Effect of Prosthesis-Patient Mismatch on Long-Term Clinical Outcomes After Bioprosthetic Aortic Valve Replacement

Michael Dismorr, MD, PhD,[a,b] Natalie Glaser, MD, PhD,[a,c] Anders Franco-Cereceda, MD, PhD,[a,b]
Ulrik Sartipy, MD, PhD[a,b]

ABSTRACT

BACKGROUND Prosthesis-patient mismatch (PPM) is common following surgical aortic valve replacement (SAVR).

OBJECTIVES The purpose of this study was to quantify the impact of PPM on all-cause mortality, heart failure hospitalization, and reintervention following bioprosthetic SAVR.

METHODS This observational nationwide cohort study from SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence based care in Heart disease Evaluated According to Recommended Therapies) and other national registers included all patients who underwent primary bioprosthetic SAVR in Sweden from 2003 to 2018. PPM was defined according to the Valve Academic Research Consortium 3 criteria. Outcomes were all-cause mortality, heart failure hospitalization, and aortic valve reintervention. Regression standardization was used to account for intergroup differences and to estimate cumulative incidence differences.

RESULTS We included 16,423 patients (no PPM: 7,377 [45%]; moderate PPM: 8,502 [52%]; and severe PPM: 544 [3%]). After regression standardization, the cumulative incidence of all-cause mortality at 10 years was 43% (95% CI: 24%-44%) in the no PPM group compared with 45% (95% CI: 43%-46%) and 48% (95% CI: 44%-51%) in the moderate and severe PPM groups, respectively. The survival difference at 10 years was 4.6% (95% CI: 0.7%-8.5%) and 1.7% (95% CI: 0.1%-3.3%) in no vs severe PPM and no vs moderate PPM, respectively. The difference in heart failure hospitalization at 10 years was 6.0% (95% CI: 2.2%-9.7%) in severe vs no PPM. There was no difference in aortic valve reintervention in patients with or without PPM.

CONCLUSIONS Increasing grades of PPM were associated with long-term mortality, and severe PPM was associated with increased heart failure. Moderate PPM was common, but the clinical significance may be negligible because the absolute risk differences in clinical outcomes were small. (J Am Coll Cardiol 2023;81:964–975) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

P rosthesis-patient mismatch (PPM) was first described in 1978 by Dr Rahimtoola,[1] who noted that valve prostheses with a small effective (valve) orifice area (EOA) seemed to be associated with hemodynamic and symptomatic worsening after valve replacement. The degree of mismatch is measured by the indexed effective orifice area (iEOA), which is equal to the EOA divided by the patient's body surface area (BSA). The definition of PPM has varied. PPM was previously defined as an iEOA <0.85 cm² and severe PPM was defined as iEOA <0.65 cm². However, a recent definition from the Valve Academic Research Consortium 3 (VARC-3) recommends taking body mass index (BMI) into

From the [a]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [b]Department of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden; and the [c]Department of Cardiology, Stockholm South General Hospital, Stockholm, Sweden.

account. The VARC-3 definition identifies PPM in patients with BMI ≥30 kg/m^2 as an iEOA ≤0.70 cm^2 and severe PPM as iEOA ≤0.55 cm^2. PPM in patients with BMI <30 kg/m^2 is still defined according to the previous definition.[2-4] Previous results are conflicting, with several studies finding an association between PPM and mortality, whereas others have failed to do so.[5-7] The effect of PPM is usually studied and described with relative effect measures, such as ORs or HRs. With the use of Swedish national health data registers and modern biostatistical methods, it is possible to estimate adjusted absolute effect measures such as survival differences between different levels of PPM. This could provide clinicians and patients with easily interpretable information to help guide the best course of action. We performed a nationwide population-based observational cohort study using national health data registers. Our study included patients undergoing bioprosthetic aortic valve replacement in Sweden from 2003 to 2018. The aim was to quantify the impact of PPM on long-term all-cause mortality, heart failure hospitalization and reintervention in patients following bioprosthetic surgical aortic valve replacement (SAVR).

METHODS

STUDY DESIGN. This was an observational, nationwide, population-based cohort study. Study reporting followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD (REporting of studies Conducted using Observational Routinely collected health Data) guidelines.[8,9] Ethical permission was acquired from the Swedish Ethical Review Authority and the requirement for informed consent was waived.

STUDY POPULATION. All adult patients who underwent stented bioprosthetic SAVR in Sweden between January 1, 2003, and December 31, 2018, with or without concomitant ascending aortic surgery and/or coronary artery bypass grafting were included in the study. Patients were excluded if they had concomitant surgery on another valve, prior cardiac surgery or a transcatheter aortic valve replacement (TAVR) procedure, use of deep hypothermia and circulatory arrest, or undetermined BSA, prosthesis model, or prosthesis size.

DATA SOURCES. Patients were identified through the SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence based care in Heart disease Evaluated According to Recommended Therapies) register.[10] SWEDEHEART is a national health data register consisting of a variety of subregisters all related to cardiac care. It includes the Swedish Cardiac Surgery register that collects preoperative, perioperative, and postoperative data on all patients who undergo cardiac surgery in Sweden. The Swedish Cardiac Surgery register has a high reliability and excellent coverage.[11] Survival status was obtained from the Swedish Cardiac Surgery register that is linked to the Total Population register in Sweden.[12] Baseline comorbidities and outcome status for heart failure and TAVR reintervention was acquired from the National Patient Register.[13] The heart failure diagnoses have been validated and shown to have high reliability.[14] Baseline characteristics for socioeconomic status were obtained from Statistics Sweden by the Longitudinal Integrated Database for Health Insurance and Labor Market Studies register.[15] Register linking was performed using the Swedish personal identity number.[16]

PROSTHESIS-PATIENT MISMATCH DEFINITIONS. Patients were categorized as having no, moderate, or severe PPM using published EOA data for each respective model and model size (Supplemental Table 1). BSA was calculated according to the Mosteller method.[17] In the primary analyses, we used the VARC-3 definition where no PPM is defined as iEOA >0.85 cm^2 in patients with BMI <30 kg/m^2 or iEOA >0.70 cm^2 in patients with BMI ≥30 kg/m^2, moderate PPM as iEOA 0.85 to 0.66 cm^2 in patients with BMI <30 kg/m^2 or iEOA 0.70 to 0.56 cm^2 in patients with BMI ≥30 kg/m^2, and severe PPM as iEOA ≤0.65 cm^2 in patients with BMI <30 kg/m^2 or iEOA ≤0.55 cm^2 in patients with BMI ≥30 kg/m^2. In some models, the smallest or largest size did not have a known reference EOA. In those cases, we used the EOA of the adjacent size.

