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ORIGINAL RESEARCH

STRUCTURAL

Prosthesis-Patient Mismatch in Young and Low-Risk Patients After Newer Generation Balloon-Expandable Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND The clinical impact of prosthesis-patient mismatch (PPM) after transcatheter aortic valve replacement (TAVR) is not well known in young and low-risk patients.

OBJECTIVES The aim of this single-center study was to evaluate the incidence, predictors, and long-term impact of PPM in young and low-risk patients with severe native aortic stenosis (AS) following TAVR.

METHODS From August 2015 to December 2022, a total of 3,549 patients underwent TAVR with newer generation balloon-expandable valves. Among them, 512 patients with severe native AS who were younger than 75 years and had Society of Thoracic Surgeons scores <4% were included. All-cause and cardiovascular mortality or heart failure hospitalization during follow-up period were compared between the PPM and non-PPM groups. PPM was defined according to the Valve Academic Research Consortium-3 criteria.

RESULTS PPM was observed in 200 of 512 patients (39.0%), with moderate and severe PPM in 162 of 512 (31.6%) and 38 of 512 (7.4%), respectively. Younger age, female sex, larger body surface area, no balloon postdilation, and smaller annular area were independent predictors of PPM. Over a median follow-up duration of 1,034 days (Q1-Q3: 550-1,567 days), compared with the non-PPM group, the PPM group had significantly higher all-cause mortality (HR: 2.55; 95% CI: 1.3-5.0; $P = 0.007$), cardiovascular mortality (HR: 2.81; 95% CI: 1.1-7.5; $P = 0.04$), and heart failure hospitalization (HR: 4.43; 95% CI: 2.0-9.9; $P < 0.001$).

CONCLUSIONS PPM is associated with worse clinical outcomes in young and low-risk patients with AS after TAVR, even with newer generation balloon-expandable valves. (JACC Cardiovasc Interv. 2025;18:1512-1523) © 2025 by the American College of Cardiology Foundation.

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In recent decades, transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of severe aortic stenosis (AS) in inoperable and high-risk patients. Subsequent randomized trials involving intermediate- and low-risk patients demonstrated that the overall clinical benefit of TAVR was comparable with that of surgical aortic valve replacement (SAVR).[1,2] As a result, TAVR has been rapidly adapted as the main treatment option for severe AS among younger adult patients.

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of the implanted prosthetic valve is small compared with the patient's body size.[3] PPM has been reported to be associated with an increased risk for mortality and cardiac rehospitalization after SAVR.[4] Compared with SAVR, the clinical impact of PPM after TAVR remains inconclusively established, with sparse and inconsistent results.[1,2,5-8] These discrepancies may be related to clinical background differences across patient populations, as TAVR patients are typically older and potentially less susceptible to the adverse effects of PPM because of lower physical demands and different comorbidity profiles.[9]

As TAVR use expands in young and low-risk patients, PPM may have a larger impact because of heightened demands and longer exposure. Until now, there has been no systemic investigation regarding the impact of PPM, specifically in young and low-risk patients who develop severe native AS following TAVR. The aim of this study was to evaluate the incidence, predictors, and outcomes of PPM after TAVR with newer generation balloon-expandable valves (BEVs) in this patient population.

METHODS

STUDY DESIGN. This single-center, retrospective, observational study included patients with severe AS who were considered young and low risk and underwent TAVR with newer generation BEVs (SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN 3 Ultra RESILIA, Edwards Lifesciences). From August 2015 to December 2022, a total of 3,549 patients underwent TAVR with the newer generation BEVs at our institution. Among them, after the exclusion of patients for whom transthoracic echocardiographic (TTE) data were not available to determine the presence of PPM and those who underwent valve-in-valve TAVR within failed surgical bioprosthesis, 512 patients were eligible for study analysis. A multidisciplinary heart team determined TAVR eligibility, selecting valve size on the basis of annular area measured using computed tomography and transesophageal echocardiography. TTE imaging was performed at baseline, discharge, 30 days, 1 year, and 3 years. Additionally, assessment of NYHA functional classification, 5-m walk test, and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score were conducted at baseline, 30 days, 1 year, and annually thereafter.

The study adhered to the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Cedars-Sinai Medical Center, with informed consent obtained from all the patients.

DEFINITIONS. Young and low-risk patients were defined as those younger than 75 years with Society of Thoracic Surgeons (STS) scores <4%. PPM was assessed at 30 days after TAVR using TTE imaging and defined according to the latest Valve Academic Research Consortium-3 criteria from the indexed EOA.[10] Predicted EOA was assessed using reference values of EOA from published data for each size and type of implanted transcatheter heart valve.[11] Moderate PPM was defined as indexed EOA >0.65 and ≤0.85 cm^2/m^2 (>0.55 and ≤0.70 cm^2/m^2 for body mass index ≥30 kg/m^2) and severe PPM as indexed EOA ≤0.65 cm^2/m^2 (≤0.55cm^2/m^2 for body mass index ≥30 kg/m^2). Clinical outcomes were defined according to the Valve Academic Research Consortium-3 criteria.[10] Percentage of oversizing was determined as follows: [(transcatheter heart valve nominal area/annular area − 1) × 100].[5]

ENDPOINTS. Clinical outcomes were compared between 2 groups on the basis of the presence of PPM, with the PPM group including moderate and severe PPM in this study. The primary study endpoint was all-cause mortality at 5 years following TAVR. The secondary endpoints were cardiovascular mortality, heart failure (HF) hospitalization and stroke or transient ischemic attack at 5 years. Functional status and quality of life (QOL) were also assessed using the NYHA functional classification, the 5-m walk test, and KCCQ overall summary score.

