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ORIGINAL RESEARCH

5-Year Echocardiographic Results of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients

Rebecca T. Hahn, MD,[a,b] Julien Ternacle, MD, PhD,[c] Iria Silva, MD,[d,e] Carlos Giuliani, MD,[e] Antonela Zanuttini, MD,[e] Alexis Théron, MD,[e,f] Nicole Cristell, MD,[a] Mathieu Bernier, MD,[e] Sabah Skaf, MD,[g] Jonathan Beaudoin, MD,[e] Susheel K. Kodali, MD,[b] Mark Russo, MD,[h] Samir R. Kapadia, MD,[i] Chris S. Malaisrie, MD,[j] David J. Cohen, MD, MSc,[a,k] Jonathon Leipsic, MD,[l] Philipp Blanke, MD,[l] Mathew R. Williams, MD,[m] James M. McCabe, MD,[n] David L. Brown, MD,[o] Vasilis Babaliaros, MD,[p] Scott Goldman, MD,[q] Wilson Y. Szeto, MD,[r] Philippe Généreux, MD,[s] Ashish Pershad, MD,[t] Brandon Park, PhD,[u] Marissa Gunnarsson, BS,[u] John G. Webb, MD,[l] Craig R. Smith, MD,[b] Raj Makkar, MD,[g] Vinod H. Thourani, MD,[v] Michael J. Mack, MD,[o] Martin B. Leon, MD,[a,b] Philippe Pibarot, DVM, PhD,[e] the PARTNER 3 Investigators

ABSTRACT

BACKGROUND The PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis) trial compared SAPIEN 3 transcatheter aortic valve replacement (TAVR) to surgery in low-risk patients with symptomatic, severe aortic stenosis. Echocardiographic outcomes at 5 years are unknown.

OBJECTIVES This study sought to compare 5-year echocardiographic results of TAVR and surgery in the PARTNER 3 trial.

METHODS Echocardiograms for 1,000 randomized patients were obtained at baseline, 30 days, 1 year, and annually through 5 years and were analyzed by a core lab consortium. The composite primary endpoint of death, stroke, or rehospitalization was adjudicated by a clinical events committee.

RESULTS At 5 years, ≥ mild aortic regurgitation was higher following TAVR vs surgery (24.5% vs 6.3%; $P < 0.001$), with low ≥ moderate aortic regurgitation in both groups. TAVR patients had higher mean transaortic gradient (12.8 ± 6.5 vs 11.7 ± 5.6 mm Hg; $P < 0.001$), stroke volume index (44.6 ± 9.7 vs 41.1 ± 9.2; $P < 0.0001$), and aortic valve area (1.87 ± 0.46 vs 1.82 ± 0.46; $P = 0.895$). Fewer TAVR patients had low-flow stroke volume index ($P < 0.001$) and left ventricular hemodynamic burden (valvulo-arterial impedance; $P < 0.01$). Tricuspid annular plane systolic excursion was also higher with TAVR ($P < 0.001$), as was right ventricular–to-pulmonary artery coupling ($P < 0.0001$). In the combined cohorts, 30-day moderate to severe prosthesis-patient mismatch, mild to severe aortic regurgitation, or low stroke volume index were not predictive of clinical outcomes; only low right ventricular–to-pulmonary artery coupling and high valvulo-arterial impedance at 30 days were associated with increased risk of the 5-year composite primary endpoint.

CONCLUSIONS In low-risk patients with severe aortic stenosis, TAVR, compared to surgery, was associated with similar, stable valve hemodynamics at 5 years with less frequent low-flow state, lower valvulo-arterial impedance, and better right ventricular function. (PARTNER 3 Trial: Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis [P3]; NCT02675114) (JACC Cardiovasc Imaging. 2025;18:625-640) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

LVOT = left ventricular outflow tract

PASP = pulmonary artery systolic pressure

PPM = patient-prosthesis mismatch

PVR = paravalvular regurgitation

RV-PA = right ventricular pulmonary artery

SVi = stroke volume index

TAPSE = tricuspid annulus plane systolic excursion

TAVR = transcatheter aortic valve replacement

Z_{va} = valvulo-arterial impedance

Transcatheter aortic valve replacement (TAVR) has been increasingly used for the treatment of patients with symptomatic, severe aortic stenosis (AS) across the spectrum of operative risk.[1-6] Recently, the PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis) trial, which compared transfemoral TAVR with the balloon-expandable SAPIEN 3 valve (Edwards Lifesciences) with surgical AVR in low-risk patients, reported no significant difference in the composite primary endpoint (death, stroke, or rehospitalization related to the procedure, valve, or heart failure) at 5 years.[7]

Echocardiography is key to assess the evolution of cardiac chamber geometry and function following AVR and to determine prosthetic valve hemodynamic performance and its stability during follow-up. We previously reported the 30-day and 1-year echocardiographic results of the PARTNER 3 trial, which revealed similar bioprosthetic valve hemodynamics and regression of left ventricular (LV) hypertrophy with both TAVR and surgery.[8] The objectives of this analysis are to compare the evolution of echocardiographic parameters from baseline to 5 years with TAVR vs surgery and to determine the association between echocardiographic parameters at 30-day and 5-year clinical outcomes.