OUTCOMES. The primary outcome was all-cause mortality. Secondary outcomes were heart failure hospitalization and reintervention defined as a subsequent aortic valve operation or a valve-in-valve TAVR procedure.

STATISTICAL METHODS. Baseline characteristics were described as mean ± SD for continuous variables and as frequency and percentage for categorical variables. Time to event was calculated as time in days from the date of surgery until date of event or the end of follow-up on December 31, 2018. The Kaplan-Meier estimator was used to assess crude survival, and the Aalen-Johansen estimator was used to assess the crude cumulative incidence while accounting for the competing risk of death. We calculated restricted

mean survival time, a robust effect measure that estimates mean survival time by integrating the Kaplan-Meier curve restricted to 15 years. A Poisson model was used to calculate age- and sex-adjusted incidence rates. Missing data were handled with *Classification and Regression Tree* imputation.[18] A short description of this method is provided in the Supplemental Appendix. To adjust for potential confounding caused by differences in baseline characteristics between the groups, we used regression standardization. Standardized cumulative survival and survival differences were estimated by regression standardized flexible parametric survival models. The resulting survival curve is an estimate of what population survival would look like had the whole population had no, moderate, or severe PPM. This technique adjusts for the population distribution of covariates and thereby adjusts for potential bias caused by differences in baseline characteristics. A detailed description of the procedure has been described previously.[19] Standardized cumulative incidences and differences of heart failure hospitalization and reintervention were calculated by flexible hazard-based regression standardization as described by Kipouro et al.[20] The resulting cumulative incidence curves can be interpreted as what the population cumulative incidence would look like had the entire population had no, moderate, or severe PPM, while accounting for the competing risk of death and adjusting for the population distribution of covariates. Differences were considered significant if the 95% CI did not include 0. Model selection was performed using clinical subject matter knowledge and guided by the Akaike Information Criterion. The final models are presented in the Supplemental Data. Data management and statistical analyses were performed using the R Programming language version 4.1.2 (R Foundation for Statistical Computing) with the survival, ggplot2, mexhaz, stdReg and rstpm2 packages.[21-25]

RESULTS

We included 16,423 patients who underwent stented bioprosthetic aortic valve replacement in Sweden between 2003 and 2018. We were unable to include 1,512 patients because of missing information on model, size, or BSA, which meant we were not able to calculate iEOA for those patients. The mean patient age was 73 years, and 63% were men. No PPM was present in 7,377 (45%) patients. PPM was present in 9,046 (55%) patients, of which 8,502 (94%) had moderate PPM and 544 (6%) had severe PPM. If categorizing without adjustment for BMI, there were

5,670 (35%) patients with no PPM and 10,753 patients with PPM, of which 9,498 (88%) had moderate PPM and 1,255 (12%) had severe PPM. The presence of moderate and severe PPM has declined since 2013 in Sweden (Supplemental Figure 1). There were low amounts of missing data, with 1.1% of patients missing data related to education level, 0.9% missing estimated glomerular filtration rate, 0.7% missing left ventricular ejection fraction (LVEF), and 0.7% missing emergent operation status. There were small but potentially important differences between the groups. Patients with severe PPM were older, with a mean age of 74 years, and included more women (57%) compared with patients with no PPM (mean age 71 years; 29% women) or moderate PPM (mean age 73 years; 43% women). Baseline characteristics are shown in **Table 1**. The Hancock II and Mosaic prostheses had the highest rates of severe PPM. The proportion of no, moderate, and severe PPM per valve prosthesis model is shown in Supplemental Figures 2 to 4.

ALL-CAUSE MORTALITY. During a total follow-up of 103,374 person-years (mean 6.3 years, max 17.2 years), 6,493 (40%) patients died. Crude and age- and sex-adjusted incidence rates are shown in **Table 2**. The crude cumulative all-cause mortality incidence at 10 years was 47% (95% CI: 46%-49%) in the no PPM group, compared with 50% (95% CI: 48%-51%) in the moderate PPM group and 52% (95% CI: 47%-57%) in the severe PPM group. The restricted mean survival time at 15 years in the no PPM group was 9.8 years (95% CI: 9.7-10.0 years), compared with 9.6 years (95% CI: 9.5-9.7 years) in the moderate PPM group and 9.2 years (95% CI: 8.8-9.7 years) in the severe PPM group. Crude cumulative incidence rates at 5, 10, and 15 years are presented in **Table 3**. After regression standardization, the estimated cumulative incidence of all-cause mortality at 10 years was 43% (95% CI: 24%-44%) in the no PPM group, compared with 45% (95% CI: 43%-46%) in the moderate PPM group and 48% (95% CI: 44%-51%) in the severe PPM group. The estimated difference between no PPM and severe PPM at 10 years was 4.6% (95% CI 0.7%-8.5%) and the estimated difference between no PPM and moderate PPM was 1.7% (95% CI: 0.1%-3.3%). The maximum survival difference between no and severe PPM was 4.8% and occurred at 11.8 years (95% CI: 0.8%-9.0%). Standardized cumulative incidence and differences in all-cause mortality at 5, 10, and 15 years are shown in **Table 4**. Regression standardized survival curves and survival differences are shown in the **Central Illustration**.

