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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

Philippe Pibarot, DVM, PHD,* Neil J. Weissman, MD,† William J. Stewart, MD,‡ Rebecca T. Hahn, MD,§‖ Brian R. Lindman, MD, MSCI,¶ Thomas McAndrew, MS,‖ Susheel K. Kodali, MD,§‖ Michael J. Mack, MD,# Vinod H. Thourani, MD,** D. Craig Miller, MD,†† Lars G. Svensson, MD, PHD,‡‡ Howard C. Herrmann, MD,§§ Craig R. Smith, MD,§‖ Josep Rodés-Cabau, MD,* John Webb, MD,‖‖ Scott Lim, MD,¶¶ Ke Xu, PHD,‖ Irene Hueter, PHD,§ Pamela S. Douglas, MD,## Martin B. Leon, MD§‖

ABSTRACT

BACKGROUND Little is known about the incidence of prosthesis-patient mismatch (PPM) and its impact on outcomes after transcatheter aortic valve replacement (TAVR).

OBJECTIVES The objectives of this study were: 1) to compare the incidence of PPM in the TAVR and surgical aortic valve replacement (SAVR) randomized control trial (RCT) arms of the PARTNER (Placement of AoRTic TraNscathetER Valves) I Trial cohort A; and 2) to assess the impact of PPM on regression of left ventricular (LV) hypertrophy and mortality in these 2 arms and in the TAVR nonrandomized continued access (NRCA) registry cohort.

METHODS The PARTNER Trial cohort A randomized patients 1:1 to TAVR or bioprosthetic SAVR. Postoperative PPM was defined as absent if the indexed effective orifice area (EOA) was >0.85 cm^2/m^2, moderate if the indexed EOA was ≥ 0.65 but ≤ 0.85 cm^2/m^2, or severe if the indexed EOA was <0.65 cm^2/m^2. LV mass regression and mortality were analyzed using the SAVR-RCT (n = 270), TAVR-RCT (n = 304), and TAVR-NRCA (n = 1,637) cohorts.

RESULTS The incidence of PPM was 60.0% (severe: 28.1%) in the SAVR-RCT cohort versus 46.4% (severe: 19.7%) in the TAVR-RCT cohort ($p < 0.001$) and 43.8% (severe: 13.6%) in the TAVR-NRCA cohort. In patients with an aortic annulus diameter <20 mm, severe PPM developed in 33.7% undergoing SAVR compared with 19.0% undergoing TAVR ($p = 0.002$). PPM was an independent predictor of less LV mass regression at 1 year in the SAVR-RCT ($p = 0.017$) and TAVR-NRCA ($p = 0.012$) cohorts but not in the TAVR-RCT cohort ($p = 0.35$). Severe PPM was an independent predictor of 2-year mortality in the SAVR-RCT cohort (hazard ratio [HR]: 1.78; $p = 0.041$) but not in the TAVR-RCT cohort (HR: 0.58; $p = 0.11$). In the TAVR-NRCA cohort, severe PPM was not a predictor of 1-year mortality in all patients (HR: 1.05; $p = 0.60$) but did independently predict mortality in the subset of patients with no post-procedural aortic regurgitation (HR: 1.88; $p = 0.02$).

CONCLUSIONS In patients with severe aortic stenosis and high surgical risk, PPM is more frequent and more often severe after SAVR than TAVR. Patients with PPM after SAVR have worse survival and less LV mass regression than those without PPM. Severe PPM also has a significant impact on survival after TAVR in the subset of patients with no post-procedural aortic regurgitation. TAVR may be preferable to SAVR in patients with a small aortic annulus who are susceptible to PPM to avoid its adverse impact on LV mass regression and survival. (The PARTNER Trial: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894) (J Am Coll Cardiol 2014;64:1323–34) © 2014 by the American College of Cardiology Foundation.

From the *Québec Heart and Lung Institute/Institut Universitaire de Cardiologie et de Pneumologie de Québec, Laval University, Québec, Canada; †Medstar Health Research Institute, Washington, DC; ‡Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio; §Columbia University Medical Center/New York-Presbyterian Hospital, New York, New York; ‖The Cardiovascular Research Foundation, New York, New York; ¶Washington University School of Medicine, St. Louis, Missouri; #Baylor Healthcare System, Dallas, Texas; **Emory University School of Medicine, Atlanta, Georgia; ††Stanford University School

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

BMI = body mass index

BSA = body surface area

CI = confidence interval

EOA = effective orifice area

HR = hazard ratio

LV = left ventricular

LVOT = left ventricular outflow tract

NRCA = nonrandomized continued access

PPM = prosthesis-patient mismatch

RCT = randomized controlled trial

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EOA) of a normally functioning prosthetic valve is too small in relation to patient body size. Several studies have reported that PPM is frequent (20% to 70%) and has a negative impact on short- and long-term outcomes after surgical aortic valve replacement (SAVR) for aortic stenosis (AS) (1). A recent meta-analysis reported that moderate and severe PPM are associated with a 1.2- and 1.8-fold increase in the risk of all-cause mortality, respectively (2). Thus, it seems important to implement preventive strategies to avoid PPM without increasing operative risk.

Transcatheter aortic valve replacement (TAVR) has emerged as a valid alternative to SAVR in selected patients (3,4). Previous nonrandomized studies suggested that TAVR may be associated with a lower incidence of PPM compared with SAVR (5,6). Some studies reported that PPM is associated with less regression of left ventricular (LV) hypertrophy, less improvement in patient functional status, and increased mortality after TAVR (7,8), whereas others found no significant impact of PPM on outcomes (9,10). No randomized trial has published data comparing TAVR with SAVR with respect to the incidence and clinical impact of PPM.

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The PARTNER (Placement of AoRTic TraNscathetER Valves) trial was a multicenter, randomized controlled trial (RCT) comparing TAVR with SAVR in high-risk patients with severe AS (cohort A) (3,4,11). Trial results showed that TAVR was noninferior to SAVR with no difference in 2-year all-cause mortality, cardiovascular mortality, or rehospitalization for heart failure (3,4). The objectives of this study were to 1) compare the incidence of PPM in the TAVR- and SAVR-RCT arms of the PARTNER I Trial cohort A; and 2) examine PPM's impact on regression of LV hypertrophy and on mortality in the RCT arms and in the TAVR-nonrandomized continued access (NRCA) registry of PARTNER IA.