METHODS

PATIENT SELECTION, STUDY DESIGN, AND MANAGEMENT. Between March 25, 2016, and October 26, 2017, a total of 1,000 patients were enrolled at 71 centers and randomized to undergo TAVR with the SAPIEN 3 valve or surgery. Details on study design, complete inclusion and exclusion criteria, procedures, and postprocedural antithrombotic regimen have been presented previously.[5] The trial was approved by the individual site Institutional Review Boards, and all patients provided written informed consent. The patient population for this analysis consisted of all "valve-implant" patients.

ECHOCARDIOGRAPHY CORE LABORATORY ANALYSES. Transthoracic echocardiograms were obtained at baseline, 30 days, 1 year, and annually through 5 years post procedure and were analyzed by a consortium of 2 echocardiography core laboratories. Image acquisition and analysis were performed according to the American Society of Echocardiography standards for echocardiography core laboratories,[9] and methods for echocardiographic measurements in the PARTNER 3 trial have been previously described.[8]

Definitions and formulas for echocardiographic parameters, including aortic valve hemodynamics and LV and right ventricular (RV) geometry and function, are outlined in the Supplemental Methods. Beyond these standard measurements, the valvulo-arterial impedance (Z_{va}) was calculated to estimate the total LV hemodynamic load: Z_{va} = (systolic blood pressure + mean transvalvular gradient) / stroke volume indexed to body surface area.[10,11] Tricuspid annulus plane systolic excursion (TAPSE) was measured on 2-dimensional images in the 4-chamber view to assess RV systolic function.[8] Pulmonary arterial systolic pressure (PASP) was assumed to be equivalent to the RV systolic pressure in the absence of pulmonic stenosis or RV outflow tract obstruction. Reduced TAPSE was defined as ≤1.6 cm, with high PASP defined as ≥35 mm Hg. Right ventricular

From the [a]Cardiovascular Research Foundation, New York, New York, USA; [b]Columbia University Irving Medical Center/New York-Presbyterian Hospital, New York, New York, USA; [c]Haut-Leveque Cardiology Hospital, Bordeaux University, Pessac, France; [d]Department of Cardiology, Hospital Universitario Central de Asturias, Oviedo, Spain; [e]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Québec, Canada; [f]Department of Cardiology, Assistance Publique, Hôpitaux de Marseille, Marseille, France; [g]Cedars Sinai Medical Center, Los Angeles, California, USA; [h]Rutgers Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA; [i]Cleveland Clinic, Cleveland, Ohio, USA; [j]Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA; [k]St Francis Hospital, Roslyn, New York, USA; [l]St Paul's Hospital, Vancouver, British Columbia, Canada; [m]NYU Langone Medical Center, New York, New York, USA; [n]University of Washington, Seattle, Washington, USA; [o]Baylor Scott and White Healthcare, Plano, Texas, USA; [p]Emory University School of Medicine, Atlanta, Georgia, USA; [q]Lankenau Medical Center, Wynnewood, Pennsylvania, USA; [r]University of Pennsylvania, Philadelphia, Pennsylvania, USA; [s]Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey, USA; [t]Chandler Regional and Mercy Gilbert Medical Center, Chandler, Arizona, USA; [u]Edwards Lifesciences, Irvine, California, USA; and the [v]Department of Cardiovascular Surgery, Piedmont Heart Institute, Atlanta, Georgia, USA.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 5-Year Echocardiographic Results: Aortic Valve and Ventricular Hemodynamics