TABLE 1 Baseline Characteristics

	Overall (N = 16,423)	No PPM (n = 7,377)	Moderate PPM (n = 8,502)	Severe PPM (n = 544)
Age, y	72.6 ± 8.4	71.4 ± 9.1	73.5 ± 7.7	74.3 ± 7.2
Male	10,320 (62.8)	5,213 (70.7)	4,873 (57.3)	234 (43.0)
Married	10,519 (64.1)	4,706 (63.8)	5,480 (64.5)	333 (61.2)
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	2.0 ± 0.2
Body mass index, kg/m^2				
<18.5	156 (1.0)	115 (1.6)	41 (0.5)	0 (0.0)
18.5-24.9	5,562 (33.9)	2,779 (37.7)	2,710 (31.9)	73 (13.5)
25-29.9	6,992 (42.6)	2,302 (31.2)	4,271 (50.2)	419 (77.4)
>30	3,710 (22.6)	2,181 (29.6)	1,480 (17.4)	49 (9.1)
Education, y				
<10	6,950 (42.8)	3,012 (41.2)	3,690 (43.9)	248 (46.0)
10-12	6,156 (37.9)	2,775 (38.0)	3,192 (38.0)	189 (35.1)
>12	3,136 (19.3)	1,515 (20.7)	1,519 (18.1)	102 (18.9)
Household income				
Q1 (lowest)	3,347 (20.4)	1,380 (18.7)	1,837 (21.6)	130 (23.9)
Q2	3,973 (24.2)	1,738 (23.6)	2,076 (24.4)	159 (29.2)
Q3	4,404 (26.8)	1,959 (26.6)	2,304 (27.1)	141 (25.9)
Q4 (highest)	4,697 (28.6)	2,299 (31.2)	2,284 (26.9)	114 (21.0)
Non-Nordic birth region	958 (5.8)	467 (6.3)	468 (5.5)	23 (4.2)
LVEF, %				
<30	832 (5.1)	463 (6.3)	357 (4.2)	12 (2.2)
30-50	3,605 (22.1)	1,852 (25.2)	1,648 (19.5)	105 (19.4)
>50	11,872 (72.8)	5,022 (68.4)	6,427 (76.2)	423 (78.3)
Prior myocardial infarction	2,709 (16.5)	1,184 (16.0)	1,415 (16.6)	110 (20.2)
Prior heart failure	3,537 (21.5)	1,746 (23.7)	1,698 (20.0)	93 (17.1)
Prior atrial fibrillation	3,075 (18.7)	1,450 (19.7)	1,520 (17.9)	105 (19.3)
Pacemaker/ICD	452 (2.8)	210 (2.8)	225 (2.6)	17 (3.1)
Prior PCI	1,490 (9.1)	663 (9.0)	772 (9.1)	55 (10.1)
Hyperlipidemia	3,827 (23.3)	1,558 (21.1)	2,138 (25.1)	131 (24.1)
Hypertension	9,437 (57.5)	4,103 (55.6)	5,018 (59.0)	316 (58.1)
Prior endocarditis	748 (4.6)	376 (5.1)	356 (4.2)	16 (2.9)
Peripheral vascular disease	2,199 (13.4)	1,125 (15.3)	1,008 (11.9)	66 (12.1)
eGFR, mL/min/1.73 m^2				
<30	433 (2.7)	191 (2.6)	223 (2.6)	19 (3.5)
30-44	1,281 (7.9)	484 (6.6)	723 (8.6)	74 (13.8)
45-59	3,069 (18.9)	1,228 (16.8)	1,722 (20.4)	119 (22.2)
>60	11,494 (70.6)	5,405 (74.0)	5,764 (68.4)	325 (60.5)
COPD	1,804 (11.0)	830 (11.3)	921 (10.8)	53 (9.7)
Diabetes mellitus	3,642 (22.2)	1,504 (20.4)	1,986 (23.4)	152 (27.9)
Prior stroke	2,024 (12.3)	936 (12.7)	1,025 (12.1)	63 (11.6)
History of cancer	2,808 (17.1)	1,293 (17.5)	1,421 (16.7)	94 (17.3)
Hepatic disease	264 (1.6)	119 (1.6)	134 (1.6)	11 (2.0)
Alcohol dependence	463 (2.8)	234 (3.2)	219 (2.6)	10 (1.8)
Period of surgery, y				
2003-2008	5,132 (31.2)	2,243 (30.4)	2,700 (31.8)	189 (34.7)
2009-2013	5,392 (32.8)	2,227 (30.2)	2,946 (34.7)	219 (40.3)
2014-2018	5,899 (35.9)	2,907 (39.4)	2,856 (33.6)	136 (25.0)
Prosthetic valve size, mm				
18-21	5,542 (33.7)	1,290 (17.5)	3,793 (44.6)	459 (84.4)
22-23	6,321 (38.5)	2,325 (31.5)	3,916 (46.1)	80 (14.7)
≥25	4,560 (27.8)	3,762 (51.0)	793 (9.3)	5 (0.9)
Concomitant CABG	6,267 (38.2)	2,565 (34.8)	3,480 (40.9)	222 (40.8)
Ascending aortic surgery	1,442 (8.8)	936 (12.7)	490 (5.8)	16 (2.9)
Emergent operation	241 (1.5)	109 (1.5)	123 (1.5)	9 (1.7)

Values are mean ± SD or n (%). Baseline characteristics of 16,423 patients who underwent bioprosthetic aortic valve replacement in Sweden between 2003 and 2018 classified according to prosthesis-patient mismatch (PPM).

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; Q = quartile.

TABLE 2 Incidence Rate

PPM	Incidence Rate/100 Person-Years (95% CI)		
	All-Cause Mortality	Heart Failure Hospitalization	Reintervention
Crude			
No PPM	6.0 (5.8-6.3)	2.10 (1.96-2.25)	0.62 (0.54-0.70)
Moderate PPM	6.4 (6.2-6.7)	2.20 (2.07-2.34)	0.48 (0.42-0.55)
Severe PPM	7.1 (6.2-8.0)	2.98 (2.40-3.67)	0.50 (0.29-0.82)
Age- and sex-adjusted			
No PPM	6.6 (6.4-6.8)	2.24 (2.10-2.38)	0.54 (0.48-0.62)
Moderate PPM	6.4 (6.2-6.6)	2.17 (2.03-2.33)	0.53 (0.47-0.61)
Severe PPM	6.9 (6.2-7.7)	2.86 (2.32-3.51)	0.64 (0.38-1.07)

Incidence rates per 100 person-years of all-cause mortality, heart failure hospitalization, and reintervention following bioprosthetic aortic valve replacement in Sweden between 2003 and 2018. Age- and sex-adjusted incidence rates were obtained from a Poisson model.

