STRUCTURAL

Prosthesis-Patient Mismatch After Aortic Valve Replacement in the PARTNER 2 Trial and Registry

Julien Ternacle, MD, PhD,[a] Philippe Pibarot, DVM, PhD,[a] Howard C. Herrmann, MD,[b] Susheel Kodali, MD,[c]
Jonathon Leipsic, MD,[d] Philipp Blanke, MD,[d] Wael Jaber, MD,[e] Michael J. Mack, MD,[f]
Marie-Annick Clavel, DVM, PhD,[a] Erwan Salaun, MD, PhD,[a] Ezequiel Guzzetti, MD,[a]
Mohamed-Salah Annabi, MD, MSc,[a] Mathieu Bernier, MD,[a] Jonathan Beaudoin, MD, PhD,[a] Omar K. Khalique, MD,[c]
Neil J. Weissman, MD,[g] Pamela Douglas, MD,[h] Jeroen Bax, MD,[i] Abdellaziz Dahou, MD, PhD,[j] Ke Xu, PhD,[k]
Maria Alu, MS,[c,j] Erin Rogers, MEng,[k] Martin Leon, MD,[c,j] Vinod H. Thourani, MD,[l] Amr E. Abbas, MD,[m,n]
Rebecca T. Hahn, MD[c,j]

ABSTRACT

OBJECTIVES This study aimed to compare incidence and impact of measured prosthesis-patient mismatch (PPM_M) versus predicted PPM (PPM_P) after surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR).

BACKGROUND TAVR studies have used measured effective orifice area indexed (EOAi) to body surface area (BSA) to define PPM, but most SAVR series have used predicted EOAi. This difference may contribute to discrepancies in incidence and outcomes of PPM between series.

METHODS The study analyzed SAVR patients from the PARTNER (Placement of Aortic Transcatheter Valves) 2A trial and TAVR patients from the PARTNER 2 SAPIEN 3 Intermediate Risk registry. PPM was classified as moderate if EOAi ≤ 0.85 cm^2/m^2 (≤ 0.70 if obese: body mass index ≥ 30 kg/m^2) and severe if EOAi ≤ 0.65 cm^2/m^2 (≤ 0.55 if obese). PPM_M was determined by the core lab-measured EOAi on 30-day echocardiogram. PPM_P was determined by 2 methods: 1) using normal EOA reference values previously reported for each valve model and size (PPM_{P1}; n = 929 SAVR, 1,069 TAVR) indexed to BSA; and 2) using normal reference EOA predicted from aortic annulus size measured by computed tomography (PPM_{P2}; n = 864 TAVR only) indexed to BSA. Primary endpoint was the composite of 5-year all-cause death and rehospitalization.

RESULTS The incidence of moderate and severe PPM_P was much lower than PPM_M in both SAVR (PPM_{P1}: 28.4% and 1.2% vs. PPM_M: 31.0% and 23.6%) and TAVR (PPM_{P1}: 21.0% and 0.1% and PPM_{P2}: 17.0% and 0% vs. PPM_M: 27.9% and 5.7%). The incidence of severe PPM_M and severe PPM_{P1} was lower in TAVR versus SAVR ($P < 0.001$). The presence of PPM by any method was associated with higher transprosthetic gradient. Severe PPM_{P1} was independently associated with events in SAVR after adjustment for sex and Society of Thoracic Surgeons score (hazard ratio: 3.18; 95% CI: 1.69-5.96; $P < 0.001$), whereas no association was observed between PPM by any method and outcomes in TAVR.

CONCLUSIONS EOAi measured by echocardiography results in a higher incidence of PPM following SAVR or TAVR than PPM based on predicted EOAi. Severe PPM_P is rare (<1.5%), but is associated with increased all-cause death and rehospitalization after SAVR, whereas it is absent following TAVR. (J Am Coll Cardiol Intv 2021;14:1466-77) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

From the [a]Québec Heart and Lung Institute, Université Laval, Quebec City, Quebec, Canada; [b]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [c]Columbia University Medical Center/NewYork-Presbyterian Hospital, New York, New York, USA; [d]St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; [e]Cleveland Clinic, Cleveland, Ohio, USA; [f]Baylor Scott and White Healthcare, Plano, Texas, USA; [g]MedStar Heath Research Institute,

Prosthesis-patient mismatch (PPM) is defined by an effective orifice area (EOA) too small in relation to patient's body surface area (BSA), therefore often resulting in high residual transvalvular pressure gradients (1). PPM is generally categorized on the basis of the indexed EOA (EOAi) (ie, the EOA divided by the patient's BSA). The cutoff values of EOAi that are recommended to define PPM are <0.85 cm²/m² for moderate and <0.65 cm²/m² for severe PPM (2-4). However, in obese patients (body mass index ≥30kg/m²), the use of these EOAi cutpoints may result in an overestimation of the incidence and severity of PPM because of an overindexation phenomenon. It is thus recommended to apply lower cutoff values in these patients: <0.70 cm²/m² for moderate and <0.55 cm²/m² for severe PPM (2). PPM is often defined with the use of the EOAi directly measured by transthoracic echocardiography at the pre-discharge or 30-day echocardiogram. However, the measured EOAi has several limitations: 1) it (and thus the determination of PPM) is not available in patients with missing echocardiograms; 2) it is subject to echocardiographic technical pitfalls and measurement errors; and 3) it is flow dependent and may thus overestimate the severity of PPM in patients with a low-flow state. To overcome this limitation, the use of the predicted EOAi has been proposed to define PPM; this parameter is calculated by dividing the normal reference value of EOA for the implanted model and size of prosthesis by the patient's BSA (2,5). The vast majority of surgical aortic valve replacement (SAVR) studies have used the predicted EOAi to examine the incidence and impact of PPM (6,7), whereas all transcatheter aortic valve replacement (TAVR) studies, to date, have only used the measured EOAi. This difference in the method used to identify and grade PPM may, at least in part, explain the discrepancies in PPM incidence and impact reported between TAVR and SAVR series. No study has assessed and compared the incidence and outcomes of PPM using the measured versus the predicted EOAi in SAVR and TAVR. The objective of this study was to determine and compare the incidence and outcomes of PPM after SAVR and TAVR using the measured versus predicted EOAi.

METHODS

STUDY DESIGN AND POPULATIONS.
In this analysis, we used the populations from the PARTNER (Placement of Aortic Transcatheter Valves; NCT01314313) 2A randomized trial (8,9) and the PARTNER 2 SAPIEN 3 intermediate-risk observational study (NCT0322128) (10,11). These 2 prospective, multicenter studies enrolled patients with symptomatic, severe aortic stenosis (AS) who were considered to be at intermediate risk for 30-day surgical mortality. Surgical risk status was evaluated by a Heart Team and patients were considered at intermediate risk based on clinical assessment or if their Society of Thoracic Surgeons (STS) predicted risk of operative mortality score was ≥4%. In those with STS score <4%, the Heart Team deemed the patient intermediate risk if they had risk factors not present within the predictive score (eg, liver disease, frailty, pulmonary hypertension).