METHODS

STUDY DESIGN AND PATIENT POPULATION. In a 1:1 ratio, cohort A of the PARTNER Trial randomized 699 patients at high surgical risk with severe,

of Medicine, Stanford, California; ‡‡Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio; §§Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; ‖‖University of British Columbia and St. Paul's Hospital, Vancouver, Canada; ¶¶University of Virginia Medical Center, Charlottesville, Virginia; and the ##Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina. The PARTNER trial was funded by Edwards Lifesciences Corporation. The current analysis was carried out by academic investigators and at the Cardiovascular Research Foundation under the auspices of the PARTNER Publications Office. Dr. Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research, Ottawa, Ontario, Canada; and has received research grant support from Edwards Lifesciences Corporation. Dr. Weissman has received grant support from Boston Scientific Corporation. Dr. Lindman was supported by K23 Grant HL116660 from the National Institutes of Health, Washington, DC. Dr. Kodali is a member of the PARTNER Trial Steering Committee and a consultant for Edwards Lifesciences Corporation; a member of the steering committee for the Portico Trial (St. Jude Medical Inc.); and a member of the scientific advisory board of Thubrikar Aortic Valve Inc. Dr. Mack has received travel reimbursements from Edwards Lifesciences Corporation relating to his participation as an unpaid member of the PARTNER Trial Executive Committee. Dr. Thourani is a member of the PARTNER Trial Steering Committee; and a consultant for Edwards Lifesciences Corporation, Sorin Medical, St. Jude Medical Inc., and DirectFlow. Dr. Miller is supported by an R01 research grant from National Heart, Lung, and Blood Institute No. HL67025; has received travel reimbursements from Edwards Lifesciences Corporation related to his work as an unpaid member of the PARTNER Trial Executive Committee; and has received consulting fees/honoraria from Abbott Vascular, St. Jude Medical Inc., and Medtronic Inc. Dr. Svensson has received travel reimbursements from Edwards Lifesciences Corporation related to his work as an unpaid member of the PARTNER Trial Executive Committee; holds equity in Cardiosolutions and ValvXchange; and has Intellectual Property Rights/Royalties from Posthorax. Dr. Herrmann has received grant support from Abbott Vascular, Boston Scientific Corporation, Edwards Lifesciences Corporation, Medtronic Inc., Siemens, and W. L. Gore & Associates Inc.; and has received consulting fees/honoraria from Paieon and W. L. Gore & Associates Inc. Dr. Smith has received travel reimbursements from Edwards Lifesciences Corporation related to work as an unpaid member of the PARTNER Trial Executive Committee. Dr. Rodés-Cabau has received grant support from Boston Scientific Corporation and Edwards Lifesciences Corporation; and has received consulting fees/honoraria from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo/Eli Lilly, GlaxoSmithKline, Janssen, Merck/Schering-Plough, and Regeneron. Dr. Webb is a member of the PARTNER Trial Executive Committee; and has received consulting fees from Edwards Lifesciences Corporation. Dr. Lim has received consulting fees/honoraria from Boston Scientific Corporation, Guerbet, and St. Jude Medical Inc. Dr. Leon has received travel reimbursements from Edwards Lifesciences Corporation related to work as an unpaid member of the PARTNER Trial Executive Committee. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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symptomatic AS between SAVR and TAVR with the Edwards-SAPIEN heart valve system (Edwards Lifesciences Corp., Irvine, California) (Online Figure 1) (3). The trial's design, inclusion and exclusion criteria, and primary results have been reported (3,11). These patients had severe AS with an aortic valve area <0.8 cm^2 (or indexed aortic valve area <0.5 cm^2/m^2) and either resting or inducible mean gradient >40 mm Hg or peak jet velocity >4 m/s. They were symptomatic from AS (New York Heart Association functional class ≥ 2) and were at high surgical risk as defined by a predicted risk of death of $\geq 15\%$ by 30 days after conventional surgery. Exclusion criteria included bicuspid or noncalcified valve, coronary artery disease requiring revascularization, an LV ejection fraction $\leq 20\%$, an aortic annulus diameter <18 mm or >25 mm, severe mitral regurgitation or aortic regurgitation (AR), and an aortic bioprosthesis. For patients assigned to SAVR, the study protocol strongly discouraged the use of surgical valves other than Edwards bovine bioprostheses and excluded patients in whom the need for a root enlargement was recognized in advance. Nonetheless, for various reasons, 10% of the surgical valves were not Edwards valves, and intraoperative findings led to root enlargement in 2 patients and root replacement in 2 patients.

Patients assigned to the TAVR group underwent transfemoral or transapical placement of the aortic valve on the basis of whether peripheral arteries could accommodate the large sheaths required (22-F for the 23-mm valve and 24-F for the 26-mm valve) (Online Figure 1). Furthermore, 1,776 patients were enrolled in the high-risk TAVR-NRCA cohort (Online Figure 1), and the inclusion and exclusion criteria for this registry were the same as those for the cohort A RCT. In addition, given that paravalvular AR has been shown to be a powerful predictor of mortality in the TAVR arm of the PARTNER I Trial cohort A (3) and that it may confound the association between PPM and outcomes, we also assessed the impact of PPM in the subset of the patients in the TAVR-NRCA group ($n = 835$) with no or trace postprocedural AR.

Echocardiograms were obtained at baseline and at 7 days, 30 days, 6 months, 1 year, and 2 years post-procedure. For this post-hoc analysis, we included patients in the SAVR-RCT and TAVR-RCT groups and patients in the TAVR-NRCA group in the as-treated population with a post-implant echocardiogram available. This analysis included 270 patients in the SAVR-RCT group, 304 patients in the TAVR-RCT group, and 1,637 patients in the TAVR-NRCA group (Online Figure 1). The first post-implant echocardiogram was the 7-day echocardiogram in 84.1% of the patients in the SAVR-RCT group and 89.5% of the patients in the TAVR-RCT group ($p = 0.06$).

DOPPLER-ECHOCARDIOGRAPHIC MEASUREMENTS. All baseline and follow-up echocardiograms were interpreted by an independent core laboratory housed at the Duke Clinical Research Institute. Study work flow, reproducibility testing, image acquisition and analysis, and quality assurance data have been published (12).

Ventricular size and function and valvular function were measured according to previously published guidelines (13,14). LV volumes and ejection fraction were measured using the biplane Simpson formula. LV mass was calculated using the formula recommended by the American Society of Echocardiography (13). The stroke volume was measured in the left ventricular outflow tract (LVOT) with the use of the diameter and velocity measured just underneath the prosthesis stent for both surgical and transcatheter valves. The EOA was calculated as the LVOT stroke volume divided by the aortic jet velocity time integral and was indexed for body surface area (BSA). An integrative, semiquantitative approach was used to assess the severity of central, paravalvular, and total regurgitation (12,14). The results of the comparison of the echocardiographic findings in the TAVR-RCT versus SAVR-RCT arms of the PARTNER Trial cohort A have been published (15).

DEFINITION OF PPM. The first available post-implant (7 days, 30 days, or 6 months) echocardiogram showing EOA indexed for BSA was used to identify and quantify PPM. The severity of PPM was graded from the echocardiograms using the indexed EOA, with absence defined as >0.85 cm^2/m^2, moderate defined as ≥ 0.65 and ≤ 0.85 cm^2/m^2, and severe defined as <0.65 cm^2/m^2 (1,2).

STUDY ENDPOINTS. The study endpoints were regression of LV mass at 1 year and all-cause mortality at 2 years for the RCT cohort. For the TAVR-NRCA cohort, 1-year mortality was used as the endpoint because events were not adjudicated beyond this time point in the registry cohort.

STATISTICAL ANALYSIS. Continuous variables are presented as mean $\pm$ SD or median (interquartile range) for variables with a skewed distribution and compared with the use of the Student *t* test or the Wilcoxon rank-sum test. The normality of variables was assessed with the Kolmogorov-Smirnov test. Categoric variables were compared with the use of the chi-square or the Fisher exact tests. The Fisher exact

test was used when the expected cell frequency was <5.