PPM = prosthesis-patient mismatch.

HEART FAILURE HOSPITALIZATION. During a mean follow-up of 5.2 years (max 16 years), 1,882 (11%) patients were hospitalized for heart failure. Crude and age- and sex-adjusted incidence rates are shown in **Table 2**. The no PPM group had a crude cumulative incidence of heart failure hospitalization at 10 years of 15.8% (95% CI: 14.6%-16.9%), the moderate PPM group had a crude cumulative incidence of 15.6% (95% CI: 14.6%-16.6%), and the severe PPM group had a crude cumulative incidence of 20.4% (95% CI: 16.2%-24.7%). Crude cumulative incidence rates at 5, 10, and 15 years are shown in **Table 3**. After regression standardization, the estimated cumulative incidence for heart failure hospitalization at 10 years was 13.3% in the no PPM group (95% CI:

TABLE 3 Crude Cumulative Incidence

	Cumulative Incidence		
	5 Years	10 Years	15 Years
All-cause mortality			
No PPM	19 (19-20)	47 (46-49)	74 (72-76)
Moderate PPM	21 (20-22)	50 (48-51)	77 (75-79)
Severe PPM	22 (18-25)	52 (47-57)	76 (69-83)
Heart failure hospitalization			
No PPM	7.1 (6.5-7.8)	15.8 (14.6-16.9)	21.0 (19.3-22.7)
Moderate PPM	7.5 (6.9-8.1)	15.6 (14.6-16.6)	22.6 (21.0-24.2)
Severe PPM	12.1 (9.2-15.0)	20.4 (16.2-24.7)	26.6 (20.0-33.3)
Reintervention			
No PPM	2.0 (1.7-2.4)	4.5 (3.9-5.1)	6.7 (5.6-7.7)
Moderate PPM	1.7 (1.4-1.9)	3.6 (3.1-4.2)	4.9 (4.1-5.6)
Severe PPM	1.7 (0.5-2.8)	2.9 (1.2-4.6)	5.6 (2.5-8.8)

Values are % (95% CI). Crude cumulative incidence for all-cause mortality, heart failure hospitalization, and reintervention according to prosthesis-patient mismatch (PPM) in patients who underwent bioprosthetic aortic valve replacement in Sweden between 2003 and 2018. Heart failure hospitalization and reintervention using Aalen-Johansen estimator accounting for the competing risk of death.

12.3%-14.4%), 14.4% in the moderate PPM group (95% CI: 13.4%-15.5%) and 19.3% in the severe PPM group (95% CI: 15.9%-23.2%). The estimated difference at 10 years between no and severe PPM was 6.0% (95% CI: 2.2%-9.7%), and the estimated difference between no and moderate PPM was 1.1% (95% CI: −0.2% to 2.5%). Regression standardized cumulative incidence curves and differences for heart failure hospitalization are shown in **Figure 1**. Regression standardized cumulative incidence and differences of rehospitalization at 5, 10, and 15 years are shown in **Table 4**.

AORTIC VALVE REINTERVENTION. During a mean follow-up of 5.4 years (max 16 years), 484 (3%) patients underwent aortic valve reintervention defined as a new surgical valve replacement or a valve-in-valve TAVR procedure. Crude and age- and sex-adjusted incidence rates per 100 person years are shown in **Table 2**. The crude cumulative incidence of reintervention at 10 years was 4.5% in the no PPM group (95% CI: 3.9%-5.1%), 3.6% in the moderate PPM group (95% CI: 3.1%-4.2%), and 2.9% in the severe PPM group (95% CI: 1.2%-4.6%). Crude cumulative incidences are reported at 5, 10, and 15 years in **Table 3**. After regression standardization, the estimated cumulative incidence of reintervention at 10 years was 4.2% in the no PPM group (95% CI: 3.6%-5.0%), 5.1% in the moderate PPM group (95% CI: 4.3%-6.0%), and 6.2% in the severe PPM group (95% CI: 3.9%-9.8%). The estimated difference at 10 years between no PPM and severe PPM was 2% (95% CI: −0.9% to 4.8%) and the estimated difference between no PPM and moderate PPM was 0.8% (95% CI: −0.05% to 1.70%). Regression standardized cumulative incidence and difference in reintervention is shown in **Figure 2**. Regression standardized cumulative incidence and differences for reintervention at 5, 10, and 15 years are shown in **Table 4**.

ADDITIONAL ANALYSES. We explored compound effects including PPM by adding interaction terms with BMI, categorical age, and LVEF, and none were significant. Risk factors for PPM and the number of aortic root enlargement procedures are shown in the Supplemental Table 2 and Supplemental Figure 5, respectively. We also repeated the main analyses using the PPM definition not adjusted for BMI, which yielded similar results. The main analyses using the PPM definition without BMI adjustment are presented in Supplemental Figures 6 to 8 and Supplemental Table 3. As a sensitivity analysis, we estimated the linear change in EOA with size and imputed the estimated EOA, and those analyses provided similar results.