	Baseline		30-Day Visit			5-Year Visit		
	TAVR (n = 495)	Surgery (n = 453)	TAVR (n = 492)	Surgery (n = 432)	*P* Value	TAVR (n = 333)	Surgery (n = 284)	*P* Value
Peak aortic velocity, cm/s	446.6 ± 52.78 (483)	444.0 ± 51.68 (442)	240.6 ± 39.79 (492)	225.3 ± 42.47 (432)	<0.001	236.3 ± 53.11 (329)	225.9 ± 49.66 (282)	0.001
Peak gradient, mm Hg	80.9 ± 19.67 (483)	79.9 ± 18.87 (442)	23.8 ± 7.96 (492)	21.0 ± 7.95 (432)	<0.001	23.5 ± 11.08 (329)	21.4 ± 9.67 (282)	<0.001
Mean gradient, mm Hg	49.4 ± 12.74 (483)	48.3 ± 11.76 (442)	12.7 ± 4.34 (492)	11.2 ± 4.29 (432)	<0.001	12.8 ± 6.52 (329)	11.7 ± 5.59 (282)	0.001
Mean gradient ≥20 mm Hg	483/483 (100.0)	441/442 (99.8)	33/492 (6.7)	17/432 (3.9)	0.080	36/329 (10.9)	22/282 (7.8)	0.214
Aortic valve area, cm^2	0.77 ± 0.160 (458)	0.77 ± 0.154 (424)	1.74 ± 0.356 (482)	1.79 ± 0.412 (415)	<0.001	1.87 ± 0.457 (320)	1.82 ± 0.463 (275)	0.895
Intended valve performance[a]	NA	NA	432/475 (90.9)	397/422 (94.1)	0.100	252/294 (85.7)	251/276 (90.9)	0.068
Indexed aortic valve area, cm^2/m^2	0.38 ± 0.078 (458)	0.38 ± 0.075 (424)	0.86 ± 0.178 (482)	0.89 ± 0.209 (415)	<0.001	0.93 ± 0.232 (320)	0.90 ± 0.222 (275)	0.993
Patient-prosthesis mismatch					0.147			0.088
Mild	NA	NA	319/483 (66.0)	301/429 (70.2)		232/320 (72.5)	185/275 (67.3)	
Moderate	NA	NA	142/483 (29.4)	101/429 (23.5)		72/320 (22.5)	74/275 (26.9)	
Severe	NA	NA	22/483 (4.6)	27/429 (6.3)		16/320 (5.0)	16/275 (5.8)	
Doppler velocity index	0.19 ± 0.053 (463)	0.20 ± 0.038 (427)	0.41 ± 0.067 (470)	0.45 ± 0.083 (422)	<0.001	0.42 ± 0.085 (292)	0.44 ± 0.095 (276)	0.003
LVOT diameter, systole	2.26 ± 0.18 (485)	2.24 ± 0.19 (443)	2.31 ± 0.18 (492)	2.25 ± 0.18 (429)	<0.001	2.36 ± 0.19 (331)	2.28 ± 0.18 (281)	0.004
LVOT VTI	20.6 ± 3.74 (463)	20.8 ± 3.90 (427)	20.1 ± 3.64 (470)	19.3 ± 3.78 (424)	<0.001	20.8 ± 4.55 (294)	20.6 ± 4.75 (277)	0.181
LV stroke volume, mL	81.7 ± 15.25 (458)	80.9 ± 15.47 (424)	84.1 ± 15.34 (482)	76.8 ± 16.29 (418)	<0.001	90.0 ± 18.79 (322)	83.7 ± 20.00 (276)	<0.001
LV stroke volume index, mL/m^2	40.7 ± 7.65 (458)	40.1 ± 7.68 (424)	41.8 ± 7.55 (482)	38.1 ± 7.97 (418)	<0.001	44.6 ± 9.69 (322)	41.1 ± 9.18 (276)	<0.001
LV stroke volume index <35 mL/m^2	107/458 (23.4)	115/424 (27.1)	102/482 (21.2)	150/418 (35.9)	<0.001	61/322 (18.9)	70/276 (25.4)	0.060
LV stroke volume index <32 mL/m^2 (female patients) <40 mL/m^2 (male patients)	173/458 (37.8)	175/424 (41.3)	150/482 (31.1)	212/418 (50.7)	<0.001	83/322 (25.8)	112/276 (40.6)	<0.001
Mild to severe paravalvular aortic regurgitation	NA	NA	144/488 (29.5)	12/429 (2.8)	<0.001	69/331 (20.8)	9/283 (3.2)	<0.001
Moderate to severe paravalvular aortic regurgitation	NA	NA	4/488 (0.8)	0/429 (0.0)	0.127	3/331 (0.9)	0/283 (0.0)	0.253
Moderate total aortic regurgitation	19/483 (3.9)	11/446 (2.5)	4/490 (0.8)	1/432 (0.2)	0.379	6/331 (1.8)	1/284 (0.4)	0.131
Nonechocardiographic parameters								
Systolic blood pressure, mm Hg	136.6 ± 18.70 (495)	136.4 ± 17.96 (453)	138.5 ± 18.55 (492)	133.0 ± 20.17 (437)	<0.001	137.6 ± 18.29 (364)	135.9 ± 17.15 (309)	0.599
Diastolic blood pressure, mm Hg	73.8 ± 10.04 (495)	73.7 ± 9.84 (453)	72.3 ± 9.99 (492)	73.0 ± 10.74 (437)	0.037	72.4 ± 11.04 (364)	73.9 ± 9.99 (309)	0.099

Values are mean ± SD (n) or n/N (%), unless otherwise indicated. Parameters evaluated in the valve implant population at baseline (n = 495 for TAVR, n = 453 for surgery). *P* values for continuous variables are based on linear mixed models and for categorical variables are based on Fisher exact test. [a]Intended valve performance was defined as having a mean gradient <20 mm Hg, peak velocity <3 m/s, Doppler velocity index ≥0.25, and aortic regurgitation that is less than moderate.