In the PARTNER 2A trial, patients were randomly assigned to receive either SAVR or TAVR using the SAPIEN XT device (Edwards Lifesciences, Irvine, California) (8). In the SAPIEN 3 single-arm study, all patients underwent TAVR with the SAPIEN 3 valve. Patients who were eligible for the PARTNER 2 trial or registry were presented on a conference call in which a screening committee reviewed imaging and clinical data and approved patients prior to enrollment. Inclusion and exclusion criteria for PARTNER 2A trial and SAPIEN 3 registry (8,10,11) were identical. Key exclusion criteria were a congenitally bicuspid aortic valve, severe aortic regurgitation, left ventricular ejection fraction (LVEF) lower than 20%, severe renal insufficiency, and estimated life expectancy of <2 years. Both trials were approved by the institutional review boards of each participating site and written informed consent was provided by all patients. In the present study, we included patients from the SAVR arm of the PARTNER 2A randomized trial and those

Georgetown University, Washington, DC, USA; ʰDuke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina, USA; ⁱDepartment of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; ʲCardiovascular Research Foundation, New York, New York, USA; ᵏEdwards Lifesciences, Irvine, California, USA; ˡDepartment of Cardiovascular Surgery, Marcus Valve Center, Piedmont Heart Institute, Atlanta, Georgia, USA; ᵐOakland University William Beaumont School of Medicine, Auburn Hills, Michigan, USA; and the ⁿBeaumont Hospital Royal Oak, Royal Oak, Michigan, USA.

from the PARTNER 2 SAPIEN 3 Intermediate-Risk registry.

DEFINITION OF PPM. For all methods (measured and predicted EOAi), PPM was defined as nonsignificant if EOAi was >0.85 cm^2/m^2, moderate if >0.65 cm^2/m^2 and ≤ 0.85 cm^2/m^2, and severe if ≤ 0.65 cm^2/m^2. Furthermore, lower cutoff values of EOAi were used in obese patients (body mass index [BMI] ≥ 30 kg/m^2) as previously recommended (2): nonsignificant if EOAi >0.70 cm^2/m^2, moderate if >0.55 cm^2/m^2 and ≤ 0.70 cm^2/m^2, and severe if ≤ 0.55 cm^2/m^2.

METHODS TO DEFINE PPM. Measured PPM$_M$. The EOA was measured at 30 days by transthoracic echocardiography using the continuity equation and then indexed for BSA to define measured PPM (PPM$_M$) (2,4). The diameter of the left ventricular outflow tract was measured just below the left ventricular border of the bioprosthetic valve stent or sewing ring from outer-to-outer border of the stent or ring (4). The pulsed-wave Doppler sample volume was positioned just apical to the prosthesis stent/ring at the same location as the left ventricular outflow tract diameter measurement (Supplemental Figure 1). The EOA value was then indexed (EOAi) to BSA calculated with the Dubois formula. All echocardiograms in patients given SAVR or TAVR were analyzed independently by a consortium of echocardiography core laboratories.

Predicted PPM$_P$. Two different methods (Supplemental Figure 1) were applied to obtain the predicted EOAi and define predicted PPM (PPM$_P$). The first method (predicted 1 [PPM$_{P1}$]) was based on the normal reference values of EOA for each size and model of implanted surgical or transcatheter valves obtained from the published data (Supplemental Tables 1 and 2) (2,12). The second method (predicted 2 [PPM$_{P2}$]) was used only for the TAVR arm with the SAPIEN 3 valve and was based on the normal reference values of EOA derived according to aortic annulus area measured by computed tomography angiography (CTA) before the TAVR procedure (Supplemental Table 2). CTA was not performed routinely in the PARTNER 2A trial; thus, PPM$_{P2}$ was not able to be determined for SAVR. The predicted EOA was then indexed to BSA.

STUDY ENDPOINTS. The primary endpoint was the composite of all-cause death and cardiac rehospitalization at 5 years. Secondary endpoints included the separate analysis of all-cause death, cardiac death and rehospitalization at 5 years. All events were classified according to Valve Academic Research Consortium-2 criteria (13). The functional status,

quality of life, and exercise capacity, assessed by the New York Heart Association functional class, Kansas City Cardiomyopathy Questionnaire, and 6-min walking test distance, respectively, were also reported.

STATISTICAL ANALYSIS. Continuous data were presented as mean $\pm$ SD or as median (interquartile range) when distribution was skewed. Categorical data were presented as percentage and fraction of occurrence. Group comparisons were analyzed with the chi-square test or Fisher exact test, as appropriate, for categorical variables; the Student's *t*-test or Wilcoxon rank sum was used for continuous variables. Paired comparisons were performed using paired Student's *t*-test or McNemar's test when appropriate. Logistic regression was used to identify variables associated with severe PPM. Kaplan-Meier estimates and log-rank test were used to compare occurrence of endpoints over 5 years stratified according to presence or absence of PPM and severity of PPM (none, any, moderate, or severe) using both measured and predicted EOAi (including the 2 predicted methods). Only the PPM definition using adjusted cutoffs for BMI was considered for the analysis of outcomes. Multivariable analysis was performed with the Cox proportional hazards model and included the STS score and variables with a *P* value <0.10 on univariable analysis. Incidence and association with outcomes of PPM (measured or predicted) were analyzed separately in both the SAVR and TAVR arms. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute) and a *P* value < 0.05 was considered statistically significant.

RESULTS

STUDY POPULATION. Overall, 2,005 patients were included in the SAVR arm of the PARTNER 2A randomized trial (n = 936) and the PARTNER 2 SAPIEN 3 Intermediate-Risk registry (n = 1,069) (Supplemental Figure 2). The median follow-up duration was 1,747 (interquartile range: 817 to 1,842) days in the SAVR cohort and 1,685 days (interquartile range: 1,010-1,854 days) in the TAVR cohort. Baseline characteristics of these 2 cohorts are described in previous publications (11). Thirty-day echocardiography to define PPM$_M$ was available in 726 (78%) patients of the SAVR cohort and 954 (89%) patients of the TAVR cohort. For PPM$_{P1}$, all patients with known prosthetic valve model and label size were included (SAVR: n = 929 [99%]; TAVR: n = 1,069 [100%]). Finally,

preprocedural CTA data to define PPM$_{P2}$ were available in 864 (81%) patients of the TAVR cohort (Supplemental Figure 2).

INCIDENCE OF PPM USING THE MEASURED EOAi VERSUS THE PREDICTED EOAi IN SAVR AND TAVR.