Absolute and percent changes in LV mass were calculated using paired data at baseline and 1 year and were compared between PPM groups in each treatment group (TAVR-RCT, SAVR-RCT, TAVR-NRCA). Multivariable analysis was performed with linear regression. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data with the use of Kaplan-Meier estimates and compared with the use of the log-rank test. Multivariable analysis was performed in each treatment group with the Cox proportional hazards model. PPM was entered into the models in binary (PPM/no PPM) or ternary (severe PPM/moderate PPM/no PPM) format. Other variables entered into the multivariable models for adjustment were the univariable predictors of mortality and the variables that showed a statistically significant difference between the PPM and no PPM groups. All statistical

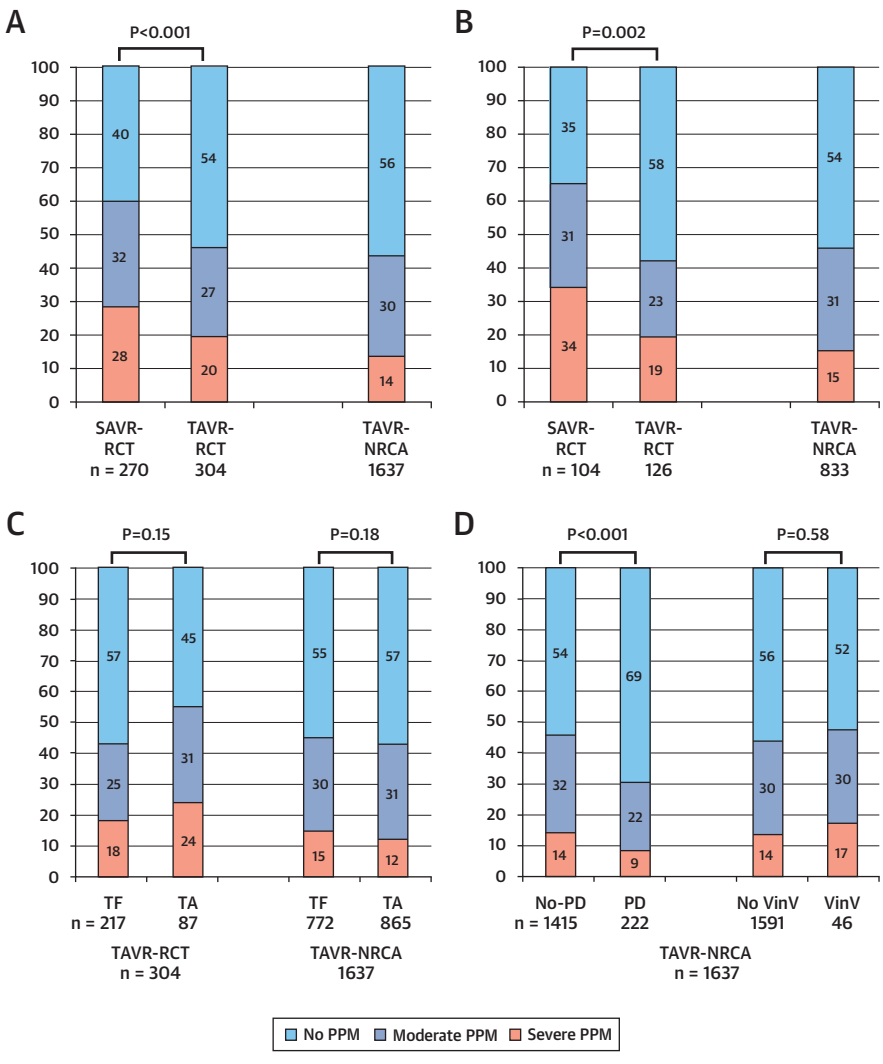


FIGURE 1 Incidence of PPM According to Treatment Type in the High-Risk Cohort of the PARTNER Trial

Incidence of PPM at first post-implant echocardiogram according to treatment group (SAVR-RCT, TAVR-RCT, and TAVR-NRCA) in the as-treated population of the PARTNER trial **(A)** and in the subsets of patients with a small aortic annulus diameter (<20 mm) **(B)**. Incidence of PPM according to the implantation approach (transfemoral vs. transapical) in the TAVR-RCT and TAVR-NRCA cohorts **(C)**. Incidence of PPM according to the use of post-dilation or intraprocedural valve-in-valve procedures in the TAVR-NRCA cohort **(D)**. CI = confidence interval; HR = hazard ratio; NRCA = nonrandomized continued access; PD = post-dilation; PPM = prosthesis-patient mismatch; RCT = randomized controlled trial; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; VinV = valve-in-valve procedure.

analyses were performed with the use of SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina).

The Cardiovascular Research Foundation (New York, New York) maintains the study's database, and independent analyses can be requested by investigators with statistical assistance provided. All of the analyses were performed with data from the as-implanted population. Data are based on an extract date of February 13, 2012.

RESULTS

COMPARISON OF THE INCIDENCE OF PPM IN TAVR-RCT VERSUS SAVR-RCT. The incidence of PPM assessed at first postoperative echocardiogram was significantly ($p < 0.001$) lower in the TAVR-RCT arm (overall PPM: 46.4% [n = 141]; moderate: 26.6% [n = 81]; severe: 19.7% [n = 60]) than in the SAVR-RCT arm (overall: 60.0% [n = 162]; moderate: 31.9%

TABLE 1 Baseline Clinical and Doppler Echocardiographic Characteristics of Patients in the TAVR and SAVR Arms of the PARTNER Trial Cohort A According to Presence or Absence of PPM