LV = left ventricular; LVOT = left ventricular outflow tract; NA = not applicable; TAVR = transcatheter aortic valve replacement; VTI = velocity time integral.

pulmonary artery (RV-PA) coupling ratio, which refers to the relationship between RV contractility and afterload, was calculated as tricuspid annulus plane systolic excursion divided by pulmonary artery systolic pressure (TAPSE/PASP). RV-PA uncoupling was defined as a TAPSE/PASP ratio <0.50 mm/mm Hg (Supplemental Figure 1).

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD, and comparisons during the 5-year follow-up were performed with linear mixed models using baseline values, treatment, visit, and interaction between treatment and visit as predictors. Categorical variables are presented as proportions and compared using Fisher exact test.

The primary clinical endpoint of the PARTNER 3 trial and for this analysis was the composite of all-cause death, stroke, and rehospitalization related to the procedure, valve, or heart failure. Time-to-event outcomes were evaluated using Kaplan-Meier estimates and the log-rank test. For the comparison of >2 Kaplan-Meier curves, the log-rank test was used to make overall and pairwise comparisons. The

TABLE 2 5-Year Echocardiographic Results: Left- and Right-Heart Size and Function

	Baseline		30-Day Visit			5-Year Visit		
	TAVR (n = 495)	Surgery (n = 453)	TAVR (n = 492)	Surgery (n = 432)	*P* Value	TAVR (n = 333)	Surgery (n = 284)	*P* Value
LV size and function								
LV end-diastolic diameter, cm	4.9 ± 0.52 (480)	4.9 ± 0.51 (441)	4.9 ± 0.50 (484)	4.8 ± 0.51 (414)	<0.001	4.9 ± 0.60 (331)	4.8 ± 0.58 (280)	0.072
LV end-systolic diameter, cm	3.0 ± 0.62 (477)	3.0 ± 0.63 (432)	3.0 ± 0.59 (480)	3.0 ± 0.59 (412)	0.149	3.0 ± 0.69 (329)	3.0 ± 0.64 (279)	0.677
LV mass index, g/m^2	104.6 ± 25.72 (475)	101.5 ± 25.38 (435)	99.0 ± 23.65 (478)	94.1 ± 25.94 (407)	0.002	87.0 ± 25.30 (330)	84.8 ± 23.34 (280)	0.121
High LV mass index group (≥91 female/ 132 male patients g/m^2)[c]	144/475 (30.3)	102/435 (23.4)	115/478 (24.1)	72/407 (17.7)	0.021	45/330 (13.6)	28/280 (10.0)	0.211
LV hypertrophy	198/475 (41.7)	138/435 (31.7)	152/478 (31.8)	95/407 (23.3)	0.005	61/330 (18.5)	45/280 (16.1)	0.454
Relative wall thickness	0.46 ± 0.09 (475)	0.45 ± 0.08 (435)	0.45 ± 0.08 (478)	0.45 ± 0.09 (407)	0.001	0.41 ± 0.09 (330)	0.42 ± 0.09 (280)	0.444
LVEF, %	65.7 ± 8.98 (471)	66.2 ± 8.58 (435)	65.7 ± 8.20 (479)	65.5 ± 8.93 (408)	0.128	62.2 ± 8.69 (313)	63.1 ± 8.59 (275)	0.464
LVEF <50%	22/471 (4.7)	21/435 (4.8)	19/479 (4.0)	20/408 (4.9)	0.515	23/313 (7.3)	15/275 (5.5)	0.403
Energy loss index, cm^2/m^2	0.4 ± 0.09 (412)	0.4 ± 0.09 (381)	1.2 ± 0.64 (412)	1.2 ± 0.48 (315)	0.039	1.2 ± 0.41 (286)	1.1 ± 0.34 (231)	0.914
Valvulo-arterial impedance, mm Hg/mL/m^2	4.7 ± 0.98 (458)	4.8 ± 0.98 (424)	3.7 ± 0.84 (482)	3.9 ± 0.94 (418)	<0.001	3.5 ± 0.80 (314)	3.8 ± 0.90 (264)	0.007
Valvulo-arterial impedance >4 mm Hg/mL/m^2	349/458 (76.2)	323/424 (76.2)	153/482 (31.7)	172/418 (41.1)	0.004	79/314 (25.2)	87/264 (33.0)	0.043