TABLE 4 Regression Standardized Cumulative Incidences and Differences

	Cumulative Incidence		
	5 Years	10 Years	15 Years
All-cause mortality			
No PPM	19 (19 to 20)	43 (42 to 44)	68 (67 to 70)
Moderate PPM	20 (20 to 21)	45 (43 to 46)	70 (68 to 72)
Severe PPM	22 (20 to 25)	48 (44 to 51)	73 (69 to 76)
Difference no vs severe PPM	−2.9 (−5.4 to −0.4)	−4.6 (−8.5 to −0.7)	−4.4 (−7.9 to −0.8)
Difference no vs moderate PPM	−1.0 (−2.0 to −0.1)	−1.7 (−3.3 to −0.1)	−1.6 (−3.2 to −0.1)
Heart failure hospitalization			
No PPM	6.2 (5.7 to 6.8)	13.3 (12.3 to 14.4)	18.4 (16.9 to 20.0)
Moderate PPM	6.9 (6.4 to 7.4)	14.4 (13.4 to 15.5)	19.7 (18.2 to 21.2)
Severe PPM	9.4 (7.7 to 11.6)	19.3 (15.9 to 23.2)	25.7 (21.3 to 30.8)
Difference no vs severe PPM	−3.2 (−5.2 to −1.2)	−6.0 (−9.7 to −2.2)	−7.3 (−12.2 to −2.4)
Difference no vs moderate PPM	−0.6 (−1.3 to 0.0)	−1.1 (−2.5 to 0.2)	−1.2 (−3.0 to 0.6)
Reintervention			
No PPM	1.6 (1.3 to 1.9)	4.2 (3.6 to 5.0)	6.8 (5.6 to 8.2)
Moderate PPM	1.9 (1.6 to 2.3)	5.1 (4.3 to 6.0)	7.9 (6.6 to 9.5)
Severe PPM	2.4 (1.5 to 4.0)	6.2 (3.9 to 9.8)	9.3 (6.1 to 14.2)
Difference no vs severe PPM	−0.9 (−2.1 to 0.4)	−2.0 (−4.8 to 0.9)	−2.5 (−6.5 to 1.4)
Difference no vs moderate PPM	−0.4 (−0.7 to 0.0)	−0.8 (−1.7 to 0.1)	−1.1 (−2.5 to 0.2)

Values are % (95% CI). Regression standardized cumulative incidence and differences for all-cause mortality, heart failure hospitalization, and reintervention at 5, 10, and 15 years for patients who underwent bioprosthetic aortic valve replacement in Sweden between 2003 and 2018. Adjusted by regression standardization. A detailed description and documentation regarding included covariates are available in the Supplemental Appendix.

PPM = prosthesis-patient mismatch.

DISCUSSION

We found that PPM was prevalent and was more common than no PPM. However, the incidence of moderate PPM and severe PPM has decreased in Sweden since 2013. We also found that an increasing PPM grade was associated with a stepwise increase in long-term all-cause mortality. Severe PPM, but not moderate PPM, was associated with an increased risk of long-term heart failure hospitalization. In our study, PPM was not associated with aortic valve reintervention. Although we found associations between PPM and survival and heart failure hospitalization, the absolute differences between moderate and severe PPM vs no PPM were small. The use of absolute effect measures together with data from high-quality, large nationwide registers with complete follow-up make this study unique compared with prior literature in the field. Another strength was the use of the VARC-3–recommended BMI-adjusted definition of PPM.[2]

SURVIVAL. In a large cohort study comprising 59,779 patients, Fallon et al[26] studied the association between PPM and all-cause mortality, heart failure hospitalization, and aortic valve reoperation. After multivariate adjustment using Cox models, they reported a stepwise increase in HR for mortality of 1.08
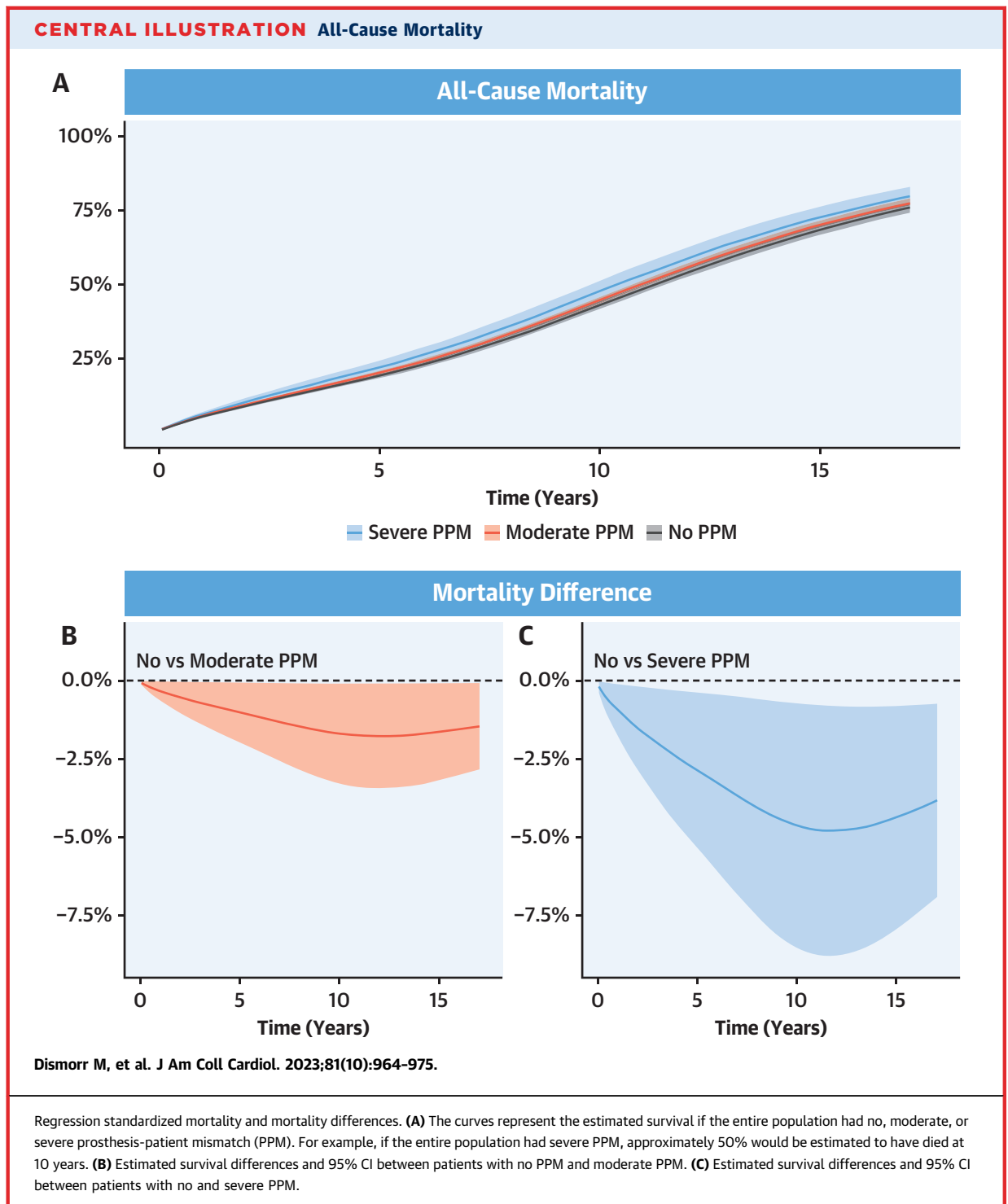
(95% CI: 1.05-1.12) for moderate vs no PPM and 1.32 (95% CI: 1.25-1.39) for severe vs no PPM.