The measured and predicted EOA and EOAi in the TAVR and SAVR arms are presented in Table 1. Using the measured EOAi, the incidence of moderate and severe PPM$_M$ were 36.4% and 27.8%, respectively (overall PPM$_M$: 64.2%), in the SAVR cohort and 37.4% and 9.3%, respectively (overall PPM$_M$: 46.8%), in the TAVR cohort (Table 1, Figure 1). When using the published expected transcatheter valve areas by bioprosthetic valve size to calculate EOAi, the incidence of moderate and severe PPM$_{P1}$ was 40.3% and 2.7%, respectively (overall PPM$_{P1}$: 42.9%), in the SAVR cohort and 40.9% and 1.7%, respectively (overall PPM$_{P1}$: 42.6%), in the TAVR cohort (Table 1, Figure 1). Using the published expected transcatheter valve areas by CTA annular area to calculated EOAi, the incidence of moderate and severe PPM$_{P2}$ was 37.0% and 0.6%, respectively (overall PPM$_{P2}$: 37.6%), in the TAVR cohort (Table 1, Figure 1B). With all 3 methods (measured, predicted 1, predicted 2), adjustment of the EOAi cutpoints in obese patients (<0.70 cm^2/m^2 instead of <0.85 cm^2/m^2 for moderate PPM and <0.55 cm^2/m^2 instead of 0.65 cm^2/m^2 for severe PPM) resulted in lower incidences of PPM (Figure 1). Baseline, procedural, and 30-day characteristics of patients with severe BMI-adjusted PPM using both the measured and the predicted 1 methods are presented in Supplemental Tables 3 and 4 for the SAVR cohort and in Supplemental Tables 5 and 6 for the TAVR cohort. The correlation and agreement of the predicted EOAi method 1 versus the measured EOAi to identify severe BMI-adjusted PPM are presented in Supplemental Figure 3. A low-flow state (ie, stroke volume index <35 ml/m^2) was observed in 91% and 79% of the SAVR and TAVR patients with severe PPM$_M$ reclassified to nonsevere PPM$_{P1}$, respectively (Supplemental Tables 7 and 8). On multivariable analysis, smaller prosthetic valve size and low-flow state at 30 day were the 2 main factors independently associated with severe PPM$_M$ (Supplemental Tables 9 and 10).

The incidence of severe PPM defined with the use of the predicted EOAi methods was markedly lower than with the use of the measured EOAi method in both SAVR (severe PPM$_{P1}$: 2.7% vs severe PPM$_M$: 27.8%) and TAVR (severe PPM$_{P1}$: 1.7% and severe PPM$_{P2}$: 0.6% vs severe PPM$_M$: 9.3%) cohorts (p < 0.001 for all). Similar results were observed with the BMI-adjusted cutpoints of EOAi in obese patients (Figure 1).

TABLE 1 Incidence of PPM According to the Method for Definition of PPM in the SAVR Versus TAVR Cohorts

	SAVR	TAVR	p Value
Measured PPM			
Measured EOAi, cm^2/m^2	0.79 ± 0.22 (726)	0.89 ± 0.21 (954)	<0.0001
Any PPM$_M$	466/726 (64.2)	446/954 (46.8)	<0.0001
Moderate PPM$_M$	264/726 (36.4)	357/954 (37.4)	0.66
Severe PPM$_M$	202/726 (27.8)	89/954 (9.3)	<0.0001
Any BMI-adjusted PPM$_M$	396/726 (54.5)	320/954 (33.5)	<0.0001
Moderate BMI-adjusted PPM$_M$	225/726 (31.0)	266/954 (27.9)	0.17
Severe BMI-adjusted PPM$_M$	171/726 (23.6)	54/954 (5.7)	<0.0001
Predicted PPM, method 1			
Predicted EOAi, cm^2/m^2	0.89 ± 0.14 (929)	0.87 ± 0.11 (1,069)	0.007
Any PPM$_{P1}$	399/929 (42.9)	455/1,069 (42.6)	0.86
Moderate PPM$_{P1}$	374/929 (40.3)	437/1,069 (40.9)	0.78
Severe PPM$_{P1}$	25/929 (2.7)	18/1,069 (1.7)	0.12
Any adjusted PPM$_{P1}$	275/929 (29.6)	226/1,069 (21.1)	<0.0001
Moderate adjusted PPM$_{P1}$	264/929 (28.4)	225/1,069 (21.0)	0.0001
Severe adjusted PPM$_{P1}$	11/929 (1.2)	1/1,069 (0.1)	0.002
Predicted PPM, method 2			
Predicted EOAi, cm^2/m^2	N/A	0.89 ± 0.10 (864)	N/A
Any PPM$_{P2}$	N/A	325/864 (37.6)	N/A
Moderate PPM$_{P2}$	N/A	320/864 (37.0)	N/A
Severe PPM$_{P2}$	N/A	5/864 (0.6)	N/A
Any adjusted PPM$_{P2}$	N/A	147/864 (17.0)	N/A
Moderate adjusted PPM$_{P2}$	N/A	147/864 (17.0)	N/A
Severe adjusted PPM$_{P2}$	N/A	0/864 (0.0)	N/A