	SAVR-RCT (n = 270)			TAVR-RCT (n = 304)			TAVR-NRCA (n = 1,637)		
	No PPM (n = 108) (40%)	PPM (n = 162) (60%)	p Value	No PPM (n = 163) (53.6%)	PPM (n = 141) (46.4%)	p Value	No PPM (n = 920) (56.2%)	PPM (n = 717) (43.8%)	p Value
Demographic and clinical data									
Age, yrs	84 ± 7	85 ± 6	0.55	85 ± 6	83 ± 8	0.02	86 ± 6	84 ± 7	<0.0001
Female	44.4 (48)	40.7 (66)	0.55	39.9 (65)	44.0 (62)	0.47	48.2 (443)	48.3 (346)	0.97
BSA, m^2	1.79 ± 0.23	1.85 ± 0.22	0.04	1.77 ± 0.23	1.90 ± 0.26	<0.001	1.75 ± 0.24	1.85 ± 0.25	<0.0001
BMI, kg/m^2	26.6 ± 5.6	27.0 ± 5.7	0.44	25.7 ± 4.8	29.7 ± 8.5	<0.001	25.5 ± 5.5	27.8 ± 6.4	<0.0001
Obesity, BMI ≥30 kg/m^2	23.0 (25)	25.9 (42)	0.67	16.2 (26)	38.0 (54)	<0.001	14.9 (137)	30.7 (220)	<0.001
STS score	11 (10-13)	11 (10-13)	0.45	11 (10-13)	11 (10-13)	0.92	11 (9-13)	11 (10-13)	0.32
Logistic euroSCORE	26 (16-37)	27 (19-42)	0.12	26 (17-38)	26 (15-39)	0.85	23 (15-34)	23 (14-35)	0.81
Diabetes	40.7 (44)	42.0 (68)	0.84	40.5 (66)	46.8 (66)	0.27	32.6 (300)	42.8 (307)	<0.0001
Hyperlipidemia	80.6 (87)	87.0 (141)	0.15	79.1 (129)	80.1 (113)	0.83	85.1 (783)	87.0 (624)	0.27
Smoking	48.1 (52)	48.8 (79)	0.92	48.5 (79)	53.2 (75)	0.41	47.1 (433)	50.2 (360)	0.21
Hypertension	96.3 (104)	93.8 (152)	0.37	85.3 (139)	93.6 (132)	0.02	94.2 (867)	93.6 (671)	0.58
NYHA functional class IV	55.6 (60)	48.1 (78)	0.23	53.4 (87)	49.6 (70)	0.52	43.9 (403)	48.6 (348)	0.056
Angina	21.3 (23)	19.1 (31)	0.66	23.9 (39)	27.0 (38)	0.55	19.0 (175)	19.2 (138)	0.91
Coronary artery disease	74.1 (80)	79.0 (128)	0.34	70.6 (115)	79.4 (112)	0.08	78.3 (720)	82.1 (589)	0.056
Prior MI	25.9 (28)	30.6 (49)	0.40	27.0 (44)	27.0 (38)	0.99	25.0 (229)	28.9 (206)	0.07
Prior PCI	29.6 (32)	33.5 (54)	0.50	29.4 (48)	35.0 (49)	0.30	44.8 (412)	39.5 (283)	0.03
Prior CABG	39.8 (43)	50.0 (81)	0.10	39.9 (65)	48.2 (68)	0.15	42.3 (389)	48.1 (345)	0.02
Stroke or TIA (last 6-12 months)	31.4 (32)	25.7 (38)	0.32	27.8 (42)	32.8 (44)	0.36	25.5 (232)	25.9 (183)	0.84
Carotid disease	28.7 (29)	23.9 (34)	0.40	28.7 (43)	31.8 (42)	0.56	24.7 (223)	28.2 (197)	0.11
Peripheral vascular disease	49.5 (53)	39.9 (63)	0.12	38.9 (63)	42.4 (59)	0.53	47.2 (431)	45.5 (320)	0.48
Porcelain aorta	0.9 (1)	0.0 (0)	0.40	1.2 (2)	0.0 (0)	0.50	1.5 (14)	0.6 (4)	0.06
Pulmonary hypertension	48.1 (52)	50.6 (82)	0.69	50.9 (83)	51.1 (72)	0.98	37.2 (337)	38.7 (276)	0.54
Major arrhythmia	50.9 (55)	53.4 (86)	0.69	45.4 (74)	47.5 (67)	0.71	47.9 (440)	56.2 (403)	0.0008
Permanent pacemaker	22.2 (24)	24.1 (39)	0.72	22.7 (37)	17.7 (25)	0.28	20.4 (188)	23.9 (171)	0.09
Renal disease (creatinine ≥2)	13.0 (14)	25.3 (41)	0.01	17.3 (28)	17.7 (25)	0.92	15.8 (145)	16.2 (116)	0.81
Liver disease	4.6 (5)	1.2 (2)	0.12	1.8 (3)	2.8 (4)	0.71	2.4 (22)	2.0 (14)	0.55
COPD	45.4 (49)	43.8 (71)	0.80	39.9 (65)	48.9 (69)	0.11	39.8 (366)	46.2 (331)	0.01
Oxygen dependent	5.6 (13)	8.0 (19)	0.44	8.6 (14)	9.2 (13)	0.85	6.3 (58)	10.2 (73)	0.004
Baseline Doppler-echocardiographic data									
Aortic annulus diameter, mm	20.3 ± 2.3	19.8 ± 2.2	0.12	19.8 ± 2.4	20.4 ± 2.4	0.18	18.9 ± 2.8	18.8 ± 2.6	0.61
LV ejection fraction, %	56 ± 13	53 ± 13	0.12	53 ± 15	50 ± 13	0.09	54 ± 12	51 ± 13	0.0001
AV mean gradient, mm Hg	45 ± 14	42 ± 15	0.053	44 ± 15	43 ± 14	0.39	45 ± 15	44 ± 14	0.22
Moderate/severe AR	10.8 (11)	15.1 (24)	0.48	10.0 (16)	4.4 (6)	0.12	10.3 (93)	8.8 (61)	0.40
Moderate/severe MR	13.7 (14)	22.8 (36)	0.16	22.4 (36)	18.8 (25)	0.46	22.5 (196)	22.9 (157)	0.46

Values are mean ± SD, % (n), or median (interquartile range). Continuous variables are reported as mean ± SD and compared with the Student *t* test, except the STS score and logistic euroSCORE, which are reported as median and (interquartile range) and compared with the Wilcoxon rank-sum test. Values in parentheses indicate the number of patients.

AR = aortic regurgitation; AV = aortic valve; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; euroSCORE = European System for Cardiac Operative Risk Evaluation; LV = left ventricular; MI = myocardial infarction; MR = mitral regurgitation; NRCA = nonrandomized continued access; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = prosthesis-patient mismatch; RCT = randomized clinical trial; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

[n = 86]; severe: 28.1% [n = 76]) (Figure 1A). Similar results were obtained if PPM was assessed at the 7-day echocardiogram (TAVR 47% vs. SAVR 61%; p < 0.001) or 30-day echocardiogram (TAVR 42% vs. SAVR 57%; p < 0.001).

In the patients with an aortic annulus diameter <20 mm, the incidence of severe PPM was 19.0% (n = 24/126) in the TAVR-RCT cohort versus 33.7% (n = 35/104) in the SAVR-RCT cohort (p = 0.002) (Figure 1B). The incidence of PPM was not significantly different between the transfemoral and transapical approaches in the TAVR-RCT cohort (Figure 1C).

Compared with patients in the SAVR-RCT group, those in the TAVR-RCT group had a significantly higher post-procedural indexed aortic valve area (p = 0.0004) and lower transprosthetic gradients (p = 0.005) despite higher stroke volume (p < 0.0001) (Online Table 1).

INCIDENCE OF PPM IN TAVR-NRCA. In the TAVR-NRCA cohort, the incidence of overall, moderate, and severe PPM was 43.8% (n = 920), 30.2% (n = 495), and 13.6% (n = 222), respectively (Figure 1A), and it did not differ between the transfemoral and transapical approaches (Figure 1C). Forty-six (2.8%) of the patients in the TAVR-NRCA cohort underwent an intraprocedural transcatheter valve-in-valve procedure for valve malposition or dysfunction, and the incidence of PPM was similar in this subset (overall: 47.8% [n = 22]; moderate: 30.4% [n = 14]; severe: 17.4% [n = 8]) compared with the patients who did not undergo this procedure (overall: 43.7% [n = 695]; moderate: 30.2% [n = 481]; severe: 13.5% [n = 214]) (Figure 1D). Patients who underwent post-dilation (n = 222; 14.2%) had significantly (p < 0.001) less PPM (overall: 30.6% [n = 68]; moderate: 22.0% [n = 49]; severe: 8.6% [n = 19]) compared with the 1,415 patients in the TAVR-NRCA cohort who did not undergo post-dilation (overall: 45.8% [n = 647]; moderate: 31.5% [n = 445]; severe: 14.3% [n = 202]) (Figure 1D).