STATISTICAL ANALYSES. Continuous variables are expressed as mean ± SD or median (Q1-Q3), depending on the distribution of the data, and categorical variables are presented as number (percentage). The Mann-Whitney *U* test, Student's *t*-test, or the Pearson chi-square test was used for comparisons between the groups for continuous and categorical variables, as appropriate. Mixed-effects models were used to evaluate changes in NYHA functional class, 5-m walk

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
BEV = balloon-expandable valve
BSA = body surface area
EOA = effective orifice area
HF = heart failure
KCCQ = Kansas City Cardiomyopathy Questionnaire
PPM = prosthesis-patient mismatch
QOL = quality of life
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement
TTE = transthoracic echocardiographic

TABLE 1 Baseline Characteristics

	PPM (n = 200)	Non-PPM (n = 312)	*P* Value
Clinical characteristics			
Age, y	68.3 (63.8-72.3)	70.0 (65.0-73.0)	0.055
Male	137 (68.5)	214 (68.6)	0.983
BSA, m^2	2.10 (1.90-2.27)	1.86 (1.71-2.02)	<0.001
BMI, kg/m^2	32.7 (28.2-37.2)	25.8 (23.4-28.7)	<0.001
Hypertension	169 (84.5)	232 (74.4)	0.007
Diabetes mellitus	78 (39)	87 (27.9)	0.009
Dyslipidemia	138 (69.0)	209 (67.0)	0.634
Current smoking	15 (7.5)	26 (8.3)	0.735
CKD (eGFR <30 mL/min)	9 (4.5)	19 (6.1)	0.440
STS score, %	1.60 (1.10-2.31)	1.47 (1.04-2.10)	0.112
NYHA functional class III or IV	174 (87.0)	265 (84.9)	0.515
Previous heart failure hospitalization	158 (79.0)	238 (76.3)	0.474
Previous CABG	11 (5.5)	19 (6.1)	0.782
Previous PCI	50 (25.0)	59 (18.9)	0.101
Coronary artery disease	44 (22.0)	48 (15.4)	0.057
Previous myocardial infarction	27 (13.5)	39 (12.5)	0.742
Peripheral vascular disease	13 (6.5)	18 (5.8)	0.735
Atrial fibrillation	37 (18.5)	42 (13.5)	0.124
Pacemaker	14 (7.0)	15 (4.8)	0.295
Hemodialysis	11 (5.5)	10 (3.2)	0.201
Stroke	14 (7.0)	17 (5.4)	0.473
TIA	8 (4.0)	7 (2.2)	0.250
Chronic respiratory insufficiency	19 (9.5)	30 (9.6)	0.965
Bicuspid aortic valve	49 (24.5)	104 (33.3)	0.033
Echocardiographic characteristics			
Peak velocity, m/s	4.13 (3.82-4.50)	4.12 (3.82-4.53)	0.871
Maximum AV gradient, mm Hg	70.0 (62.0-81.5)	70.0 (60.0-82.3)	0.756
Mean AV gradient, mm Hg	43.0 (40.0-52.0)	43.0 (37.0-52.0)	0.620
AVA, cm^2	0.70 (0.60-0.88)	0.70 (0.60-0.90)	0.095
LVEF, %	61.5 (55.0-68.0)	64.0 (58.0-67.0)	0.078
LV mass, g	237.8 (190.4-297.3)	212.0 (167.8-261.5)	<0.001
LV mass index, g/m^2	111.6 (93.6-140.1)	113.3 (91.4-137.9)	0.730
AR moderate or greater	8 (4.0)	20 (6.4)	0.242
MR moderate or greater	14 (7.0)	15 (4.8)	0.295
TR moderate or greater	8 (4.0)	12 (3.8)	0.930
TRPG, mm Hg	24.0 (18.3-33.0)	25.0 (19.0-29.0)	0.614
PAP, mm Hg	28.0 (21.3-37.0)	28.0 (22.0-33.0)	0.545
Computed tomographic characteristics			
Annular area, mm^2	481.1 (424.9-555.7)	495.0 (431.3-572.9)	0.410
Annular area-to-BSA ratio, mm^2	233.2 (206.1-260.2)	263.8 (234.4-300.1)	<0.001
Perimeter, mm	78.9 (74.0-84.5)	79.8 (75.0-86.2)	0.313
Mean annular diameter, mm	25.0 (23.5-26.6)	25.1 (23.4-27.0)	0.438

Values are median (Q1-Q3) or n (%).

AR = aortic valve regurgitation; AV = aortic valve; AVA = aortic valve area; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral valve regurgitation; PAP = pulmonary artery pressure; PCI = percutaneous coronary intervention; PPM = prosthesis-patient mismatch; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack; TR = tricuspid regurgitation; TRPG = tricuspid regurgitation pressure gradient.

distance, and KCCQ overall summary score. Multivariate logistic regression was conducted to identify risk factors for PPM and all-cause mortality. Candidate variables were selected using a theory-driven strategy based on prior literature. Cumulative survival rates were analyzed using the Kaplan-Meier method, and differences were assessed using Cox regression analyses. The proportional hazards assumption was evaluated using Schoenfeld residuals and log-log survival plots. The global test showed no significant violations, and no individual covariate demonstrated significant time-dependent effects. To account for the competing risk for death when evaluating changes in health status, ordinal logistic regression analyses were conducted. Categories were defined on the basis of established thresholds for clinically meaningful changes in the KCCQ overall summary score:[12] 1) dead; 2) worse (>5-point decrease from baseline); 3) no change (5-point decrease to <5-point increase); 4) slight improvement (5- to <10-point increase); 5) moderate improvement (10- to <20-point increase); and 6) substantial improvement (≥20-point increase). Significance was set at $P < 0.05$. All statistical analyses were conducted using SPSS version 24.0 (IBM).

RESULTS

BASELINE CHARACTERISTICS. In 512 studied patients, the median age of the overall population was 69.4 years (Q1-Q3: 65.0-72.9 years) and the median STS score was 1.50 (Q1-Q3: 1.08-2.20). PPM, according to measured indexed EOA, was observed in 200 of 512 patients (39.0%), with moderate and severe PPM in 162 (31.6%) and 38 (7.4%) patients, respectively. When classified by predicted EOA on the basis of transcatheter heart valve size, the frequency of moderate and severe predicted PPM was 75 of 512 (14.6%) and 8 of 512 (1.6%), respectively.

Baseline clinical, TTE, and computed tomographic characteristics between the PPM and non-PPM groups are summarized in Table 1. Patients with PPM had larger body surface area (BSA) and more frequent histories of hypertension and diabetes. At baseline, patients with PPM had lower left ventricular ejection fractions than those without PPM. Peak velocities, both maximum and mean gradients across the diseased valve, and left ventricular mass index were not different between the groups. Computed tomography-derived annular area was not different between the groups.