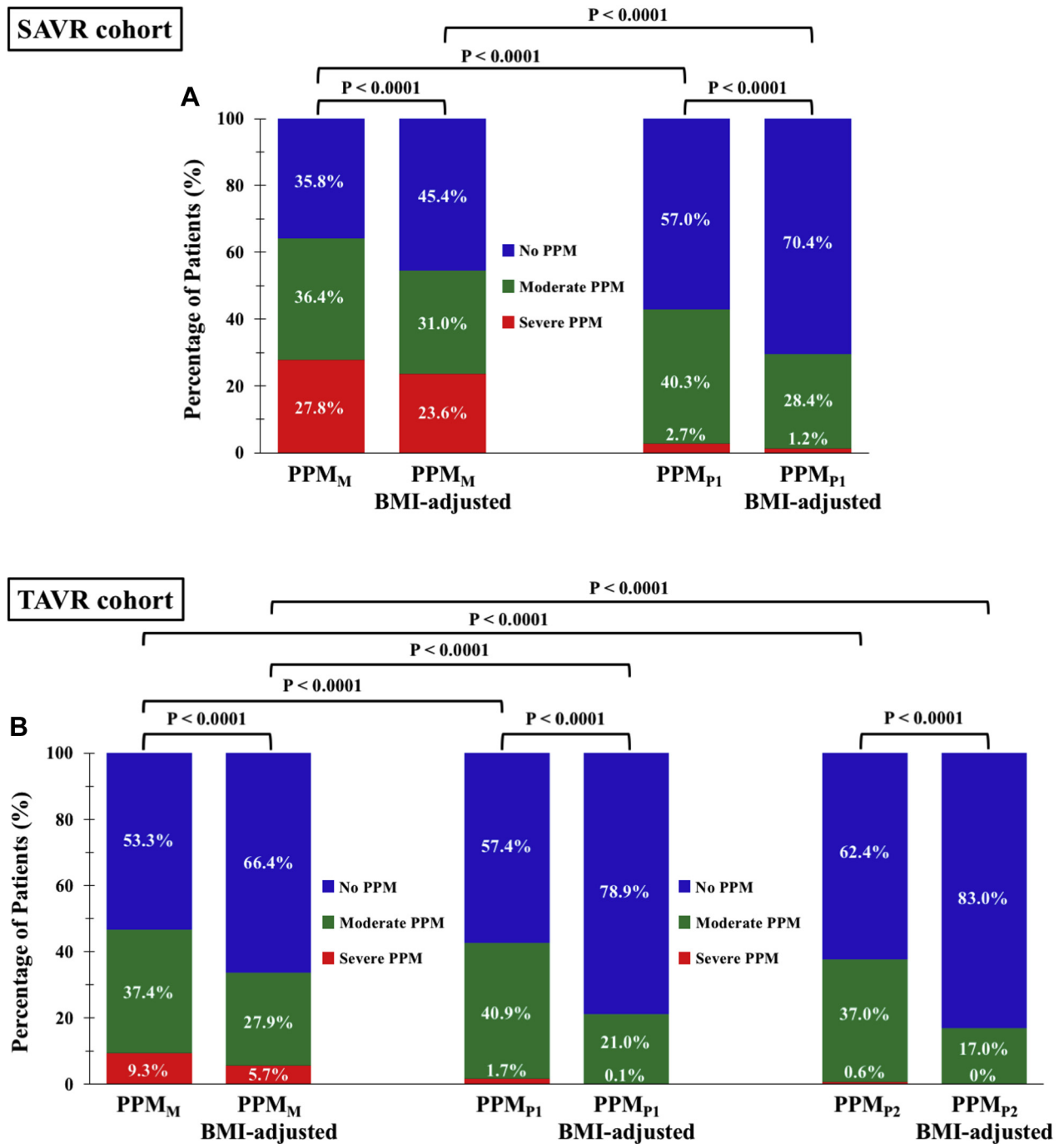Values are mean ± SD (n) or n/N (%).

EOAi = indexed effective orifice area; EOAi$_M$ = measured indexed effective orifice area; EOAi$_{P1}$ = method 1 predicted indexed effective orifice area; EOAi$_{P2}$ = method 2 predicted indexed effective orifice area; N/A = not applicable; PPM = prosthesis-patient mismatch; PPM$_M$ = measured prosthesis-patient mismatch; PPM$_{P1}$ = method 1 predicted prosthesis-patient mismatch; PPM$_{P2}$ = method 2 predicted prosthesis-patient mismatch; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

The rates of any and severe PPM$_M$ or any and severe PPMP1 were significantly lower in TAVR versus SAVR whether adjusted or not for BMI (Table 1). The mean transprosthetic gradient was higher in moderate PPM versus no PPM and in severe PPM versus no or moderate PPM, regardless of the method used to define PPM (Table 2). The presence of PPM by any method was associated with higher mean transprosthetic gradient (Table 2).

ASSOCIATION OF PPM WITH CLINICAL OUTCOMES.

In the SAVR cohort, severe PPM$_M$ or any and severe PPMP1 adjusted for BMI was associated with a 1.34-fold increase ($P = 0.031$) in the risk of all-cause death or rehospitalization at 5 years, whereas severe PPM$_{P1}$ adjusted for BMI was associated with a 3.30-fold increase ($P < 0.001$) in the risk of event (Figure 2). These associations persisted after adjustment for comorbidities (for PPM$_M$, hazard ratio: 1.29; 95% CI: 1.01-1.65; $P = 0.0433$; and for PPM$_{P1}$, HR: 3.18; 95% CI: 1.69-5.96; $P = 0.0003$) (Table 3). Moderate PPM by any method was not associated with

FIGURE 1   Incidence of PPM by Measured or Predicted Methods

(A) Incidence of prosthesis-patient mismatch (PPM) following surgical aortic valve replacement (SAVR) by indexed effective orifice area (EOAi) measured by echocardiography (PPM$_M$) or predicted by method 1 from published expected EOA according to valve model and size (PPM$_{P1}$), with and without adjustment for obesity. (B) Incidence of PPM following transcatheter aortic valve replacement (TAVR) by measured EOAi method (PPMm), by predicted EOAi method 1 (PPMp1), or predicted by method 2 from published expected EOA according to CTA aortic annulus area (PPM$_{P2}$), with and without adjustment for obesity. BMI = body mass index.

TABLE 2 Transprosthetic Aortic Valve Mean Gradient According to PPM Groups and Methods in Both SAVR and TAVR Cohorts

Cohort	No PPM	BMI-Adjusted Moderate PPM	BMI-Adjusted Severe PPM
SAVR			
PPM_M, mm Hg	9.5 ± 3.5 (330)	10.7 ± 3.8 (225)*	13.3 ± 4.7 (171)*†
PPM_M, MG ≥20 mm Hg	3/330 (0.9)	6/225 (2.7)	16/171 (9.4)*†
PPM_{P1}, mm Hg	9.9 ± 3.6 (556)	13.2 ± 4.9 (219)*	14.3 ± 5.8 (6)*
PPM_{P1}, MG ≥20 mm Hg	9/556 (1.6)	20/219 (9.1)*	1/6 (16.7)*
TAVR			
PPM_M, mm Hg	10.3 ± 3.8 (634)	12.7 ± 4.6 (266)*	15.8 ± 8.4 (54)*†
PPM_M, MG ≥20 mm Hg	13/634 (2.1)	21/266 (7.9)*	11/54 (20.4)*†
PPM_{P1}, mm Hg	10.7 ± 4.3 (799)	14.0 ± 6.3 (210)*	20.2 (1)*
PPM_{P1}, MG ≥20 mm Hg	25/799 (3.1)	25/210 (11.9)*	1/1 (100.0)*†
PPM_{P2}, mm Hg	11.0 ± 4.7 (682)	13.0 ± 5.2 (138)*	N/A (0)
PPM_{P2}, MG ≥20 mm Hg	30/682 (4.4)	14/138 (10.1)*	N/A (0.0)

Values are mean ± SD (n) or n/N (%). All PPM definitions are adjusted for BMI. *$p < 0.05$ vs no PPM. †$p < 0.05$ vs moderate PPM.

MG = mean gradient; PPM_M: prosthesis-patient mismatch defined with the measured indexed effective orifice area; PPM_{P1}: prosthesis-patient mismatch defined with predicted indexed effective orifice area method 1; PPM_{P2}: prosthesis-patient mismatch defined with predicted indexed effective orifice area method 2; other abbreviations as in **table 1**.

increased risk of events in SAVR. The presence of high residual gradient (mean gradient ≥20 mm Hg) at 30 days was also not associated with the risk of all-cause death or rehospitalization at 5 years.