A more recent study from the FinnValve Registry included 4,074 patients. They also reported a significant association between severe PPM and all-cause mortality (HR: 1.72; 95% CI: 1.07-2.76), but not between moderate PPM and all-cause mortality.[27]

We did find a small but significant difference in survival between no vs moderate PPM (1.7%; 95% CI: 0.1%-3.3% at 10 years). Given the small absolute difference in survival between no and moderate PPM, it is possible that the study by Dahlbacka et al[27] was underpowered to detect this difference regarding moderate PPM.
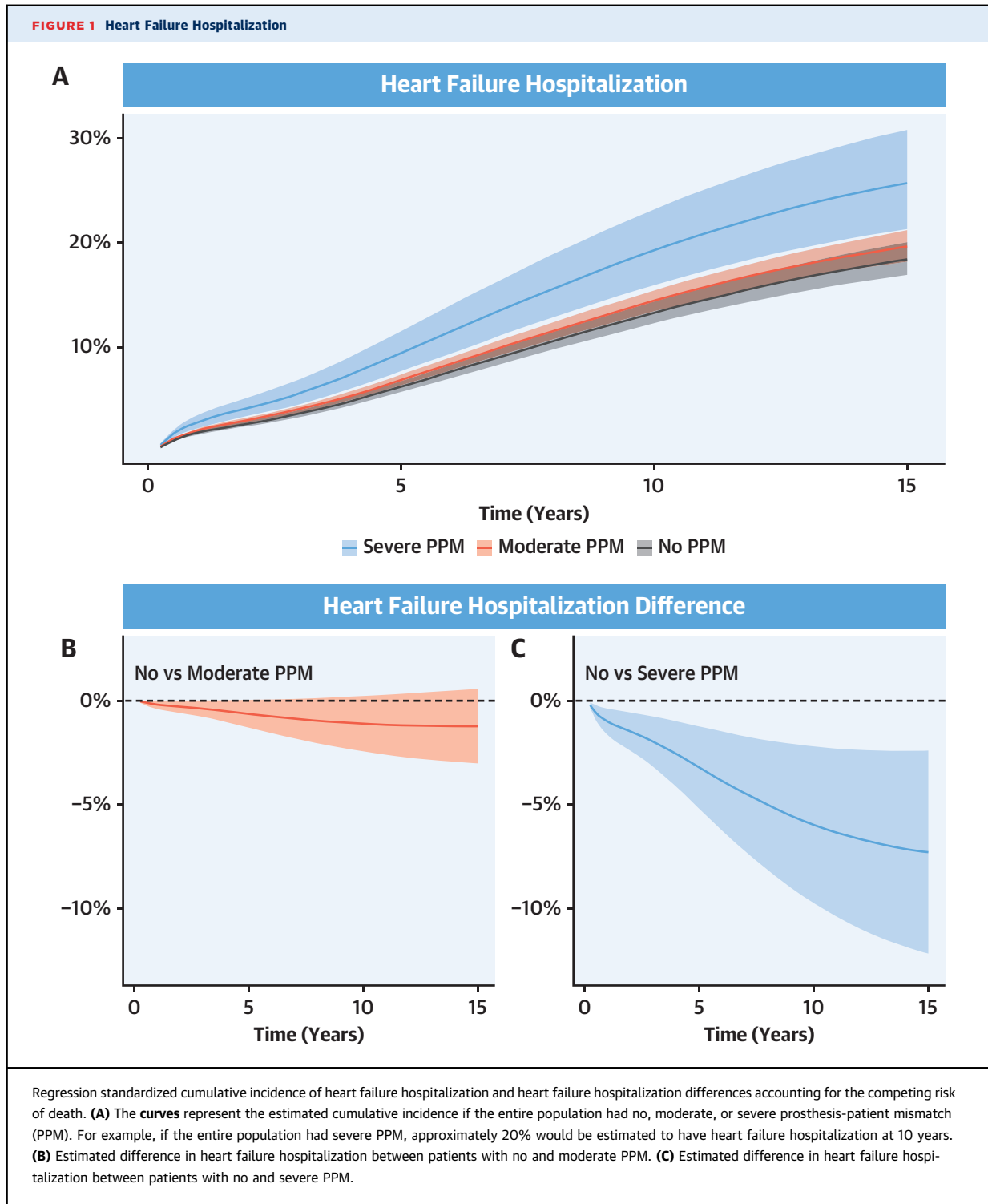
In another study, Blais et al[28] found a significant association between moderate and severe PPM and early mortality. They also reported a significant compound effect of severe PPM and LVEF below 40% on 30-day mortality (risk ratio: 77.1; $P < 0.001$).[28] We examined the possible effect modification of LVEF on the association between PPM and long-term survival. However, we did not find any evidence to support different effects of PPM on survival across LVEF categories.

A systematic review and meta-analysis by Sá et al[5] found a significant association between both moderate and severe PPM and perioperative mortality and

CENTRAL ILLUSTRATION All-Cause Mortality

Regression standardized mortality and mortality differences. **(A)** The curves represent the estimated survival if the entire population had no, moderate, or severe prosthesis-patient mismatch (PPM). For example, if the entire population had severe PPM, approximately 50% would be estimated to have died at 10 years. **(B)** Estimated survival differences and 95% CI between patients with no PPM and moderate PPM. **(C)** Estimated survival differences and 95% CI between patients with no and severe PPM.