PROCEDURAL DATA AND ECHOCARDIOGRAPHIC OUTCOMES. As presented in Table 2, devices used were the SAPIEN 3 in 260 of 512 patients (50.8%), the SAPIEN 3 Ultra in 237 (46.3%), and the SAPIEN 3 Ultra RESILIA in 15 (2.9%). Although the rate of predilation and the sizes of the implanted valves were similar between the groups, postdilation was performed less frequently in the PPM group.

On TTE imaging at discharge, patients with PPM demonstrated higher peak velocities and maximum and mean gradients across the valve, along with

smaller EOA measurements. These significant differences were persistently observed up to 3 years after TAVR (Table 3). Both groups experienced significant left ventricular mass regression over time. However, the reduction was less pronounced in the PPM group than in the non-PPM group (Supplemental Figure 1).

PREDICTORS OF PPM. The logistic regression analysis for assessing associations between the clinical and procedural characteristics and PPM is presented in Table 4. In the logistic multivariate regression analysis, younger age, female sex, larger BSA, no balloon postdilation, and smaller annular area were identified as independent predictors of PPM. To evaluate the effect of postdilation on PPM, we conducted an analysis to assess its associations with other variables potentially linked to PPM (Supplemental Figure 2). Among patients with oversizing of ≥10%, the incidence of PPM was significantly lower in those who underwent postdilation compared with those who did not (OR: 0.32; 95% CI: 0.1-0.9; $P = 0.004$).

IMPACT OF PPM ON LONG-TERM OUTCOMES. At a median follow-up of 1,034 days (Q1-Q3: 550-1,567 days), a total of 36 of 512 patients (7.0%) had died. Causes of death are described in Supplemental Table 1. As illustrated in Figure 1A, PPM was significantly associated with increased all-cause mortality (HR: 2.55; 95% CI: 1.3-5.0; $P = 0.007$). Cardiovascular mortality (HR: 2.81; 95% CI: 1.1-7.5; $P = 0.04$) (Figure 1B) and HF hospitalization (HR: 4.43; 95% CI: 2.0-9.9; $P < 0.001$) (Figure 1C) were also higher in the PPM group. No difference in stroke or transient ischemic attack was observed between the groups (Figure 1D). The determinant factors of all-cause mortality were also evaluated. After multivariate regression analysis, chronic kidney disease, STS score, and PPM were identified as independent predictors of all-cause mortality (Table 5). Additional clinical outcomes, including myocardial infarction, major bleeding, new permanent pacemaker implantation, valve thrombosis, and valve reintervention at 5 years, are summarized in Supplemental Table 2.

Clinical outcomes at 5 years according to predicted PPM are summarized in Supplemental Figure 3. None of the patients with severe predicted PPM died, and there were no significant differences between the groups in all-cause mortality, cardiovascular mortality, HF hospitalization, and stroke or transient ischemic attack.

FUNCTIONAL STATUS AND QOL. Longitudinal changes in NYHA functional class, 5-m walk distance, and KCCQ overall summary score are presented in Figure 2. Improvement was less pronounced in the PPM group compared with the non-PPM group. Linear mixed-effects models demonstrated a significant time-group interaction ($P < 0.01$, $P = 0.002$, and $P = 0.002$, respectively). Furthermore, when ordinal logistic regression analyses were performed with death as the worst outcome, non-PPM was superior to PPM at 3- and 5-year follow-up (Central Illustration).

TABLE 2 Procedural Characteristics in Patients With or Without PPM

	PPM (n = 200)	Non-PPM (n = 312)	*P* Value
Prosthesis			0.112
SAPIEN 3	102 (51.0)	158 (50.6)	
SAPIEN 3 Ultra	96 (48.0)	141 (45.2)	
SAPIEN 3 Ultra RESILIA	2 (1.0)	13 (4.2)	
Valve size			0.654
20 mm	4 (2.0)	0 (0)	
23 mm	45 (22.5)	72 (23.1)	
26 mm	87 (43.5)	133 (42.6)	
29 mm	64 (32.0)	107 (34.3)	
Small valve size (<26 mm)	49 (24.5)	72 (23.1)	0.916
Approach			0.444
Transfemoral	199 (99.5)	307 (98.4)	
Transapical	1 (0.5)	1 (0.3)	
Transcarotid	0 (0)	3 (1.0)	
Trans-subclavian	0 (0)	1 (0.3)	
Balloon predilation	13 (6.5)	27 (8.9)	0.331
Balloon postdilation	16 (8.0)	44 (14.5)	0.029
Contrast volume, ml	70 (50.0-90.0)	70 (50.0-100.0)	0.787
Fluoroscopy time, min	14.8 (10.7-19.1)	15.1 (11.3-19.1)	0.263

Values are n (%) or median (Q1-Q3).
PPM = prosthesis-patient mismatch.

SUBGROUP ANALYSIS. To further evaluate the association between PPM severity and outcomes, subgroup analysis with the 3-group comparison among patients with no, moderate, and severe PPM was performed. Baseline characteristics, procedural data, and echocardiographic outcomes among the patients are presented in Supplemental Tables 3 to 5. Kaplan-Meier estimates of all-cause mortality by PPM severity are illustrated in Figure 3A. There was a trend toward increased overall mortality, as well as higher cardiovascular mortality and HF hospitalization rates, correlating with the severity of PPM. When compared between the groups, all-cause mortality was significantly higher in the severe PPM group compared with the non-PPM group (HR: 3.25; 95% CI: 1.4-7.6; $P = 0.007$), while a numerical trend was observed for increase of all-cause mortality from the non-PPM to the moderate PPM group (HR: 2.31; 95% CI: 0.9-4.9; $P = 0.054$). Cardiovascular mortality (HR: 5.29; 95% CI: 1.8-15.8; $P = 0.003$) and HF hospitalization