In the TAVR cohort, severe PPM_M adjusted for BMI was not associated with the composite of all-cause death and rehospitalization at 5 years (**Figure 3A**). Severe PPM_{P1} or severe PPM_{P2} were absent or extremely rare, and association with outcomes could not be examined (**Figures 3B and 3C**). There was no association between moderate PPM by any method and outcomes in TAVR.

The secondary endpoints of all-cause death, cardiac death, and rehospitalization at 5 years by BMI-adjusted PPM methods are shown in Supplemental Figures 4, 5, and 6. In the SAVR cohort, severe BMI-adjusted PPM_{P1} was associated with 5-year all-cause death and cardiac death (Supplemental Figures 4B and 5B) and severe BMI-adjusted PPM_M and PPM_{P1} was associated with 5-year risk of rehospitalization (Supplemental Figure 6A and 6B). Notably, severe BMI-adjusted PPM_M was not associated with 5-year risk of all-cause death or cardiac death in either the SAVR or TAVR cohorts (Supplemental Figures 4A, 4C, 5A, and 5C). The functional status, quality of life questionnaire, and exercise capacity test were not significantly different across the BMI-adjusted PPM severity groups in both SAVR and TAVR cohorts, regardless of the method used to define PPM (Supplemental Table 11).

DISCUSSION

The main findings of this study are: 1) the utilization of the predicted EOAi instead of the measured EOAi yielded a markedly lower rate of severe PPM in both the SAVR and TAVR cohorts; 2) adjustment (ie, lowering) of EOAi cutpoints in obese individuals resulted in further reduction in the rate of severe PPM; 3) when using the predicted EOAi with adjustment for BMI, severe PPM was nearly absent in TAVR and was rare in contemporary SAVR; 4) severe PPM was less frequent following TAVR versus SAVR with both the measured and predicted methods; 5) the presence of PPM by any method was associated with higher transprosthetic gradient; 6) severe PPM adjusted for BMI was independently associated with outcomes in SAVR, but the association was stronger with the predicted versus measured PPM; and 7) in TAVR, severe PPM_M was present in only 54 patients and was not associated with outcomes, whereas the association with severe PPM_{P1} or PPM_{P2} could not be assessed because there were too few patients with severe PPM_P in this cohort.

INCIDENCE OF PPM AFTER AVR. The parameter that is logically used to define PPM is the EOA indexed to BSA, the latter being the main determinant of patient's cardiac output requirements. In obese patients, the indexation of the EOA to the BSA may, however, overestimate the frequency and severity of PPM. This may explain why several studies reported an association between EOAi and clinical outcomes in lean or overweight patients but not in obese patients (14-16). To overcome this issue of overindexation of EOA in obese patients, Valve Academic Research Consortium-2 and European Association of Cardiovascular Imaging guidelines recommended applying lower EOAi cutpoint values to define PPM in patients with a BMI ≥30 kg/m² (2,3). In the present study, the

FIGURE 2 All-Cause Death or Rehospitalization for SAVR by PPM Severity
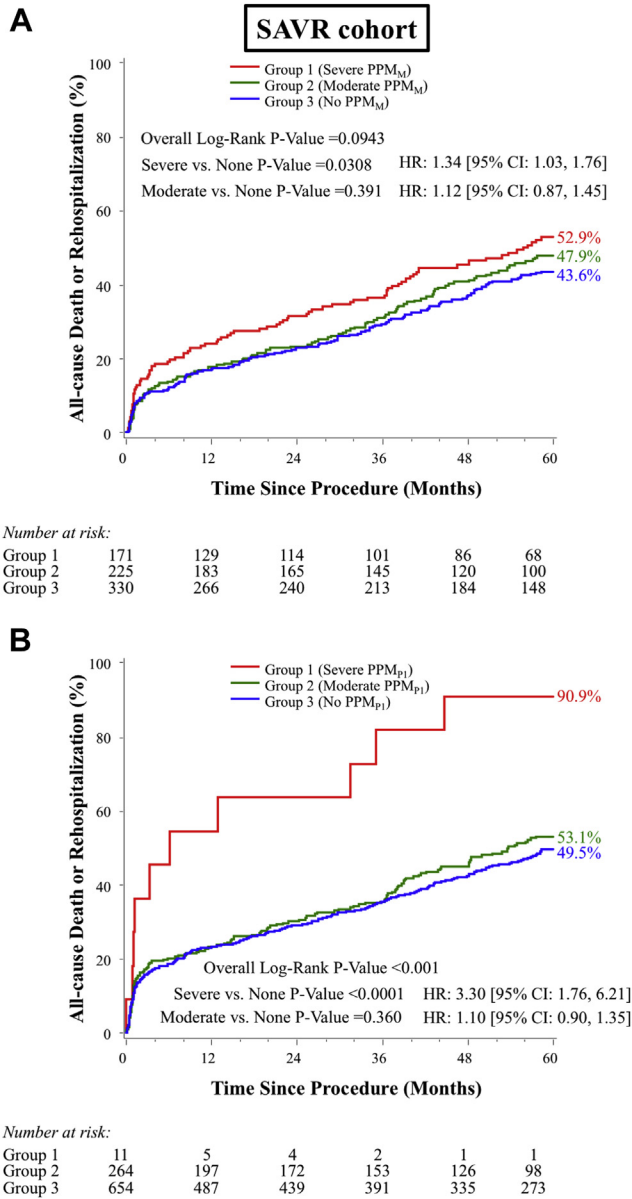
The time to all-cause death or rehospitalization curves are shown in the SAVR cohort for **(A)** PPM$_M$ and **(B)** PPM$_{P1}$, both adjusted for obesity. Abbreviations as in **Figure 1**.

use of BMI-adjusted EOAi cutpoints resulted in significantly lower incidence of PPM in both SAVR and TAVR cohorts (**Central Illustration**). The implementation of these BMI-adjusted EOAi cutpoints may be more relevant in the context of low-risk populations such as the PARTNER 3 trial population because of the higher prevalence of obesity compared with intermediate or high-risk populations (9,17).