TABLE 2 Impact of PPM on LV Mass Regression at 1 Year in the SAVR-RCT and TAVR-RCT Arms and the TAVR-NRCA Registry

	LV Mass		
	Baseline	Absolute Change Baseline to 1 Year	Percent Change Baseline to 1 Year
SAVR-RCT			
No PPM	275 ± 80 g	−61 ± 51 g*	−23% (−32 to −12)*
PPM	280 ± 88 g	−36 ± 68 g*	−15% (−28 to −3)*
p Value	0.70	0.02*	0.007*
TAVR-RCT			
No PPM	275 ± 84 g*	−27 ± 56 g	−9% (−19 to 4)
PPM	295 ± 84 g*	−44 ± 63 g	−10% (−24 to −1)
p Value	0.05*	0.07	0.27
TAVR-NRCA			
No PPM	237 ± 70 g*	−40 ± 61 g	−17% (−30 to −4)
PPM	247 ± 73 g*	−32 ± 61 g	−13% (−24 to 2)
p Value	0.01*	0.24	0.09

Values are mean ± SD or median (interquartile range). The p value is for PPM versus no PPM in each of the 3 cohorts. *These values underline the differences that are statistically significant.
Abbreviations as in Table 1.

COMPARISON OF BASELINE CHARACTERISTICS ACCORDING TO PPM. In the SAVR-RCT arm, patients with PPM on their first postoperative echocardiogram had similar age, sex distribution, body mass index (BMI), and Society of Thoracic Surgeons (STS) score compared with those with no PPM (Table 1). However, patients in the SAVR-RCT group with PPM had significantly larger BSA and higher prevalence of renal disease than those without PPM. The incidence of moderate or greater total prosthetic AR was 3%, 0%, and 0% in the no PPM, moderate PPM, and severe PPM groups of the SAVR-RCT cohort, respectively (p = 0.13).

In the TAVR-RCT arm, patients with PPM were significantly younger and had higher BSA and BMI and larger baseline LV mass compared with those with no PPM (Tables 1 and 2). In the TAVR-RCT cohort, the incidence of mild or greater total prosthetic AR at first post-implant echocardiography was 63.1%, 57.0%, and 63.2% (p = 0.42) in the no PPM, moderate PPM, and severe PPM groups, respectively, and the incidence of at least moderate total regurgitation was 11.5%, 10.1%, and 7.0%, respectively (p = 0.63).

Table 1 shows the comparison of the baseline characteristics between the PPM and no PPM groups in the TAVR-NRCA arm. In this cohort, the incidence of mild or greater AR was 56.0%, 47.3%, and 43.4% (p < 0.001) and that of at least moderate AR was 10.6%, 8.3%, and 5.9% (p = 0.07) in the no PPM, moderate PPM, and severe PPM groups, respectively.

IMPACT OF PPM ON THE REGRESSION OF LV HYPERTROPHY IN TAVR AND SAVR. In the SAVR-RCT arm, there was significantly less LV mass regression at 1 year in the PPM group compared with the no PPM group (Figure 2, Table 2). However, LV mass regression was similar between the PPM and no PPM groups in the TAVR-RCT arm. Among the patients with no PPM, those in the SAVR-RCT group experienced significantly more LV mass regression than those in the TAVR-RCT group (p < 0.001), whereas among those with PPM the extent of LV mass regression was similar in both arms (p = 0.46). In the TAVR-NRCA cohort, there was a trend for a lesser percent of LV mass regression in patients with PPM than in those with no PPM in univariable analysis (Table 2).

In multivariable analysis including age, sex, baseline LV mass, baseline mitral regurgitation, and post-procedural total AR, PPM independently predicted lower absolute LV mass regression at 1 year in the SAVR-RCT group (β coefficient: −21 ± 9; p = 0.017) but not in the TAVR-RCT group (β coefficient: 7 ± 8; p = 0.35). However, PPM was independently associated with less LV mass regression in the TAVR-NRCA group (β coefficient: −13 ± 5; p = 0.012). Similar results were obtained when using percent of LV mass regression in the multivariable analysis (SAVR-RCT: p = 0.016; TAVR-RCT: p = 0.38, TAVR-NRCA: p = 0.017). Higher "residual" mean gradient at first post-implant echocardiography also was associated with less LV mass regression in both the TAVR-RCT (p = 0.014) and TAVR-NRCA (p < 0.001) groups. On multivariable analysis, there was an independent association between higher mean gradient and less absolute LV mass regression in the TAVR-NRCA group (β coefficient: −0.61 ± 0.18; p < 0.001) but not in the TAVR-RCT group.

We found no significant association between PPM and change in LV ejection fraction from baseline to 1 year in the SAVR-RCT, TAVR-RCT, and TAVR-NRCA groups. Similar results were obtained when the analyses were restricted to the subsets of patients with LV ejection fraction <50% at baseline.

IMPACT OF PPM ON MORTALITY IN TAVR AND SAVR. Thirty-day mortality was similar in the PPM and no PPM groups in the SAVR-RCT (4.3% vs. 5.6%), TAVR-RCT (1.8% vs. 2.1%), and TAVR-NRCA (1.6% vs. 2.2%) groups (all p = NS). **Figure 3** shows the curves of all-cause mortality according to PPM.

In the SAVR-RCT arm, patients with any degree of PPM demonstrated significantly higher 2-year mortality (hazard ratio [HR]: 1.64; 95% confidence interval [CI]: 1.01 to 2.67; p = 0.047) than patients with no PPM (**Figure 3A**, **Table 3**). Compared with patients with no PPM, those with severe PPM had an increased risk of 2-year mortality (HR: 1.79; 95% CI: 1.03 to 3.12; p = 0.04), but those with moderate PPM did not (HR: 1.51; 95% CI: 0.87 to 2.64; p = 0.14) (**Figure 3B**, **Table 3**). The other predictors of 2-year mortality in univariable analysis are presented in Online Table 2. In multivariable analysis including age, sex, BMI, STS score, major arrhythmia, pulmonary hypertension, renal disease, and post-procedural AR (**Table 3**), severe PPM independently predicted 2-year mortality (HR: 1.78; 95% CI: 1.02 to 3.11; p = 0.041) in the SAVR-RCT arm. There was also a trend toward an independent association between overall PPM and 2-year mortality (HR: 1.52; 95% CI: 0.93 to 2.48; p = 0.09). When restricting analysis of mortality rates to the 1-year time period, the univariable HR was 1.82, (95% CI: 0.96 to 3.45; p = 0.06) for severe PPM and 1.48 (95% CI: 0.78 to 2.83; p = 0.23) for moderate PPM.

In the TAVR-RCT arm, overall PPM was not significantly (p = 0.16) associated with 2-year

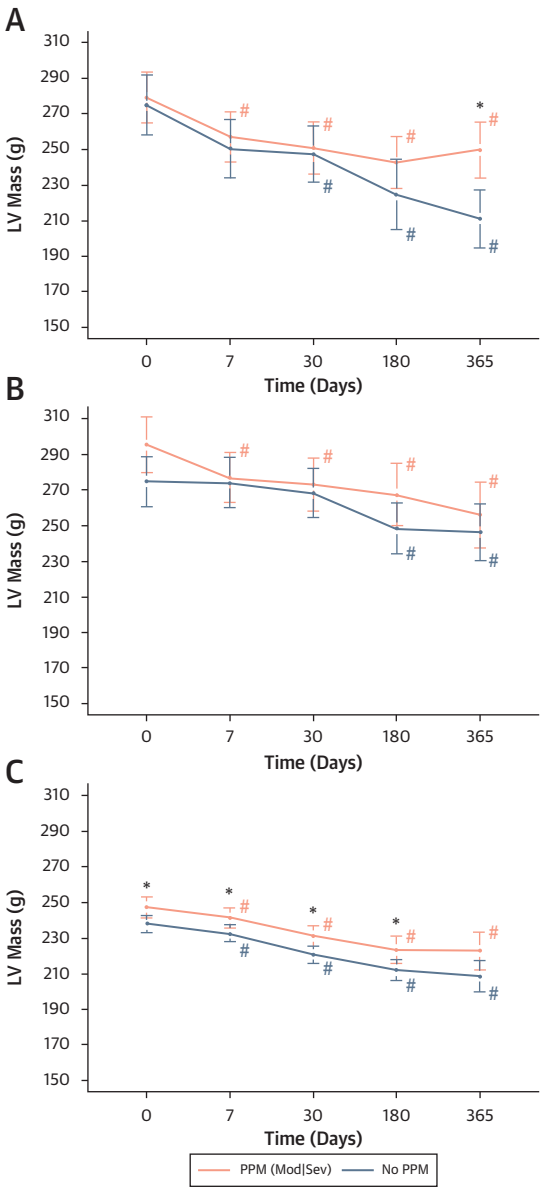


FIGURE 2 LV Mass Regression Over Time for the Groups of Patients With PPM Versus no PPM