TABLE 3 Postprocedural Echocardiographic Data

Discharge	PPM (n = 200)	Non-PPM (n = 312)	*P* Value
LVEF, %	60.0 (50.3-67.0)	62.0 (56.5-69.0)	0.441
Peak velocity, m/s	2.50 (2.11-2.70)	2.27 (1.97-2.51)	0.001
Aortic peak gradient, mm Hg	24.0 (18.0-28.8)	21.0 (16.0-25.0)	0.002
Aortic mean gradient, mm Hg	13.0 (10.3-16.8)	11.0 (8.0-14.0)	0.001
EOA, cm^2	1.40 (1.18-1.62)	1.71 (1.49-2.00)	<0.001
AR moderate or greater	0 (0)	2 (0.6)	0.257
MR moderate or greater	7 (3.5)	7 (2.2)	0.395
TR moderate or greater	6 (3.0)	13 (4.2)	0.496
TRPG, mm Hg	26.0 (19.0-34.0)	23.0 (16.0-27.0)	0.011
PAP, mm Hg	30.0 (24.5-42.5)	27.0 (19.0-34.0)	0.030
30 d	(n = 200)	(n = 312)	
LVEF, %	61.5 (55.3-67.0)	64.0 (59.0-69.0)	0.009
Peak velocity, m/s	2.48 (2.20-2.76)	2.27 (1.97-2.57)	<0.001
Aortic peak gradient, mm Hg	25.0 (20.0-31.0)	20.2 (15.3-26.0)	<0.001
Aortic mean gradient, mm Hg	13.0 (11.0-17.0)	11.0 (8.0-14.0)	<0.001
Aortic mean gradient ≥20 mm Hg	27 (13.5)	12 (3.8)	<0.001
EOA, cm^2	1.30 (1.12-1.54)	1.66 (1.46-1.95)	<0.001
LV mass, g	215.0 (183.3-265.3)	187.2 (149.5-244.8)	<0.001
LV mass index, g/m^2	103.2 (88.8-128.0)	101.6 (80.7-127.3)	0.294
AR moderate or greater	0 (0)	2 (0.6)	0.257
MR moderate or greater	7 (3.5)	7 (2.2)	0.395
TR moderate or greater	6 (3.0)	13 (4.2)	0.496
TRPG, mm Hg	23.0 (17.0-30.3)	21.0 (17.0-27.0)	0.020
PAP, mm Hg	27.0 (21.0-33.3)	25.0 (20.0-30.0)	0.027
1 y	(n = 111)	(n = 171)	
LVEF, %	62.0 (60-67.0)	63.0 (59.0-67.0)	0.957
Peak velocity, m/s	2.51 (2.23-2.82)	2.31 (1.97-2.58)	0.001
Aortic peak gradient, mm Hg	25.0 (20.0-30.5)	22.0 (16.0-27.0)	0.002
Aortic mean gradient, mm Hg	14.0 (11.0-17.0)	12.0 (9.0-15.5)	<0.001
EOA, cm^2	1.38 (1.14-1.58)	1.57 (1.19-1.86)	0.004
LV mass, g	204.9 (168.5-258.1)	181.3 (136.2-230.2)	0.002
LV mass index, g/m^2	99.3 (80.4-118.7)	93.9 (74.5-115.7)	0.251
AR moderate or greater	0 (0)	4 (2.3)	0.117
MR moderate or greater	1 (0.9)	3 (1.8)	0.597
TR moderate or greater	1 (0.9)	7 (4.1)	0.134
TRPG, mm Hg	21.0 (16.0-30.0)	23.0 (19.0-28.0)	0.390
PAP, mm Hg	25.0 (19.0-33.0)	26.0 (22.0-31.0)	0.507
3 y	(n = 63)	(n = 107)	
LVEF, %	62.0 (57.0-66.0)	63.0 (57.0-65.0)	0.623
Peak velocity, m/s	2.47 (2.23-2.94)	2.34 (2.03-2.52)	0.001
Aortic peak gradient, mm Hg	24.5 (20.0-34.3)	22.0 (17.0-25.3)	0.001
Aortic mean gradient, mm Hg	14.0 (12.0-18.0)	12.0 (9.0-14.0)	<0.001
EOA, cm^2	1.29 (1.13-1.55)	1.53 (1.35-1.77)	0.007
LV mass, g	208.7 (152.6-267.9)	168.9 (137.8-218.9)	0.003
LV mass index, g/m^2	95.9 (81.1-128.3)	90.8 (74.3-110.9)	0.153
AR moderate or greater	0 (0)	3 (2.8)	0.169
MR moderate or greater	1 (1.6)	1 (0.9)	0.719
TR moderate or greater	1 (1.6)	4 (3.7)	0.397
TRPG, mm Hg	22.0 (17.0-28.5)	23.0 (17.3-28.0)	0.711
PAP, mm Hg	25.0 (20.0-32.5)	26.0 (21.0-31.0)	0.691

Values are median (Q1-Q3) or n (%).
EOA = effective orifice area; other abbreviations as in Table 1.

(HR: 8.83; 95% CI: 3.7-21.1; $P < 0.001$) were also significantly higher in the severe PPM group compared with the non-PPM group.

DISCUSSION

We investigated the incidence, predictors, and long-term clinical impact of PPM in young and low-risk patients following TAVR using BEVs. The major findings of this study were as follows: 1) moderate and severe PPM was fairly frequently detected in the young and low-risk patients; 2) younger age, female sex, larger BSA, no balloon postdilation, and smaller annular area were identified as predictors of PPM; 3) all-cause mortality, cardiovascular mortality, and HF hospitalization in the PPM group were higher than in the non-PPM group; and 4) improvements in functional status and QOL were less significant in the PPM group compared with the non-PPM group.

The incidence of at least moderate PPM in this study was 200 of 512 (39.0%), with 162 of 512 (31.6%) for moderate PPM and 38 of 512 (7.4%) for severe PPM. This rate is higher compared with rates observed in previous studies that used the latest Valve Academic Research Consortium-3 definition. The incidence of moderate and severe PPM in those reports ranged from 8.9% to 27.0% and 0.7% to 8.7%, respectively.[5,7,8,13] However, those studies included self-expandable valve, older generation devices, and patients older than 80 years. All these factors are reportedly not associated with PPM[1,14,15] and may have a favorable impact in lowering PPM incidence. BSA is strongly associated with PPM[1,5] and in fact was identified as an independent predictor of PPM in our study. The median BSA in our study was 1.94 m^2, whereas the median BSA in previous studies was smaller (1.41 m^2 in an Asian cohort and 1.87 m^2 in a U.S. population in the STS/American College of Cardiology TVT [Transcatheter Valve Therapy] Registry).[5,16] The larger BSA in our study population therefore may contribute to higher PPM incidence.