The method used to determine EOA and thus to classify PPM is likely the most important source of discrepancy among the reported rates and clinical impact of PPM in TAVR versus SAVR series. Indeed, the vast majority of SAVR series have used the predicted EOAi to define PPM (6,7,15), whereas all TAVR series, until now, have used the measured EOAi (18-20). The main limitation of the measured EOAi is that it is subject to measurement errors and variability and is influenced by the patient's hemodynamic status, especially the flow state. Two-dimensional echocardiography may underestimate the left ventricular outflow tract diameter and thus the EOA and EOAi, which may, in turn, yield to an overestimation of PPM (1,21). Furthermore, a low-flow state may be observed in up to 45% of patients following TAVR (22,23). In presence of low transvalvular flow, the EOA may not be opened maximally and may thus lead to the erroneous diagnosis of a severe PPM (2,24). This phenomenon of "pseudo-severe" PPM is similar to that of "pseudo-severe" stenosis in patients with low-flow, low-gradient native AS (1,2,24). Hence, one of the main reasons for the much higher incidence of severe PPM with the measured versus predicted EOAi in the present study may be that a large proportion of patients were in low-flow state at 30-day echocardiogram and, thus, in fact, had pseudo-severe rather than true severe PPM on the basis of the measured EOAi. The predicted EOAi allows, at least in part, overcoming these issues of measurement variability and pseudo-severe PPM and may thus improve the identification of patients with true-severe PPM. To this effect, the prevalence of low-flow state was markedly higher in patients reclassified from severe measured PPM to nonsevere predicted PPM compared with those without severe PPM, especially in the TAVR cohort (Supplemental Tables 7 and 8). Furthermore, low-flow state was independently associated with the presence of severe measured PPM. Another advantage of the predicted EOAi and of PPM$_P$ is that it can be determined in every patient as long as reliable normal reference value of EOA is available for the model and size of bioprosthesis, whereas the measured EOAi and PPM$_M$ cannot be obtained if the pre-discharge and 30-day echocardiogram are missing (Supplemental Figure 1).

There are also limitations to the use of the predicted EOAi to assess PPM. The predicted EOAis for SAVR or TAVR based on published values are also derived from measured echocardiographic data and are thus affected to some extent by measurement variability and low-flow state (2,12). The use of computed tomography annular area pre-TAVR to predict EOA and PPM may not reflect the actual

TABLE 3 Multivariable Analysis of the Association Between PPM$_{P1}$ and Primary and Secondary Endpoints in the SAVR Cohort

Outcome	Multivariable Model*	HR (95% CI)	P Value
Death or rehospitalization	Male	1.19 (0.99-1.44)	0.071
	Severe PPM$_{P1}$ adjusted for obesity	3.18 (1.69-5.96)	0.0003
	STS score	1.10 (1.05-1.16)	<0.0001
All-cause death	Male	1.35 (1.07-1.69)	0.0098
	Prior CABG	0.80 (0.62-1.03)	0.0894
	Severe PPM$_{P1}$ adjusted for obesity	2.87 (1.48-5.57)	0.0019
	STS score	1.10 (1.04-1.16)	0.0004
Cardiac death	Male	1.36 (1.03-1.80)	0.0327
	Diabetes	0.77 (0.57-1.04)	0.0838
	Severe PPM$_{P1}$ adjusted for obesity	3.54 (1.55-8.08)	0.0027
	STS score	1.08 (1.00-1.15)	0.0379
Rehospitalization	Male	1.29 (0.97-1.70)	0.0767
	Severe PPM$_{P1}$ adjusted for obesity	2.89 (1.18-7.03)	0.0198
	STS score	1.10 (1.03-1.18)	0.0041

*The multivariable model included all variables with a P value < 0.10 on univariable analysis.

CABG = coronary artery bypass graft; PPM$_{P1}$: method 1 predicted prosthesis-patient mismatch, STS score: Society of Thoracic Surgeons; other abbreviations as in **Table 1**.

annular area following circularization and expansion with a balloon-expanded prosthesis and may not take into account the final inner diameter of the prosthesis where flow occurs.

INCIDENCE OF PPM IN SAVR VERSUS TAVR. The incidence of severe PPM after SAVR, reported in previous studies, ranges between 5% and 25% (6,7,15,24-26). Intriguingly, a similar or even higher incidence of severe PPM was reported in TAVR series, although randomized studies reported better hemo-dynamic profile (ie, larger EOA and EOAi and lower gradients and incidence of PPM$_M$) in TAVR versus SAVR arms (27-29). For example, the incidence of severe PPM after TAVR was 9.3% in the TVT (Trans-catheter Valve Therapy) registry (20) versus 11% after SAVR in the STS registry (7) and 9.8% in a meta-analysis of PPM in SAVR (6,7). The discrepancy in these findings between SAVR and TAVR is likely related to the difference in the methods used to identify PPM: predicted EOAi in SAVR versus measured EOAi in TAVR (6,7,15,18,19,30,31).
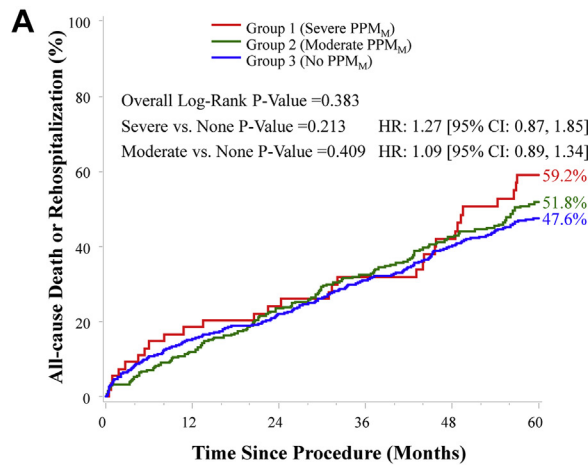
The present study further confirms and extends the findings of previous studies, which performed head-to-head comparison of the incidence of PPM in TAVR versus SAVR and found that severe PPM was generally less frequent with TAVR (18,19,31,32). However, given that these previous studies only used the measured EOAi to define PPM, the incidence of severe PPM may have been overestimated in both treatment groups, and potentially to a larger extent in SAVR because of the higher prevalence of low-flow state and thus of pseudo-severe PPM at pre-discharge or 30 days echocardiogram in this arm.

The incidence of measured PPM may also have been overestimated because the Doppler echocardio-graphic evaluation does not take into account the pressure recovery phenomenon (33). The present study reports that the incidence of true severe PPM as identified with predicted EOAi was significantly lower in TAVR with the SAPIEN 3 valve versus SAVR.