E/e′	15.39 ± 6.070 (440)	14.82 ± 5.587 (416)	15.12 ± 5.963 (470)	13.68 ± 5.336 (410)	<0.001	16.72 ± 7.044 (312)	14.74 ± 6.702 (269)	0.004
e′ lateral velocity,[a] cm/s	6.3 ± 1.99 (433)	6.8 ± 2.31 (407)	7.0 ± 2.31 (466)	8.6 ± 2.73 (408)	<0.001	6.8 ± 2.04 (316)	8.3 ± 2.76 (269)	<0.001
e′ medial velocity, cm/s	5.4 ± 1.46 (412)	5.5 ± 1.58 (392)	5.6 ± 1.59 (460)	5.7 ± 1.60 (400)	0.001	5.6 ± 1.63 (314)	6.0 ± 1.68 (270)	0.004
LA volume index, mL/m^2	35.7 ± 11.28 (479)	36.0 ± 11.15 (441)	35.2 ± 10.65 (489)	34.9 ± 11.17 (426)	0.810	36.6 ± 12.55 (328)	37.0 ± 12.34 (282)	0.351
Mild to severe mitral regurgitation	174/476 (36.6)	154/437 (35.2)	129/492 (26.2)	143/431 (33.2)	0.025	125/326 (38.3)	96/281 (34.2)	0.310
Moderate to severe mitral regurgitation	6/476 (1.3)	14/437 (3.2)	3/492 (0.6)	15/431 (3.5)	0.002	9/326 (2.8)	10/281 (3.6)	0.644
RV size and function								
RV base, cm	3.9 ± 0.59 (467)	3.9 ± 0.60 (423)	3.9 ± 0.58 (480)	4.0 ± 0.58 (408)	<0.001	3.9 ± 0.63 (323)	4.2 ± 0.75 (276)	<0.001
RV mid, cm	3.0 ± 0.58 (457)	3.0 ± 0.56 (422)	3.0 ± 0.56 (470)	3.1 ± 0.55 (398)	0.575	3.2 ± 0.63 (320)	3.3 ± 0.70 (268)	0.360
RV TAPSE, cm	2.10 ± 0.42 (460)	2.12 ± 0.40 (420)	2.05 ± 0.43 (477)	1.37 ± 0.40 (395)	<0.001	1.95 ± 0.46 (320)	1.51 ± 0.40 (272)	<0.001
PASP, mm Hg	35.4 ± 9.98 (318)	36.6 ± 9.66 (281)	33.4 ± 7.35 (328)	32.9 ± 7.14 (310)	0.978	34.5 ± 8.95 (261)	33.6 ± 8.77 (236)	0.454
PASP <35 mm Hg[a]	180/318 (56.6)	126/281 (44.8)	205/328 (62.5)	209/310 (67.4)	0.213	147/261 (56.3)	153/236 (64.8)	0.055
RV-PA coupling,[b] mm/mm Hg	0.62 ± 0.20 (300)	0.61 ± 0.19 (270)	0.64 ± 0.20 (316)	0.43 ± 0.17 (288)	<0.001	0.61 ± 0.20 (254)	0.48 ± 0.19 (230)	<0.001
RV-PA coupling <0.50 mm/mm Hg	79/300 (26.3)	79/270 (29.3)	80/316 (25.3)	208/288 (72.2)	<0.001	86/254 (33.9)	136/230 (59.1)	<0.001
Mild to severe tricuspid regurgitation	152/472 (32.2)	141/431 (32.7)	137/492 (27.8)	182/432 (42.1)	<0.001	100/328 (30.5)	129/282 (45.7)	<0.001
Moderate to severe tricuspid regurgitation	8/472 (1.7)	10/431 (2.3)	4/492 (0.8)	23/432 (5.3)	<0.001	7/328 (2.1)	17/282 (6.0)	0.020
Tricuspid regurgitation peak gradient, mm Hg	27.4 ± 9.98 (318)	28.6 ± 9.66 (281)	25.4 ± 7.35 (328)	24.9 ± 7.14 (310)	0.979	26.5 ± 8.95 (261)	25.6 ± 8.77 (236)	0.454
Tricuspid annulus tissue velocity, cm/s	12.4 ± 2.88 (263)	12.6 ± 3.43 (247)	12.5 ± 2.75 (273)	9.3 ± 2.25 (254)	<0.001	12.2 ± 3.10 (240)	10.0 ± 2.32 (204)	<0.001

Values are mean ± SD (n) or n/N (%), unless otherwise indicated. Parameters evaluated in the valve implant population at baseline (n = 495 for TAVR, n = 453 for surgery). *P* values for continuous variables are based on linear mixed models and for categorical variables are based on Fisher exact test. [a]Parameter significant at baseline ($P < 0.05$ for high LV mass index, PASP <35 mm Hg, and e' lateral velocity). [b]RV-PA coupling defined as TAPSE/PASP. [c]Parameter significant at baseline ($P < 0.05$ for high LV mass index, PASP <35 mm Hg, and e′ lateral velocity).