In this study, measured EOA was used primarily for the assessment of PPM. Recent TAVR studies have suggested that the approach to obtain EOA may affect the frequency of PPM.[17] The use of predicted EOA to define significance of PPM (predicted PPM) has been suggested to underestimate frequency and severity of PPM compared with PPM obtained by measured EOA (measured PPM).[15] In a SAVR series, predicated PPM was associated with mortality.[4] Contrary, in TAVR, no increased risk for death was observed in patients according to the severity of predicted PPM.[13] Consistent with this reported result, our study found no significant association between predicted PPM severity and mortality. One possible explanation is that predicted EOA in TAVR patients may not accurately reflect actual EOA. Anatomical variability such as significant device landing zone calcification and/or annular ellipticity may affect TAVR valve sizing and expansion. These anatomical factors may cause physiologically suboptimal prosthesis expansion, leading to smaller EOA than predicated EOA, even when deployed correctly.[18] Pressure recovery phenomenon is another factor that may affect measured EOA. To minimize its impact, we used measured PPM assessed at 30 days, a time point that minimizes the contribution of low-flow states to the calculation of measured EOA. Last, a high prevalence of low-flow state may lead to "pseudosevere" PPM. In the present study, only 9 patients were identified as having low stroke volumes (defined as <35 mL) at 30 days. Even after excluding these low-flow patients, a significant difference was still observed in survival between the PPM and non-PPM groups.

Consistent with previous studies,[1,5,19] this study demonstrated that postdilation was independently associated with PPM occurrence. Specifically, postdilation in patients with ≥10% oversizing was associated with a lower PPM incidence (Supplemental Figure 2). Although postdilation is generally performed to reduce post-TAVR paravalvular leak,[20] it is also associated with lower rates of moderate or severe PPM by improvement of frame expansion, thus further optimizing EOA. The balance of risk and benefit of aggressive postdilation needs to be carefully assessed on an individual case basis, as an increased risk for cerebrovascular events after postdilation has been reported.[19,20]

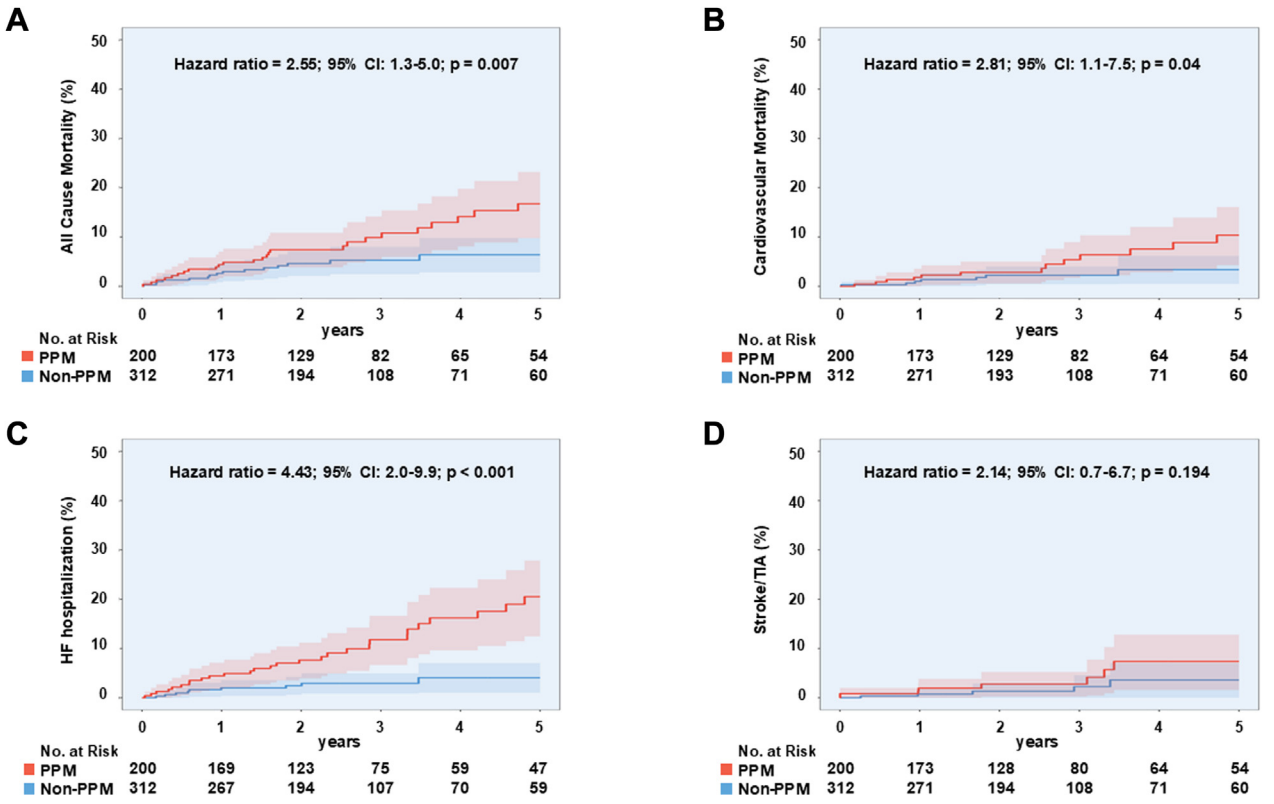
In this study, "measured" PPM was independently associated with 5-year all-cause and cardiovascular mortality. These findings highlight the adverse

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

	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.97 (0.95-0.99)	0.036	0.95 (0.92-0.99)	0.015
Female	1.01 (0.69-1.47)	0.983	2.32 (1.24-4.35)	0.009
BSA (per 0.1-m^2 increase)	1.51 (1.38-1.65)	<0.001	1.70 (1.50-1.93)	<0.001
Hypertension	1.95 (1.23-3.11)	0.005	1.36 (0.76-2.45)	0.300
Diabetes mellitus	1.65 (1.13-2.41)	0.009	1.36 (0.85-2.17)	0.207
CKD (eGFR <30 mL/min)	0.73 (0.32-1.64)	0.442	0.55 (0.17-1.78)	0.317
Balloon postdilation	0.52 (0.28-0.94)	0.032	0.53 (0.28-0.99)	0.048
Bicuspid aortic valve	0.65 (0.44-0.97)	0.034	0.74 (0.42-1.29)	0.287
Annular area (per 10-mm^2 increase)	0.99 (0.98-1.02)	0.473	0.96 (0.94-0.99)	0.018

Abbreviations as in Table 1.