ASSOCIATION OF PPM WITH OUTCOMES. On the one hand, the vast majority of SAVR studies have reported a negative impact of PPM, and especially of severe PPM, on outcomes including worse post-operative functional status, smaller regression of left ventricular mass, and higher all-cause and cardio-vascular mortality (6,7,15,19,25,26,30). On the other hand, the association between PPM and outcomes was absent or modest after TAVR (18-20,27,28,34,35). Again, these discrepancies in the association between PPM and outcomes in TAVR vs. SAVR may be related to differences in the methods used to determine EOAi and define PPM. The TAVR study from the STS/ American College of Cardiology TVT registry reported a significant but modest association between severe PPM$_M$ after TAVR and outcomes. However, in this previous study, valve-in-valve procedures were also included, and PPM association with outcomes was stronger in this subgroup than in patients with native AS. Furthermore, the stroke volume was not reported, and the poor outcomes could be related, at least in part, to the low-flow state and not to PPM per se (ie, pseudo-severe PPM). In the present study, severe PPM$_M$ defined with the EOAi measured at 30 days showed no or weak association with outcomes in TAVR, although the small number of patients with
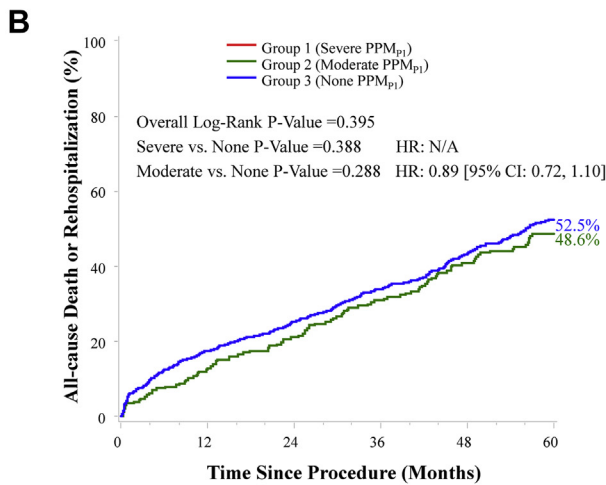
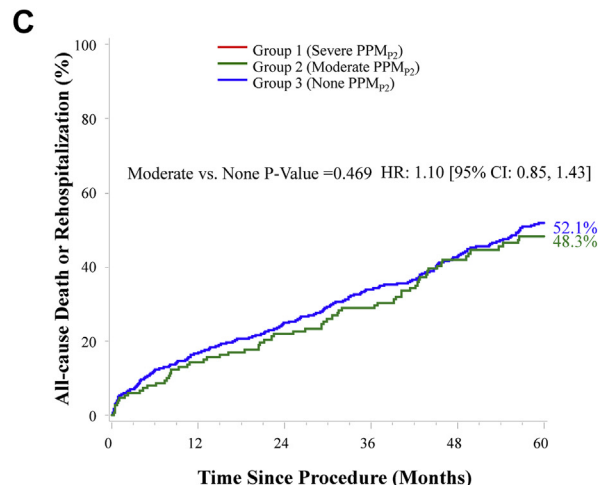**FIGURE 3 All-Cause Death or Rehospitalization for TAVR by PPM Severity**

The time to all-cause death or rehospitalization curves are shown in the transcatheter aortic valve replacement (TAVR) cohort for **(A)** PPM$_M$ and **(B)** PPM$_{P1}$, and for **(C)** PPM$_{P2}$, all adjusted for obesity. Abbreviations as in **Figures 1 and 2**.

severe PPM also in this subset precludes a definitive conclusion. Severe PPM$_P$ defined with the predicted EOAi was strongly and independently associated with outcomes in SAVR. This association between severe PPM$_{P1}$ and outcomes could not be assessed in TAVR because there were no patients with this risk factor.

STUDY LIMITATIONS. The purpose of the predicted EOA derived from the model and label size of the valve is to provide an estimate of the hemodynamic "fingerprint" of the valve once implanted in the patient. However, during TAVR, the implantation of a given valve model and size in aortic annuli of different size may yield to different degrees of valve expansion and thus somewhat different EOAs. Over- or undersizing and, thus, overexpansion or underexpansion of the device may explain some of the burden of PPM. To overcome this limitation, we also used a second method (PPM$_{P2}$) that derives the EOAs

**CENTRAL ILLUSTRATION** Incidence and Impact of PPM by Measured and Predicted EOAi Methods

INCIDENCE OF PROSTHESIS-PATIENT MISMATCH

1- Incidence of severe PPM is markedly lower with predicted vs. measured EOAi.

2- TAVR has lower incidence of severe PPM compared to SAVR, regardless of the EOAi method used to identify PPM.
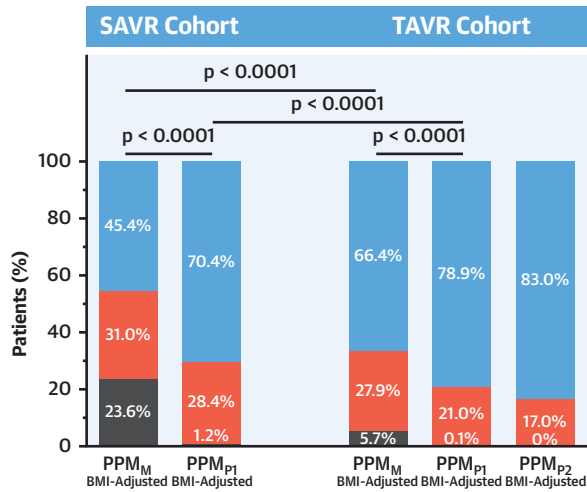
IMPACT OF PROSTHESIS-PATIENT MISMATCH ON OUTCOMES

1- In SAVR, severe PPM by the predicted EOAi method is rare but independently associated with worse outcomes.

2- In TAVR, severe PPM by the predicted EOAi method is absent.

3- In both SAVR and TAVR, moderate PPM is not associated with worse outcomes.
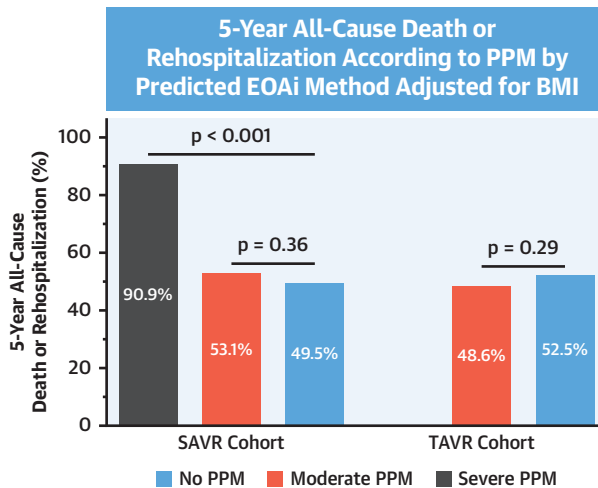
Ternacle, J. et al. J Am Coll Cardiol Intv. 2021;14(13):1466–77.

