patient mismatch after transcatheter versus surgical aortic valve replacement in intermediate- and low-risk patients with severe aortic valve stenosis at mid-term follow-up: an analysis from the NOTION trial. Eur J Cardiothorac Surg 2016;50:721–8.

**33.** Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

**34.** de Simone G, Devereux RB, Daniels SR, et al. Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. Circulation 1997;95:1837–43.

**KEY WORDS** body surface area, clinical outcome, PPM, small body size, TAVR

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