LV mass (mean ± SEM) at baseline and different follow-up times according to the presence or absence of PPM in the SAVR-RCT arm **(A)**, TAVR-RCT arm **(B)**, and TAVR-NRCA cohort **(C)**. *Significant difference (p < 0.05) between the PPM and no PPM groups. #Significant difference (p < 0.05) from baseline within each PPM group. LV = left ventricular; other abbreviations as in **Figure 1**.

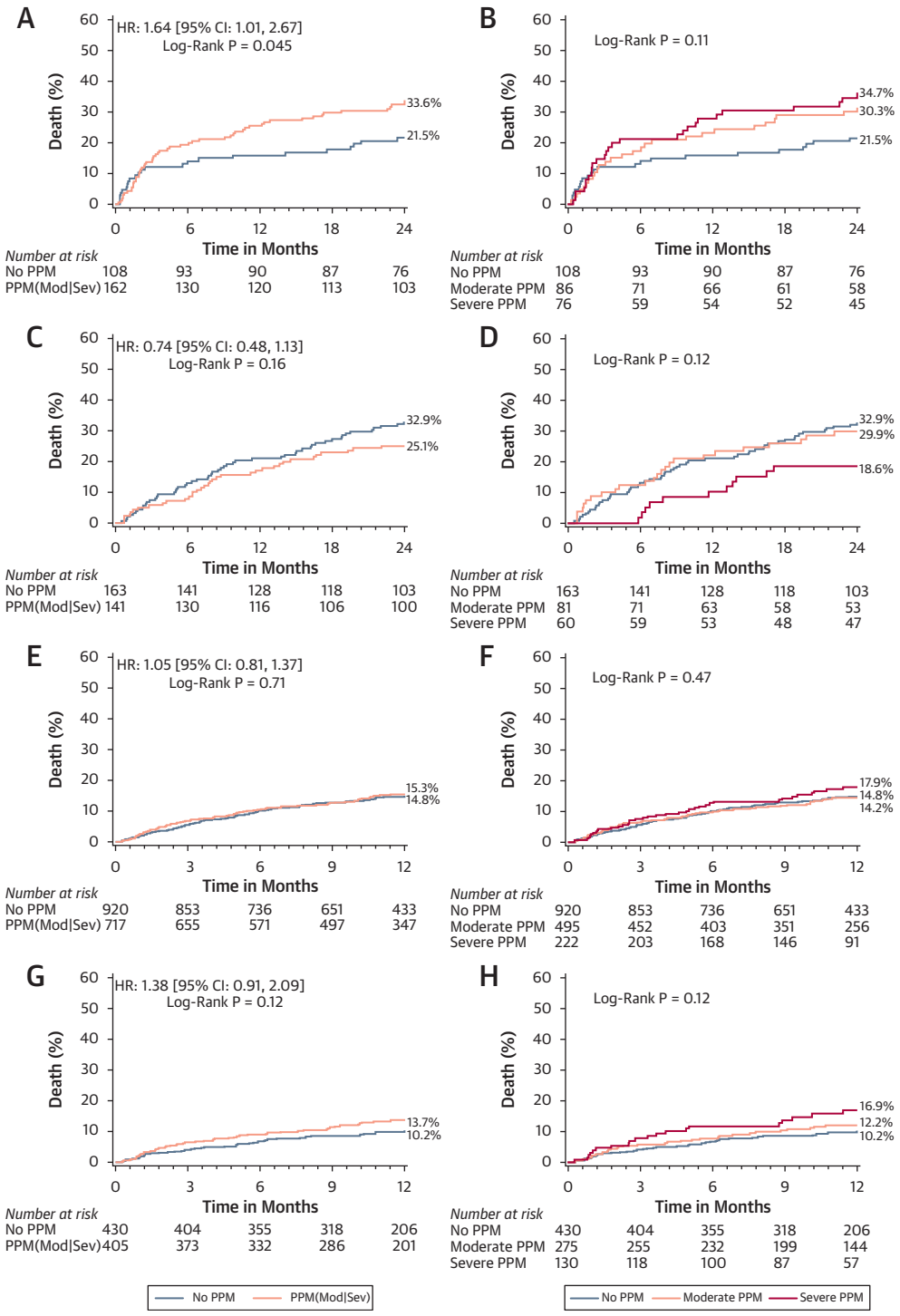


FIGURE 3 All-Cause Mortality According to Presence and Severity of PPM

Time-to-death curves for PPM stratified in 2 groups (overall [i.e., moderate + severe] PPM vs. no PPM) or in 3 groups (severe PPM, moderate PPM, no PPM) for death from any cause in SAVR-RCT **(A and B)**, TAVR-RCT **(C and D)**, TAVR-NRCA **(E and F)**, and TAVR-NRCA excluding patients with mild or greater total AR **(G and H)**. In **B, D, F, and H**, the log-rank p values refer to the 3-group comparison. AR = aortic regurgitation; other abbreviations as in Figure 1.

mortality (**Figures 3C and 3D**, **Table 3**), whereas severe PPM was associated with significantly lower mortality (HR: 0.51; 95% CI: 0.27 to 0.98; p = 0.041) in univariable analysis. (Other univariate predictors of mortality in TAVR-RCT are shown in Online Table 2.) In multivariable analysis including age, sex, BMI, STS score, major arrhythmia, pulmonary hypertension, renal disease, and post-procedural AR (**Table 3**), the association between severe PPM and 2-year mortality was no longer significant (p = 0.11). When restricting the analysis of mortality rates to the 1-year time period, the univariable HR was 0.44 (95% CI: 0.19 to 1.06; p = 0.07) for severe PPM and 1.08 (95% CI: 0.61 to 1.91; p = 0.80) for moderate PPM.

The univariate predictors of 1-year mortality in the TAVR-NRCA cohort are presented in Online Table 2. PPM was not significantly associated with 1-year mortality in both univariable (HR: 1.05; 95% CI: 0.85 to 1.28, p = 0.60) (**Figures 3E and 3F**) and multivariable analyses (**Table 4**). However, after excluding patients with mild or greater total prosthetic AR, severe PPM in the TAVR-NRCA group was independently associated with increased mortality (HR: 1.88, 95% CI: 1.09 to 3.22, p = 0.02), and there was a trend (p = 0.056) toward an independent association between overall PPM and mortality (**Table 4**). The impact of PPM on mortality was not statistically different in patients with a transfemoral approach versus those with a transapical approach (p_{int} = 0.85).