LA = left atrium; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; RV = right ventricle; RV-PA = right ventricular-to-pulmonary artery; TAPSE = tricuspid annular plane systolic excursion; TAPSE/PASP = tricuspid annular plane systolic excursion divided by pulmonary artery systolic pressure; other abbreviation as in Table 1.

association between 30-day echocardiographic parameters and the composite endpoint through 5 years was analyzed with a Cox proportional hazards model using treatment, 30-day dichotomized echocardiographic parameters, and the interaction between treatment and 30-day dichotomized echocardiographic parameters as covariates. If the interaction was statistically significant at the 0.05 level, the analysis was performed separately by treatment cohort. Otherwise, the interaction was considered statistically nonsignificant, and the analysis was performed on the combined cohort. Six echo parameters (patient-prosthesis mismatch [PPM], mean gradient, paravalvular regurgitation [PVR], stroke volume index [SVi], Z_{va}, and RV-PA coupling) were analyzed as described to evaluate the association with respect to the composite endpoint. These 6 parameters were selected on a clinical rationale because they were shown to be associated with clinical outcomes in previous analyses of the PARTNER (Placement of Aortic Transcatheter Valves) trials.[8,12-14]

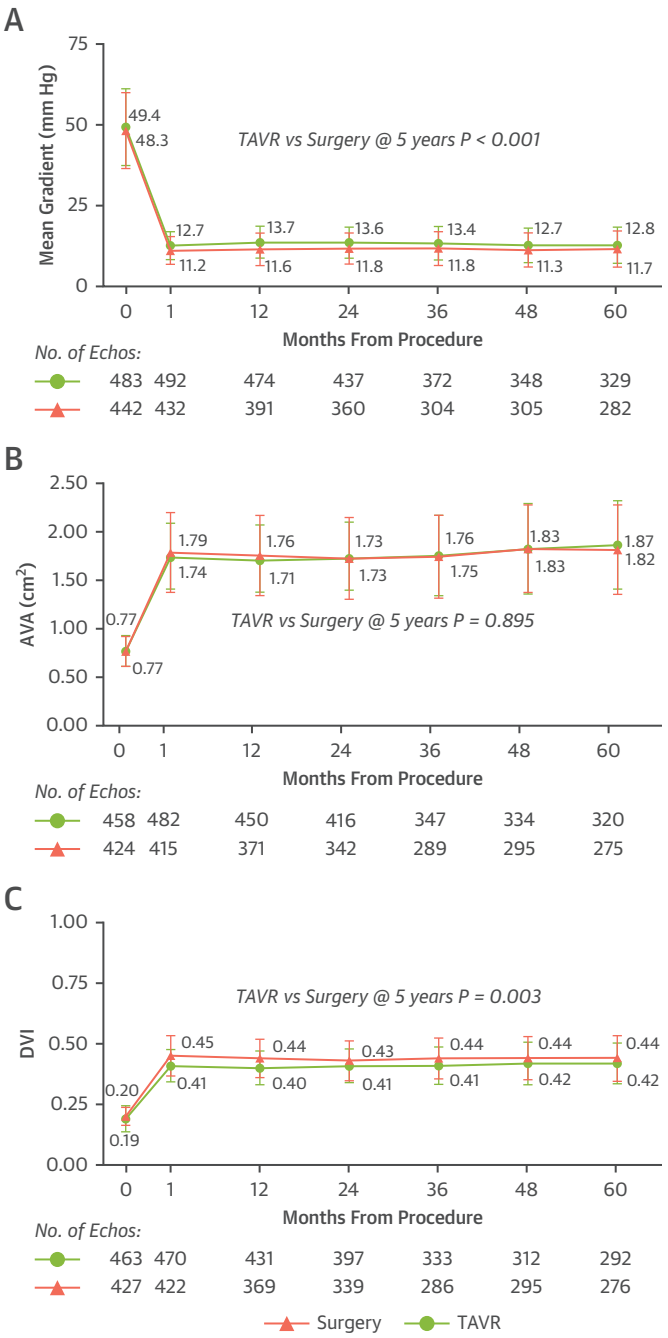
For all analyses, a 2-sided value of $P < 0.05$ was considered statistically significant without adjustment for multiple comparisons. All statistical analyses were performed with the use of SAS software (version 9.4, SAS Institute).