FIGURE 1 Kaplan-Meier Curves for Time to Event



Each endpoint was calculated using the Kaplan-Meier method and compared using Cox proportional hazards regression for prosthesis-patient mismatch (PPM) vs non-PPM: (A) all-cause mortality, (B) cardiovascular mortality, (C) heart failure (HF) hospitalization, and (D) stroke or transient ischemic attack (TIA). Shaded areas represent 95% CIs.

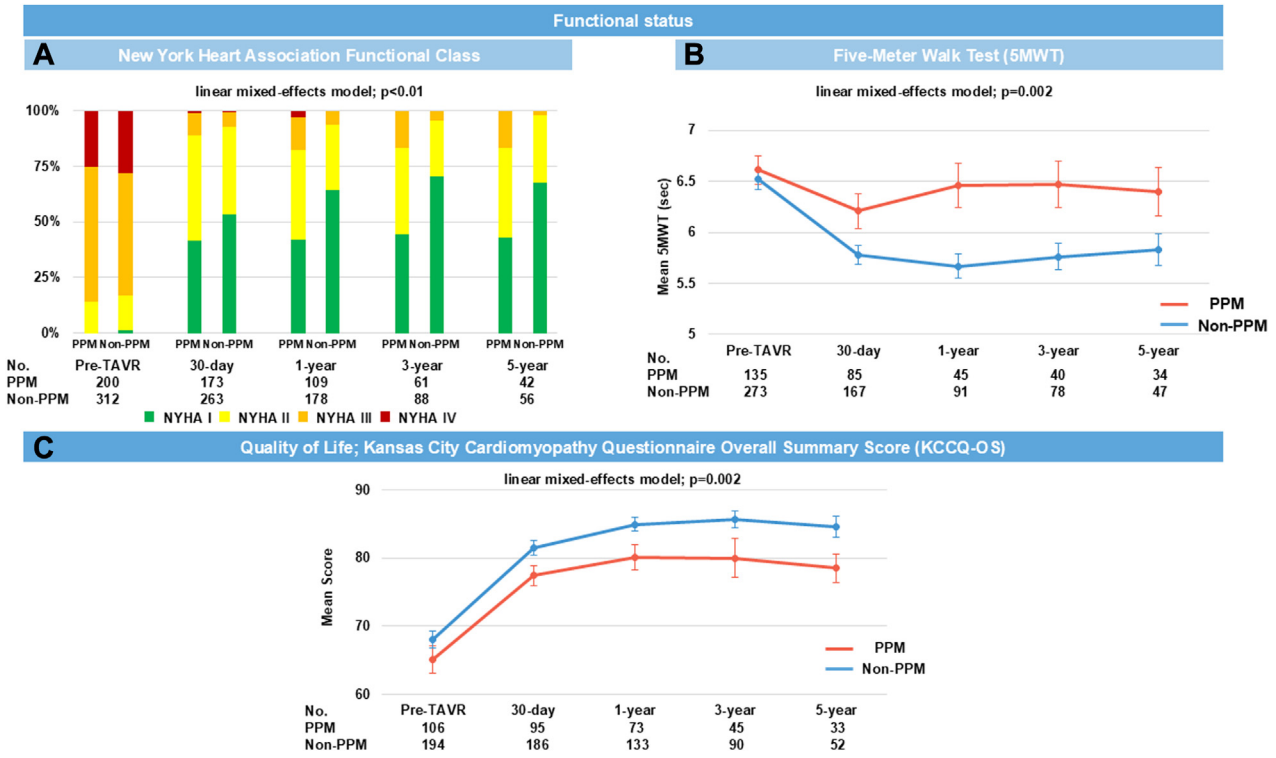
TABLE 5 Multivariable Cox Model for Probability of All-Cause Mortality

	Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	0.99 (0.94-1.03)	0.531		
Male	1.98 (0.85-4.62)	0.114		
BSA (per 0.1-m^2 increase)	0.92 (0.80-1.05)	0.229		
Hypertension	0.81 (0.37-1.77)	0.595		
Diabetes mellitus	1.55 (0.78-3.10)	0.212		
Atrial fibrillation	1.93 (0.87-4.29)	0.104	1.55 (0.66-3.65)	0.314
CKD (eGFR <30 mL/min)	5.23 (2.06-13.31)	0.001	3.60 (1.24-10.46)	0.019
STS score (per 1% increase)	2.16 (1.53-3.05)	<0.001	1.84 (1.26-2.70)	0.002
Previous PCI	1.95 (0.94-4.05)	0.071	1.28 (0.58-2.81)	0.543
LVEF (per 10% increase)	1.05 (0.98-1.14)	0.182		
Mean AV gradient ≥20 mm Hg	1.11 (0.33-3.80)	0.867		
PPM (moderate or greater)	2.99 (1.48-6.05)	0.002	3.20 (1.52-6.76)	0.002

Abbreviations as in Table 1.

impact of PPM on long-term clinical outcomes, in young and low-risk patients. Previous studies have reported inconsistent results regarding the association between PPM and mortality after TAVR.[1,2,5-8] One possible explanation for this is the variation in follow-up periods. A potential pathophysiological mechanism underlying the increased mortality associated with PPM is the persistent residual left ventricular afterload and less regression of left ventricular hypertrophy, which may impair the postoperative normalization of coronary flow reserve.[21] In the present study, less left ventricle mass regression was observed during the follow-up period in patients with PPM compared with those without PPM. Together with a previous study,[22] our findings further support the notion that suboptimal left ventricular mass regression may contribute to adverse clinical outcomes. Levesque et al[8]

FIGURE 2 **Functional Status and Quality-of-Life Outcomes**



(A) Bar graph showing the distribution of NYHA functional class at pre-transcatheter aortic valve replacement (TAVR) and follow-up intervals for patients in the prosthesis-patient mismatch (PPM) and non-PPM groups. Linear mixed-effects models revealed significant differences between groups across time points ($P < 0.01$). (B) Five-meter walk test (5MWT). (C) Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS). Line graphs illustrating changes in mean walking time and KCCQ-OS in the PPM and non-PPM groups at pre-TAVR and follow-up intervals. Significant differences between the groups over time were identified using linear mixed-effects models for each parameter ($P = 0.002$). Error bars represent the SEM.

demonstrated that PPM had a negative long-term impact on outcomes after TAVR but only beyond 4-year follow-up. In our study, the notable survival curve dissociation after 1-year with continuous separation over the remaining follow-up period reaffirms a potential negative long-term impact of PPM on clinical outcomes.