TABLE 3 Impact of PPM on 2-Year Mortality in the SAVR-RCT and TAVR-RCT Arms

	2-Year Mortality			
	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
SAVR-RCT (n = 270)				
PPM	1.64 (1.01–2.67)†	0.047†	1.52 (0.93–2.48)	0.09
Moderate PPM	1.51 (0.87–2.64)	0.14	1.44 (0.82–2.52)	0.20
Severe PPM	1.79 (1.03–3.12)†	0.04†	1.78 (1.02–3.11)†	0.041†
TAVR-RCT (n = 304)				
PPM	0.74 (0.48–1.13)	0.16	0.85 (0.55–1.31)	0.46
Moderate PPM	0.92 (0.57–1.49)	0.74	1.10 (0.67–1.80)	0.70
Severe PPM	0.51 (0.27–0.98)†	0.045†	0.58 (0.30–1.13)	0.11

*Adjusted for age, sex, BMI, STS score, pulmonary hypertension, major arrhythmia, renal disease, and post-procedural AR. †These values underline the differences that are statistically significant.

CI = confidence interval; HR = hazard ratio; other abbreviations as in **Table 1**.

DISCUSSION

The main findings of this study are as follows: 1) PPM is more frequent and more often severe after SAVR than TAVR in cohort A of the PARTNER I trial; 2) PPM is associated with less regression of LV hypertrophy in the SAVR-RCT arm and the TAVR-NRCA cohort, but this association is not present in the TAVR-RCT arm; 3) PPM is associated with increased 2-year mortality in the SAVR-RCT arm but not in the TAVR-RCT arm; and 4) PPM is not associated with increased risk of 1-year mortality in the whole TAVR-NRCA cohort; however, severe PPM is independently associated with higher mortality in the subset of patients with no residual prosthetic AR (**Central Illustration**).

INCIDENCE OF PPM IN TAVR VERSUS SAVR. The incidence of PPM was lower with TAVR than with SAVR, particularly in patients with a small aortic annulus. This difference may be related to the superior hemodynamic performance of transcatheter versus surgical valves (5,16) (**Central Illustration**). Although the transcatheter valves are stented valves, the stent is thinner and no sewing ring occupies the annular space, which causes less obstruction to blood flow, a difference that would be more important when implanted in a small aortic annulus (5,16).

The present study reveals that post-dilation may help to reduce the degree of PPM, most likely by achieving more complete valve expansion. Previous studies reported that balloon post-dilation also successfully reduced paravalvular regurgitation in the majority of patients, but may be associated with an increased risk of cerebrovascular events (17,18). Further studies are needed to determine whether the benefits of post-dilation outweigh its risks.

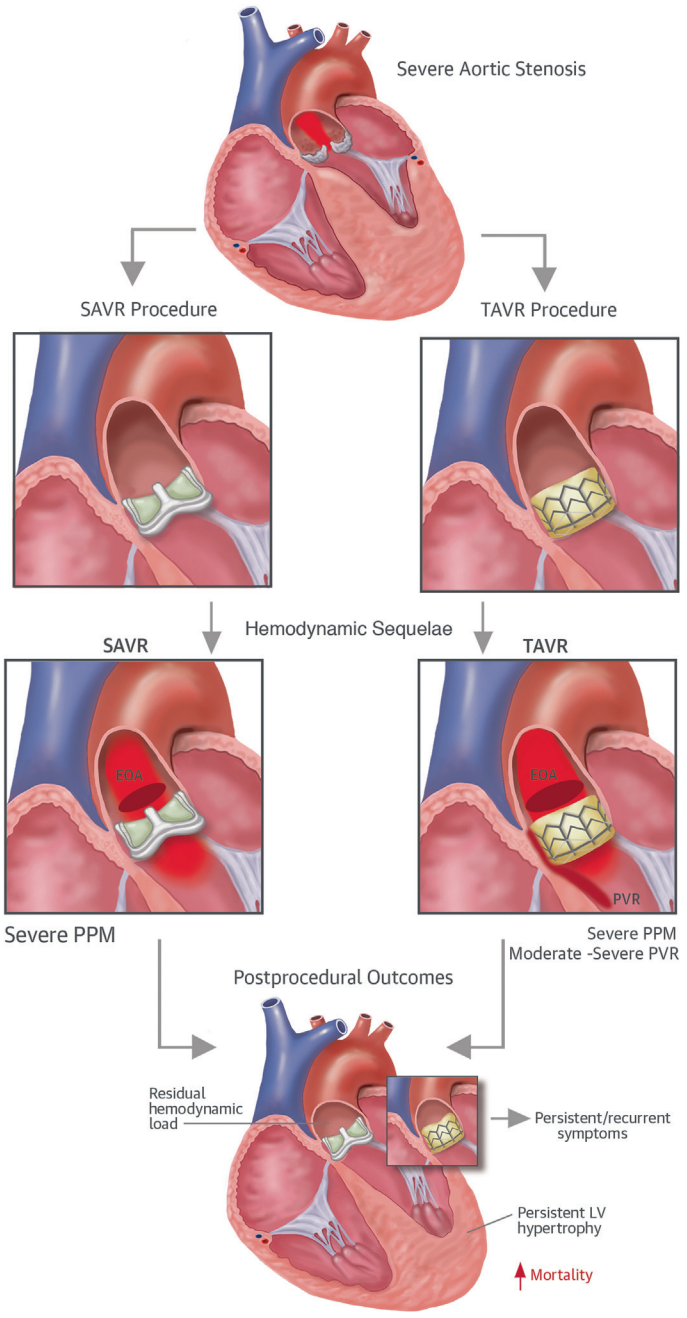
IMPACT OF PPM ON OUTCOMES IN TAVR AND SAVR. Several previous studies and meta-analyses have reported that PPM, particularly severe PPM, negatively affects outcomes after SAVR (1,2). However, this is the first prospective multicenter study with

TABLE 4 Impact of PPM on 1-Year Mortality in the TAVR-NRCA Cohort

	1-Year Mortality			
	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	p Value	HR (95% CI)	p Value
TAVR-NRCA – whole cohort (n = 1,637)				
PPM	1.05 (0.85–1.28)	0.60	1.05 (0.76–1.44)	0.77
Moderate PPM	0.97 (0.72–1.31)	0.85	0.94 (0.69–1.29)	0.98
Severe PPM	1.23 (0.85–1.79)	0.27	1.20 (0.81–1.78)	0.35
TAVR-NRCA – subset with no AR† (n = 835)				
PPM	1.38 (0.91–2.09)	0.12	1.50 (0.99–2.29)	0.056
Moderate PPM	1.22 (0.76–1.95)	0.41	1.36 (0.85–2.20)	0.21
Severe PPM	1.74 (1.02–1.98)‡	0.04‡	1.88 (1.09–3.22)‡	0.02‡

*Adjusted for age, sex, BMI, STS score, major arrhythmia, pulmonary hypertension, renal disease, baseline mitral regurgitation, mean transaortic gradient, LV ejection fraction, and post-procedural AR. †Subset in the TAVR-NRCA cohort with no or trace post-procedural total AR. In this subset, there was no adjustment for post-procedural AR in the models. ‡These values underline the differences that are statistically significant.

Abbreviations as in **Tables 1 and 3**.