RESULTS

The study flowchart (Supplemental Figure 2) shows that 79% of patients in both treatment arms had available echocardiograms for analysis at 5 years. Baseline clinical characteristics are listed in Supplemental Table 1. Baseline echocardiographic characteristics were similar in both cohorts (**Tables 1 and 2**). Whereas patients in the surgery arm were more likely to have a baseline PASP ≥35 mm Hg, PASP and related parameters—namely RV-PA coupling—were not evaluable in a higher proportion of patients than most other parameters (~40% at baseline, ~35% at 30 days, and ~21% at 5 years); however, sensitivity analyses using 2 imputation methods yielded consistent results for this parameter at 5 years (Supplemental Table 2).

VALVE HEMODYNAMICS. Mean aortic valve gradient, aortic valve area (AVA), AVA index, Doppler velocity index, SVi, peak aortic velocity, and peak transvalvular pressure gradients were stable through 5-year follow-up (**Figure 1**, **Table 1**). The complete case analysis of these parameters using baseline, 30-day,

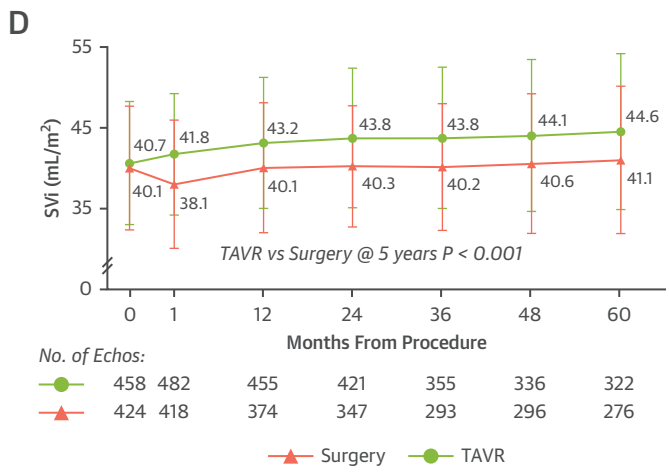
FIGURE 1 Valve Hemodynamic Function



Valve hemodynamic function from baseline to 5 years assessed by mean transvalvular gradient (A); AVA (B); DVI (C); and Svi (D). AVA = aortic valve area; DVI = Doppler velocity index; SVi = stroke volume index; TAVR= transcatheter aortic valve replacement.

Continued on the next page

FIGURE 1 Continued



1-year, and 5-year paired data demonstrated similar results (Supplemental Figure 3). There was an equivalent and sustained reduction in mean transvalvular gradients with both TAVR and surgery. Whereas the ~1 mm Hg difference was significantly higher with TAVR vs surgery, the percentage of patients with a residual gradient ≥20 mm Hg was not significantly different. The calculated AVA at 5 years was also not significantly different between TAVR and surgery (1.87 ± 0.46 vs 1.82 ± 0.46; $P = 0.895$) despite a significantly lower Doppler velocity index (0.42 ± 0.09 vs 0.44 ± 0.10; $P = 0.003$), due to a larger left ventricular outflow tract (LVOT) diameter (2.36 ± 0.19 vs 2.28 ± 0.18; $P = 0.004$). SVi was significantly higher among TAVR patients through 5-year follow-up, and 25.4% of surgery patients were in a low-flow state vs 18.9% of TAVR patients ($P = 0.060$).

The prevalence of mild to severe total aortic regurgitation was significantly higher in the TAVR arm, driven by mild to severe PVR with no differences in transvalvular regurgitation between treatment groups (**Figure 2**, **Table 1**). Notably, moderate PVR was seen in only 4 patients in the TAVR arm at 30 days, with no patients experiencing severe PVR throughout follow-up. Complete case analyses demonstrated similar results (Supplemental Figure 4).