Another potential reason for the conflicting outcomes among the studies is the differences in patient populations. Tang et al[23] suggested that the absence of clinical influence from PPM in their study may have been due to significant comorbidities, high surgical risk cohort (median STS score 7.4%), and high mortality from noncardiovascular causes. Additionally, these patients were often frail, with lower cardiac output demands, which may reduce the physiological strain and diminish the hemodynamic impact of PPM. Other published studies including SAVR patients have suggested that the impact of PPM on mortality was only observed in younger patients (age <70 years).[9] Our study enrolled patients with a median STS score of 1.50 and a median age of 69 years. Moreover, noncardiovascular mortality at 5 years after TAVR was only 12 of 36 (33%), which is relatively low compared with that previously reported in a systematic review (52%).[24] With a longer life expectancy, young and low-risk patients are likely exposed to the long-term risk for PPM.

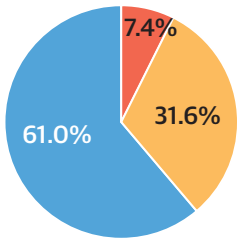
In our subgroup analysis, all-cause mortality trended toward an increase even in the moderate PPM group. In a meta-analysis, only severe PPM is associated with higher risk for mortality after TAVR, with no observed trend toward increased mortality in patients with moderate PPM.[25] The extended negative hemodynamic impact of PPM, particularly in younger and low-risk patients who have higher physiological demands, may contribute to progressively increasing mortality even in patients with moderate PPM. These findings highlight the importance of preventive intervention of even moderate PPM in young and

CENTRAL ILLUSTRATION **Prosthesis-Patient Mismatch in Young and Low-Risk Patients**

Incidence, Predictors, and Long-Term Impact of PPM in Young and Low-Risk Patients With Severe Aortic Stenosis Following Transcatheter Aortic Valve Replacement

Age <75 years, STS score <4 %
(N = 512)

Incidence



Significant Predictors

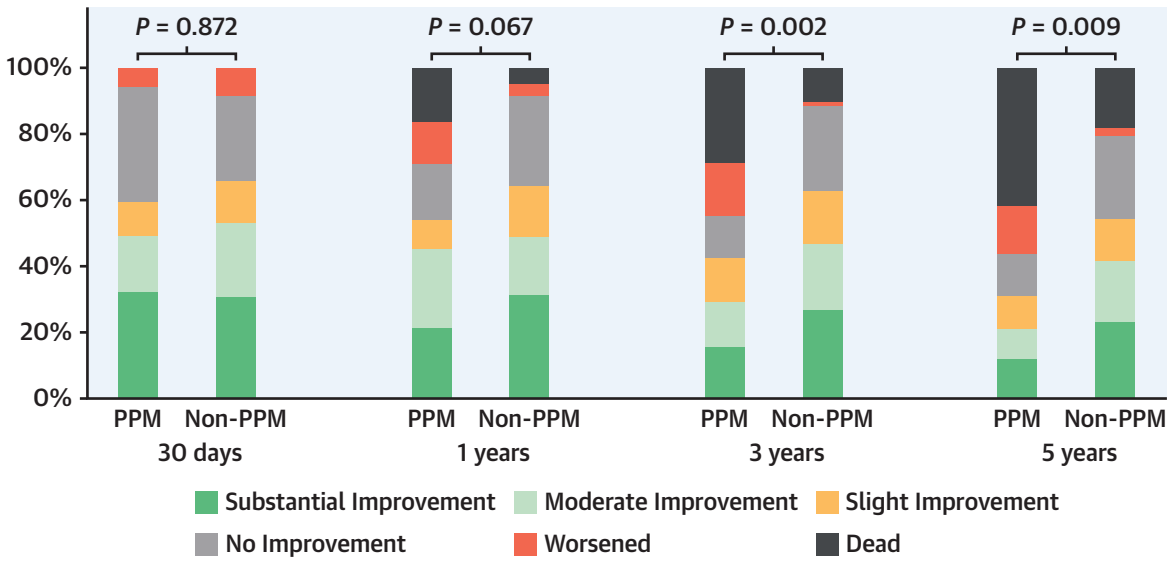
- Younger age
- Female
- Larger BSA
- No balloon postdilation
- Smaller annulus area