CENTRAL ILLUSTRATION Hemodynamic Sequelae After TAVR or SAVR

In patients with severe AS and high surgical risk, PPM is less frequent and less often severe after TAVR than SAVR because of a larger EOA for a given patient's annulus size; this hemodynamic sequela is associated with less LV mass regression and higher mortality. On the other hand, as shown in previous studies, paravalvular regurgitation is more frequent after TAVR than SAVR and is associated with persistent LV hypertrophy and increased mortality. The hemodynamic benefit of TAVR over SAVR seems to be more important in the subset of patients with a small aortic annulus. AS = aortic stenosis; EOA = effective orifice area; LV = left ventricular; PPM = prosthesis-patient mismatch; PVR = paravalvular regurgitation; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

adjudication of events and central analyses of echocardiographic studies to examine the incidence and impact of PPM on outcomes in patients randomized to receive SAVR or TAVR. In addition, this is the first large multicenter study to examine the impact of PPM on LV mass regression and survival in patients undergoing TAVR.

This study shows that PPM is associated with persistence of LV hypertrophy and increased 2-year mortality in high-risk patients with severe AS undergoing SAVR. The HR for severe PPM we reported is similar to that reported in the recent meta-analysis by Head et al. (2). One hypothesis to explain the increased mortality associated with PPM is that the persistence of residual LV afterload and hypertrophy negatively affect post-operative normalization of coronary flow reserve (1,19). In addition, patients with PPM experience significantly less LV hypertrophy regression, as seen in the SAVR group of the present study.

However, as opposed to what was observed in the SAVR-RCT arm, PPM was not associated with decreased regression of LV hypertrophy or increased mortality in the TAVR-RCT arm. The differential impact of PPM on survival in the TAVR-RCT versus the SAVR-RCT is intriguing but may be explained, at least in part, by the following factors:

1. In the TAVR-RCT arm, patients with PPM were younger, had larger BMI, and had a higher prevalence of obesity compared with those with no PPM, whereas these differences between the PPM and no PPM groups were not present in the SAVR-RCT arm. To this effect, Kodali et al. (4) reported that greater BMI is a powerful independent predictor of better 2-year survival (i.e., obesity paradox) in the TAVR-RCT arm of the PARTNER Trial cohort A. Furthermore, the indexation of the prosthetic valve EOA to the patient's BSA may overestimate PPM severity in obese patients (20). This overestimation may have been more important in the severe PPM group of the TAVR-RCT because there was a high prevalence of obesity in this group. These 2 phenomena may have contributed to the absence of negative impact of PPM on LV mass regression and survival in TAVR-RCT.
2. Several studies have reported that moderate-severe AR is associated with increased mortality after TAVR (4,21). In the TAVR cohorts of the present study, patients with PPM had less post-procedural AR compared with those without PPM, whereas paravalvular regurgitation was rare in SAVR, regardless of PPM status. Furthermore, patients in the no PPM SAVR group appeared to have better LV mass regression and survival than

patients in the no PPM TAVR group. This finding may be explained by the fact that the former subset had an optimal valve hemodynamic performance (i.e., no residual AS and no paravalvular regurgitation), whereas the latter subset had no residual stenosis but often had paravalvular regurgitation that may impair LV mass regression and adversely affect survival (**Central Illustration**). Thus, paravalvular regurgitation may have confounded or masked the effect of PPM on LV mass regression and survival in TAVR. This hypothesis is supported by the fact that when excluding patients with post-procedural AR, severe PPM became an independent predictor of 1-year mortality in the TAVR-NRCA cohort with an HR similar to that obtained in the SAVR-RCT arm.

3. The counterintuitive association between severe PPM and improved survival observed on univariable analysis in the TAVR-RCT arm was not confirmed in the TAVR-NRCA arm, which suggests that factors related to initial experience and learning curve might have contributed to this association. To this effect, the analysis of the patients in the TAVR-NRCA group with no post-procedural AR is important because, in this subset, the learning curve effect was likely less powerful than in the TAVR-RCT group and, as in the SAVR-RCT group, there was no confounding effect of paravalvular regurgitation. In this subset, the results with respect to the impact of PPM on mortality were highly consistent with those observed in the SAVR-RCT group.

STUDY LIMITATIONS AND STRENGTHS. In this study, we used the data from a large, randomized study with core laboratory echocardiographic data and adjudicated outcome data. However, this analysis was retrospective and subject to the limitations of an observational study. In addition, 2-year outcomes were unavailable in the NRCA cohort because events were not adjudicated in this registry beyond 1 year.

We chose a definition of PPM on the basis of commonly used indexed EOA criteria included in the guidelines; other cut-points might produce different results. Errors can occur in estimating prosthetic valve EOA by Doppler echocardiography, particularly in patients with transcatheter aortic valves in whom the measurement of stroke volume in the LVOT is challenging. However, the stroke volume measured by Doppler in the LVOT was consistent with that measured by the 2-dimensional echocardiographic method (Online Table 1).

Patients who died in the periprocedural period and/or who did not have a post-procedural echocardiographic examination were excluded, possibly introducing a survival bias. Several previous studies have used the projected indexed EOA (i.e., the indexed EOA calculated by dividing the normal reference value of EOA of the prosthesis by the patient's BSA) to identify PPM, and these studies have demonstrated that PPM significantly affects operative mortality after SAVR (1,2).

In the TAVR-NRCA cohort, we performed a subanalysis after excluding patients with AR. Such an analysis could not be performed in the TAVR-RCT arm because of the limited number of patients.

In the present study, small aortic annulus was defined as an annulus diameter <20 mm as measured by transthoracic echocardiography. This cut-point likely corresponds to a larger diameter value when measured by computed tomography before TAVR or by the surgeon during SAVR. However, comparing the incidence of PPM between TAVR and SAVR in the small annulus subsets remains valid given that we used the same method and criteria to define small annulus in both arms.

It is important to emphasize that the protocol of the PARTNER I Trial cohort A strongly discouraged the use of valves other than the Edwards bioprostheses and excluded patients with a root enlargement planned in advance; therefore, the incidence of PPM in the SAVR arm of this randomized study may be higher than if other prosthetic valves with higher EOA had been used. We cannot extrapolate our results to patients who undergo alternative surgical procedures to prevent PPM (i.e., aortic annulus enlargement, implantation of a stentless bioprosthesis, insertion of a homograft), although these procedures are associated with their own perioperative risks.

CONCLUSIONS

In high-risk patients with severe AS, the incidence of PPM is reduced after TAVR compared with SAVR. Patients with PPM after SAVR have worse survival and less LV mass regression than those without PPM. Severe PPM also significantly affected survival after TAVR in the subset of patients with no post-procedural AR. TAVR may be preferable to SAVR in patients with a small aortic annulus susceptible to PPM to enhance LV mass regression and reduce postoperative mortality.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Philippe Pibarot, Québec Heart and Lung Institute, 2725 Chemin Ste-Foy, Québec QC G1V-4G5, Canada. E-mail: philippe.pibarot@med.ulaval.ca.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TAVR may be preferred over SAVR in high-risk patients with severe AS and small aortic annulus diameter susceptible to PPM to enhance regression of LV hypertrophy and reduce post-procedural mortality.

TRANSLATIONAL OUTLOOK: Longer follow-up of patients in clinical trials and studies of a wider variety of prostheses are needed to fully characterize differences in hemodynamic responses to TAVR versus SAVR.

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KEY WORDS aortic regurgitation, Doppler echocardiography, left ventricular mass regression, mortality

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