BMI = body mass index; CTA = computed tomography angiography; EOA = effective orifice area; EOAi = indexed effective orifice area; PPM = prosthesis-patient mismatch; PPM_M = prosthesis-patient mismatch defined with the measured indexed effective orifice area; PPM_{P1} = prosthesis-patient mismatch defined with predicted indexed effective orifice area method 1; PPM_{P2} = prosthesis-patient mismatch defined with predicted indexed effective orifice area method 2 (only for transcatheter aortic valve replacement); SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

from the aortic annulus area measured by computed tomography prior to the procedure. However, this second method cannot account for the final valve circularization and expansion after the procedure and may not take into account the final inner diameter of the prosthesis where flow occurs. This limitation likely had no or minimal impact on the results of this study because the normal reference values of EOA (12) have been obtained from the same population as the one included in the present study (i.e., the PARTNER 2 SAPIEN 3 registry). Furthermore, the percentage of valve oversizing was not associated with the occurrence of severe measured PPM or with the reclassification of severe measured PPM to nonsevere predicted PPM in the TAVR cohort. The normal reference values of EOA used to predict the EOAi of the TAVR patients in the in the present study were derived from measured echocardiographic data of the whole PARTNER 2 SAPIEN 3 registry, which included approximately 30% of patients with a low-flow state

at 30 days. If the average normal EOA values for the SAPIEN 3 valve had been derived only from the patients with normal flow, they would be somewhat larger than those obtained from the whole cohort and used in the present study. In such case, the predicted EOAi would be even larger and the incidence of predicted PPM even lower. This would not change the conclusion of the paper, given that the incidence of predicted PPM was already extremely low in the TAVR group.

CONCLUSIONS

Our findings suggest that the EOAi measured by echocardiography overestimates the incidence and severity of PPM following SAVR or TAVR, relative to the predicted EOAi. The predicted EOAi indeed yields to a much lower rate of PPM compared with the measured EOAi and reveals that "true-severe" PPM is rare (<1.5%) but is associated with clinical outcomes in contemporary SAVR, whereas it is absent following TAVR with the SAPIEN 3 valve.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

ADDRESS FOR CORRESPONDENCE: Dr Philippe Pibarot, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec, G1V-4G5, Canada. E-mail: philippe.pibarot@med.ulaval.ca. Twitter: @PPibarot.

PERSPECTIVES

WHAT IS KNOWN? The vast majority of previous SAVR studies have used the predicted EOAi to define PPM and generally reported a significant and strong association between severe PPM and clinical outcomes. All TAVR series have used the measured EOAi to define PPM and found no or weak association between severe PPM and outcomes.

WHAT IS NEW? Severe PPM defined by the predicted EOAi is rare (<2%) but is independently associated with increased all-cause death and rehospitalization after SAVR. Severe PPM by the predicted EOAi is absent following TAVR with the SAPIEN 3 valve.

WHAT IS NEXT? The incidence and clinical impact of severe PPM defined with the use of the predicted EOAi need to be investigated in larger series with other types of TAVR valves and with longer follow-up.

REFERENCES

1. Pibarot P, Magne J, Leipsic J, et al. Imaging for predicting and assessing prosthesis-patient mismatch after aortic valve replacement. J Am Coll Cardiol Img 2019;12:149-62.

2. 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 Interamerican Society of Echocardiography and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:589-90.

3. 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. Eur J Cardiothorac Surg 2012;42: S45-60.

4. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22: 975-1014.

5. Pibarot P, Dumesnil JG, Cartier PC, Métras J, Lemieux M. Patient-prosthesis mismatch can be predicted at the time of operation. Ann Thorac Surg 2001;71:S265-8.

6. Head S, Mokhles M, Osnabrugge R, 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.

7. Fallon JM, DeSimone JP, Brennan JM, et al. The incidence and consequence of prosthesis-patient mismatch after surgical aortic valve replacement. Ann Thorac Surg 2018;106:14-22.

8. 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.

9. Makkar RR, Thourani VH, Mack MJ, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med 2020;382: 799-809.

10. Kodali S VHT, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in

inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J 2016;37: 2252–62.

11. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218–25.

12. Hahn RT, Leipsic J, Douglas PS, et al. Comprehensive echocardiographic assessment of normal transcatheter valve function. J Am Coll Cardiol Img 2019;12:25–34.

13. Kappetein AP, Head SJ, Genereux 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;60:1438–54.

14. 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.

15. 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.

16. Coisne A, Ninni S, Edmé JL, et al. Obesity paradox in the clinical significance of effective prosthetic orifice area after aortic valve replacement. J Am Coll Cardiol Img 2019;12:208–10.

17. 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;380:1695–705.

18. 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 Cardio 2014;64:1323–34.

19. Zorn GL 3rd, Little SH, Tadros P, et al. Prosthesis-patient mismatch in high-risk patients with severe aortic stenosis: a randomized trial of a self-expanding prosthesis. J Thorac Cardiovasc Surg 2016;151:1014–23.e3.

20. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. J Am Coll Cardiol 2018;72:2701–11.

21. 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 transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2017;10:1578–87.

22. Le Ven F, Thébault C, Dahou A, et al. Evolution and prognostic impact of low flow after transcatheter aortic valve replacement. Heart 2015;101: 1196–203.

23. Anjan VY, Herrmann HC, Pibarot P, et al. Evaluation of flow after transcatheter aortic valve replacement in patients with low-flow aortic stenosis. A secondary analysis of the PARTNER randomized clinical trial. JAMA Cardiol 2016;1:584–92.

24. Pibarot P, Clavel MA. Prosthesis-patient mismatch after transcatheter aortic valve replacement: It is neither rare nor benign. J Am Coll Cardiol 2018;72:2712–6.

25. Popma JJ, Khabbaz K. Prosthesis-patient mismatch after "high-risk" aortic valve replacement. J Am Coll Cardiol 2014;64:1335–8.

26. Sa M, de Carvalho MMB, Sobral Filho DC, et al. Surgical aortic valve replacement and patient-prosthesis mismatch: a meta-analysis of 108 182 patients. Eur J Cardiothorac Surg 2019;56:44–54.

27. Tzikas A, Piazza N, Geleijnse ML, et al. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic CoreValve system in patients with aortic stenosis. Am J Cardiol 2010;106:255–60.

28. 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.

29. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol 2009;53:1883–91.

30. 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.

31. Herrmann HC. Prosthesis-patient mismatch after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2019;12:2183–5.

32. Pibarot P, Salaun E, Dahou A, et al. Echocardiographic results of transcatheter versus surgical aortic valve replacement in low-risk patients: the PARTNER 3 trial. Circulation 2020;141:1527–37.

33. Abbas AE, Mando R, Hanzel G, Goldstein J, Shannon F, Pibarot P. Hemodynamic principles of prosthetic aortic valve evaluation in the transcatheter aortic valve replacement era. Echocardiography 2020;37:738–57.

34. Sengupta A, Zaid S, Kamioka N, et al. Mid-term outcomes of transcatheter aortic valve replacement in extremely large annuli with Edwards SA-PIEN 3 valve. J Am Coll Cardiol Intv 2020;13: 210–6.

35. Halim SA, Edwards FH, Dai D, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation 2020;141:1071–9.