Clinical Outcomes

↑ All-cause mortality or cardiovascular mortality

↑ HF hospitalizations

Quality of Life (QOL); KCCQ-OS Over Time

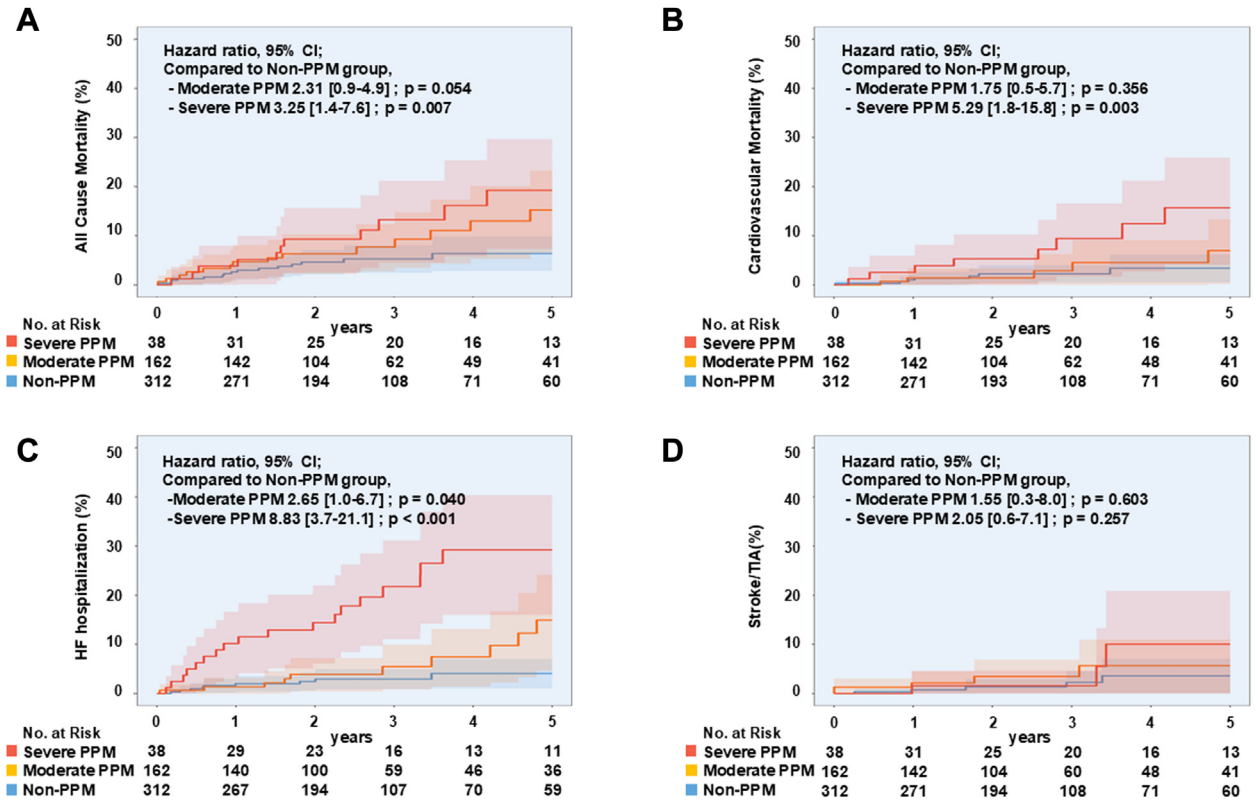


- In young and low-risk patients, PPM was associated with higher all-cause and cardiovascular mortality and increased HF hospitalization over a 5-year follow-up and less QOL improvement.

Suruga K, et al. JACC Cardiovasc Interv. 2025;18(12):1512-1523.

Prosthesis-patient mismatch (PPM) is associated with increased risk for all-cause mortality, cardiovascular mortality, and heart failure (HF) hospitalization. Proportions of PPM and non-PPM patients achieving specific levels of change in Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS) from baseline to 30 days, 1 year, 3 years, and 5 years. Percentages are based on patients with complete follow-up data at each time point. Missing follow-up data are not included in the calculations. *P* values are based on ordinal logistic regression run separately for each time point. BSA = body surface area; QOL = quality of life; STS = Society of Thoracic Surgeons.

FIGURE 3 Kaplan-Meier Curves for Time-to-Event (According to PPM Severity)



Each endpoint was calculated using the Kaplan-Meier method and compared using Cox proportional hazards regression by PPM severity: (A) all-cause mortality, (B) cardiovascular mortality, (C) HF hospitalization, and (D) stroke or TIA. Shaded areas represent 95% CIs. Abbreviations as in Figure 1.

low-risk patients. Bearing in mind these patient background factors, the present results further emphasize the importance of prospective and long-term follow-up in younger patients who develop PPM following TAVR.

An additional key finding in this study is less improvement in QOL assessed by KCCQ overall summary score in the PPM group compared with the non-PPM group after TAVR, contradicting previously reported findings in an older cohort, and demonstrated no difference in KCCQ overall summary score regardless of PPM degree.[16] Although studies of PPM following SAVR suggest no significant association with QOL in older populations,[26] research focused on younger cohorts reveals a potential link between PPM and diminished QOL.[27] Together with reported studies, our findings further support more clinical vulnerability of younger population from the effects of PPM following TAVR.

Recent studies have reported that the SAPIEN 3 Ultra RESILIA has a larger EOA and a lower incidence of PPM compared with the SAPIEN 3 or SAPIEN 3 Ultra.[28] With rapid adaptation of the SAPIEN 3 Ultra RESILIA as the standard BEV treatment system, the risk for PPM, specifically in cases with small annuli, may be further mitigated even compared with self-expanding valve systems, as SMART (Small Annulus Randomized to Evolut™ or SAPIEN™ Trial; NCT04722250), which demonstrated superior performance of self-expanding valves over BEVs, included only the SAPIEN 3 or SAPIEN 3 Ultra as the treatment devices in the BEV cohort.[29] In our study, only 15 of 512 patients (2.9%) received the SAPIEN 3 Ultra RESILIA, limiting the ability to establish its direct impact on reduction of PPM and associated improvement of clinical outcomes. Further studies will be needed to establish the real beneficial impact of this newest generation BEV.

STUDY LIMITATIONS. First, this was a single-center, retrospective study. Second, echocardiography was performed by multiple echocardiographers when

estimating the prosthetic valve EOA. Furthermore, the variability in the timing of discharge echocardiography—whether performed on the same day, the following day, or later—may have influenced the measured echocardiographic parameters.

Third, although this study is the largest and longest to examine the clinical impact of predicted PPM in young and low-risk patients, the low prevalence of severe predicted PPM and the relatively short median follow-up period warrant cautious interpretation of the findings.

Finally, longer follow-up might be necessary to evaluate the true impact of PPM on clinical outcomes after TAVR.

CONCLUSIONS

PPM was frequently observed in young and low-risk patients following TAVR with newer generation BEVs, specifically in association with younger age, female sex, larger BSA, no balloon postdilation, and smaller annular area. PPM was associated with higher all-cause and cardiovascular mortality, increased HF hospitalization, and less QOL improvement over a 5-year follow-up period. These findings support the importance of placing effort on minimizing PPM during TAVR to improve long-term outcomes in this particular patient population.

DATA STATEMENT. The data that support the findings of this study are available upon reasonable request from the corresponding author.

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Dr Makkar has received grant support from Edwards Lifesciences; is a consultant for Abbott Vascular, Cordis, and Medtronic; and holds equity in Entourage Medical. Dr Chakravarty is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic; is a consultant for Abbott Lifesciences; and is a consultant and speaker for Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? TAVR has become a standard treatment for severe AS across all risk profiles, including younger and low-risk patients. However, little information is available on PPM after TAVR in these patients.

WHAT IS NEW? The incidence of PPM in young and low-risk patients undergoing TAVR with newer generation BEVs was 200 of 512 (39.0%), with 162 of 512 (31.6%) with moderate PPM and 38 of 512 (7.4%) with severe PPM. The study demonstrates that PPM is independently associated with higher all-cause and cardiovascular mortality as well as increased HF hospitalization at 5-year follow-up.

WHAT IS NEXT? Long-term studies are needed to validate these findings and explore additional predictors and preventive measures for PPM.

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KEY WORDS low surgical risk, prosthesis-patient mismatch, transcatheter aortic valve replacement, young age

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