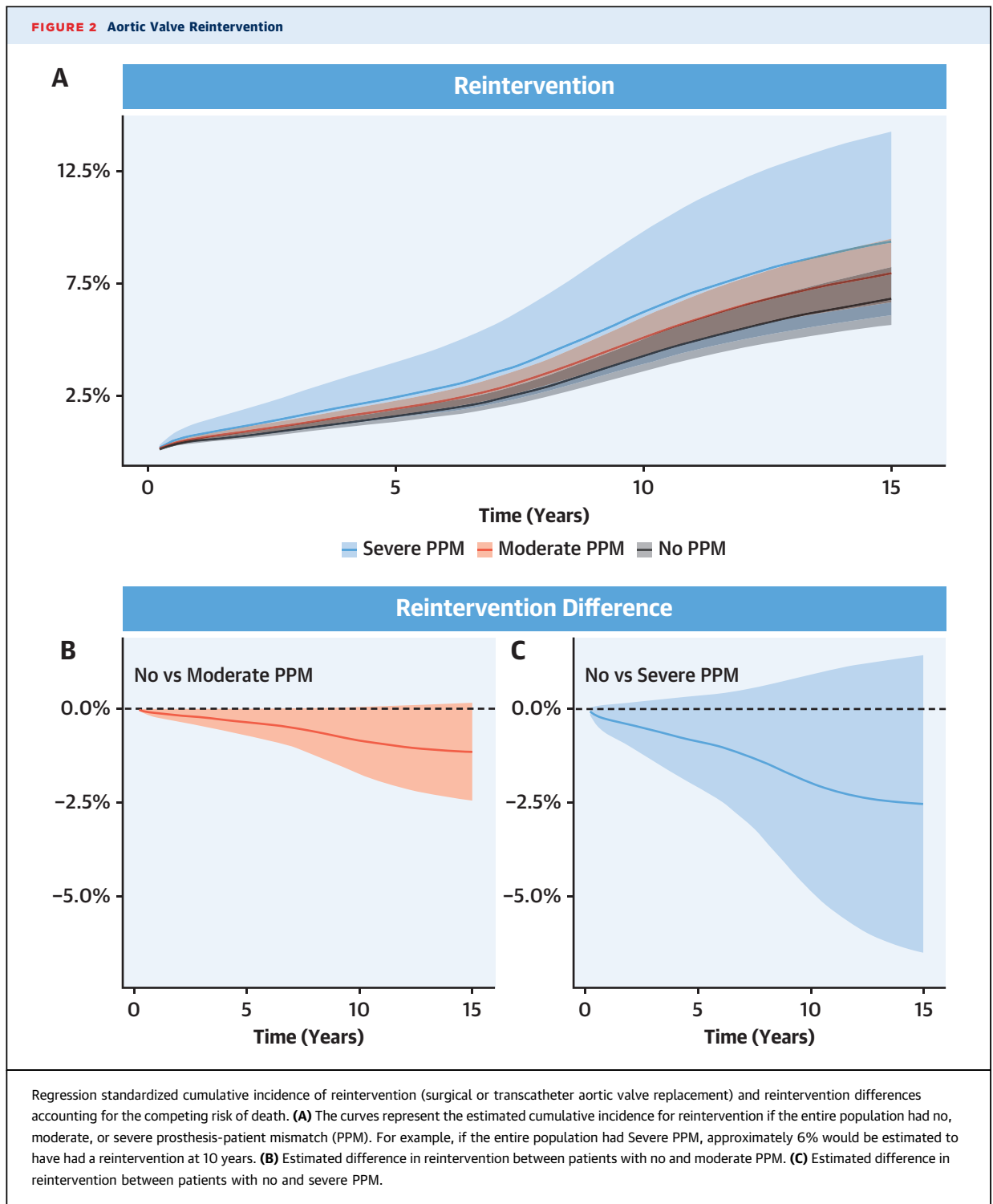Dismorr M, et al. J Am Coll Cardiol. 2023;81(10):964–975.

mortality at 1, 5, and 10 years. They reported an OR at 10 years for severe and moderate PPM vs no PPM of 1.96 (95% CI: 1.17-3.29) and 1.31 (95% CI: 1.03-1.67), respectively.[5]

The results from the study by Fallon et al[26] and the meta-analysis by Sá et al[5] are mostly in line with our findings. In our study, we found a significant difference between moderate, severe, and any

FIGURE 1 Heart Failure Hospitalization

Regression standardized cumulative incidence of heart failure hospitalization and heart failure hospitalization differences accounting for the competing risk of death. **(A)** The **curves** represent the estimated cumulative incidence if the entire population had no, moderate, or severe prosthesis-patient mismatch (PPM). For example, if the entire population had severe PPM, approximately 20% would be estimated to have heart failure hospitalization at 10 years. **(B)** Estimated difference in heart failure hospitalization between patients with no and moderate PPM. **(C)** Estimated difference in heart failure hospitalization between patients with no and severe PPM.

PPM vs no PPM at 5, 10, and 15 years. We reported an absolute effect measure of an estimated survival difference at 10 years of 1.7% (95% CI: 0.1%-3.3%) between no and moderate PPM and 4.6% (95% CI: 0.7%-8.5%) between no and severe PPM. The survival difference between no and severe PPM increased to reach a maximum at 11.8 years and then started to decrease. These data might indicate

FIGURE 2   Aortic Valve Reintervention

Regression standardized cumulative incidence of reintervention (surgical or transcatheter aortic valve replacement) and reintervention differences accounting for the competing risk of death. **(A)** The curves represent the estimated cumulative incidence for reintervention if the entire population had no, moderate, or severe prosthesis-patient mismatch (PPM). For example, if the entire population had Severe PPM, approximately 6% would be estimated to have had a reintervention at 10 years. **(B)** Estimated difference in reintervention between patients with no and moderate PPM. **(C)** Estimated difference in reintervention between patients with no and severe PPM.

that PPM has a long-term effect on survival, but after a certain time other factors, such as age, might play a more important role.

HEART FAILURE HOSPITALIZATION. Fallon et al[26] also reported a stepwise increase in HR for heart failure hospitalization with increasing grades of PPM (HR: 1.37 [95% CI: 1.25-1.48] for severe vs no PPM). Ternacle et al[29] used data from the PARTNER 2A (Placement of Aortic Transcatheter Valve 2A) trial and found a significant association between severe PPM

and heart failure hospitalization (HR: 2.89; 95% CI: 1.18-7.30).

We found a significant difference between no and severe PPM, but not between no and moderate PPM. In fact, we found that no and moderate PPM were similar, and significance was retained between moderate and severe PPM with a 10-year difference in cumulative incidence of −4.9% (95% CI: −8.4 to −1.3%). The heart failure hospitalization difference between no and severe PPM increased continuously during follow-up. This might indicate that the detrimental effects of PPM on heart failure remain if the condition is untreated.

REINTERVENTION. Fallon et al[26] found an even stronger association between PPM and aortic valve reoperation (HR: 2.68; 95% CI: 2.01-3.56 for severe vs no PPM) than between PPM and mortality. This association was not found in the FinnValve study by Dahlbacka et al,[27] who reported nonsignificant coefficients between severe and moderate PPM and reintervention.

Similarly, we did not find a significant difference in reintervention among the PPM groups. We did, however, find an increasing trend in reintervention with increasing PPM grades. It is possible that our results did not reach significance because of overall low event rates and our smaller cohort compared with that of Fallon et al.[26] Furthermore, as pointed out by Dahlbacka et al,[27] the Fallon study did not include the valve model in the multivariate analyses, which may have introduced bias in terms of risk for reintervention.[19,30]

MITIGATING TECHNIQUES. The estimation of absolute effect measures provides additional information and can help to put relative effect measures such as ORs or HRs into context. We would say that a 4.6% survival difference (as found between no and severe PPM at 10 years) is not without clinical significance, but 0.7% (the lower CI between no and severe PPM at 10 years) is of more questionable importance. We believe that absolute estimates are important to consider when assessing alternative approaches to avoid PPM. Pibarot and Dumesnil[31] suggested 3 options to prevent potential PPM: change the planned prosthesis to a model with larger EOA (eg, a new-generation mechanical valve); perform surgical aortic root enlargement; or "accept PPM in light of other clinical conditions." Changing the prosthetic model may be feasible, but different prostheses might perform differently, and a mechanical valve may not be suitable because of risk of bleeding.[19,32] There is an increasing body of evidence that PPM may be less prevalent in TAVR compared with that in

bioprosthetic SAVR.[29,33,34] Therefore, a plausible alternative might be to consider a TAVR procedure in patients with high risk for PPM. However, given the small absolute differences in survival between PPM and no PPM in our study, the drawbacks of using a TAVR valve in a patient otherwise suitable for surgery must be weighed against the risks associated with PPM.

A more aggressive method is to perform a surgical aortic root enlargement. Sá et al[35] performed a systematic review and meta-analysis and found an association between surgical aortic root enlargement and perioperative mortality (OR: 1.5; 95% CI: 1.2-1.9). This illustrates the complex balance that needs to be achieved when weighing the risk of perioperative mortality associated with aortic root enlargement against the perioperative and long-term mortality associated with PPM. In a multicenter propensity score-matched analysis including 809 matched pairs by Tam et al,[36] no association was found between aortic root enlargement and early mortality (2.0% vs 2.1%; $P = 1.00$). They also reported similar rates of postoperative bleeding and permanent pacemaker implantation.[36] Whether aortic root enlargement or novel techniques such as the Yang procedure[37] can provide a safe and efficient way to avoid PPM likely depends on the center and surgeon experience.

STUDY LIMITATIONS. In this study, we did not have access to echocardiography, and thus were unable to accurately diagnose the presence or degree of PPM in each patient, as well as pressure gradients and flow. Rather, we used the reported EOA from published literature. Although this method does not accurately diagnose PPM, it is the same method surgeons have at hand when assessing the risk of PPM for a patient at the time of surgery. However, predicted PPM might overestimate the degree of PPM, and thereby dilute the risks associated with severe PPM when used in studies on PPM.[29] It is important to note that the EOA measurements obtained from the literature will vary compared with the individual patient's EOA, and rather reflect the average EOAs in previously studied patients. In this study, we aimed to use EOA values from in vivo measurements to avoid some of the pitfalls related to in vitro or manufacturer-generated charts.[38] The establishment of accepted charts based on in vivo measurements for specific models and sizes would be beneficial to the field. Some model sizes lacked reliable published EOA estimates. Therefore, we may have slightly underestimated the presence of severe PPM, because, in these cases, we used the EOA for the next smallest size. Our study had some missing data that was handled with

classification and regression tree estimation. Overall, the number of missing data was low and therefore was unlikely to bias the results. This study was an observational cohort study and is thus at risk for residual confounding.

CONCLUSIONS

The incidence of moderate and severe PPM has decreased in Sweden since 2013 but was still common. An increasing PPM grade was associated with a stepwise increase in long-term all-cause mortality. Severe PPM was associated with an increased risk of long-term heart failure hospitalization. Moderate PPM was common, but the clinical significance may be negligible. In patients with moderate PPM, the absolute risk differences in clinical outcomes were small and might be smaller than the risks associated with preventive techniques to avoid PPM.

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ADDRESS FOR CORRESPONDENCE: Dr Michael Dismorr, Department of Molecular Medicine and Surgery, Karolinska Institutet, SE-171 76 Stockholm, Sweden. E-mail: Michael.Dismorr@ki.se. Twitter: @Michael-Dismorr, @NatalieGlaser10, @RealSwedeheart.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PPM, which occurs when a prosthesis is small in proportion to a patient's body surface area, is associated with heart failure and increased mortality after bioprosthetic surgical aortic valve replacement. The clinical relevance of moderate PPM may be negligible because of small absolute differences in clinical outcomes compared with no PPM.

TRANSLATIONAL OUTLOOK: Further research is needed to devise safe and efficient ways to avoid PPM in patients undergoing aortic valve replacement.

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APPENDIX For an expanded Methods section as well as supplemental figures and tables, please see the online version of this paper.