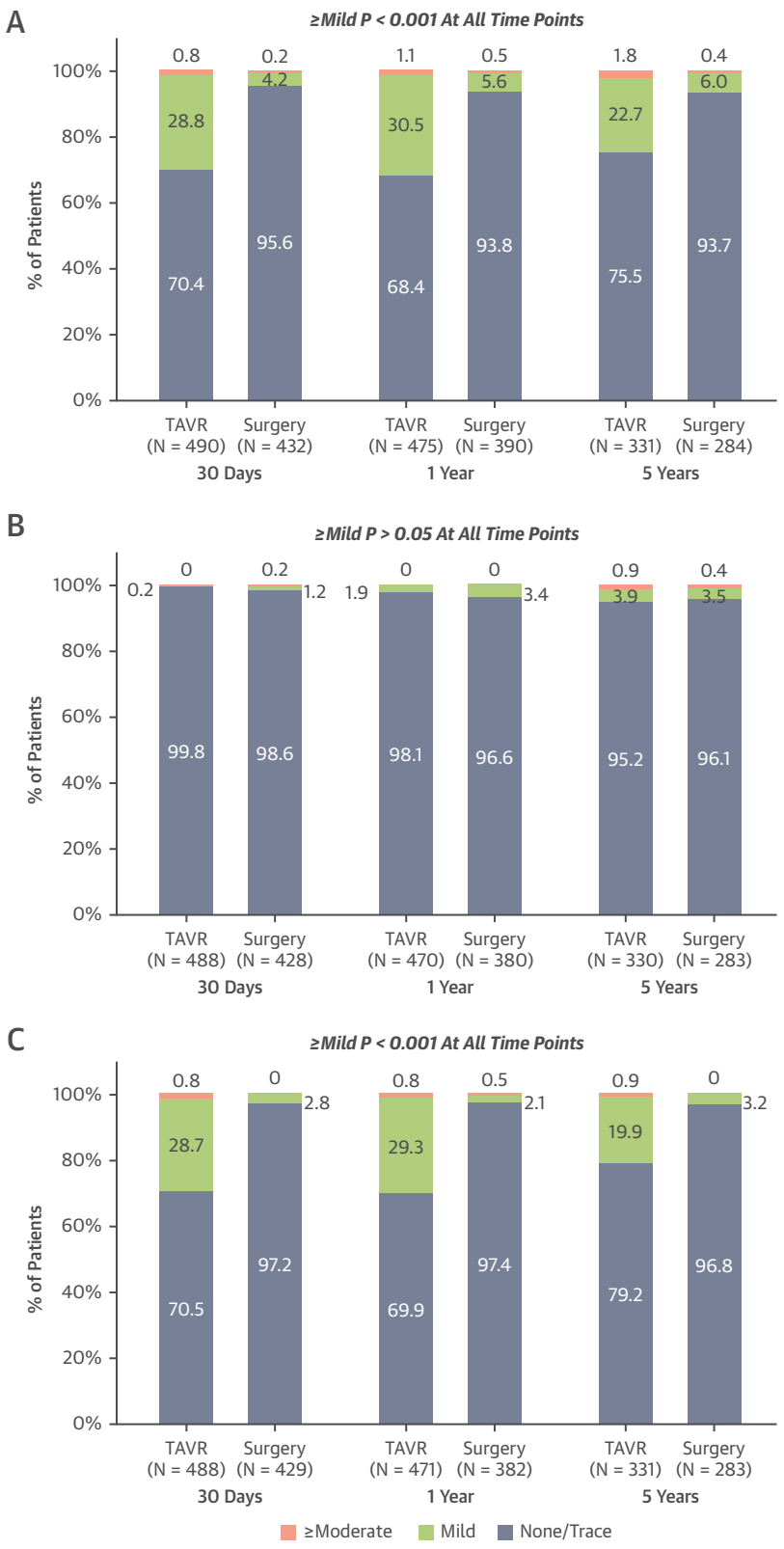
HEART SIZE AND FUNCTION. LV mass regression occurred similarly after TAVR and surgery, reaching normal values by 1 year and continuing to decrease over 5 years (**Figure 3A**). There was no significant difference between TAVR and surgery in LV ejection fraction, with both cohorts exhibiting a nonsignificant decline that remained within normal range (**Figure 3B**). The degree of LV concentric remodeling, as reflected by the relative wall thickness ratio, also decreased to a similar extent in TAVR vs surgery (**Figure 3C**). The Z_{va}, which reflects global LV hemodynamic burden, diverged at 1 month and remained significantly higher in surgery patients compared with TAVR patients throughout follow-up (**Figure 3D**). At 5 years, 33.0% of surgery patients had Z_{va} >4 mm Hg/mL/m^2, compared with 25.2% in TAVR patients ($P = 0.0425$) (**Central Illustration**). Complete case analyses showed similar results (Supplemental Figure 5). The percentage of moderate to severe mitral regurgitation was slightly higher following surgery vs TAVR (3.6% vs 2.8%; $P = 0.644$) at 5 years (**Table 2**).

TAPSE exhibited an acute decrease at 30 days following surgery, with minimal recovery during follow-up, whereas there was no significant change in the TAVR arm (**Figure 4A**). PASP decreased slightly following AVR and remained stable and similar in both arms throughout follow-up (**Figure 4B**). The TAPSE/PASP ratio was significantly lower in surgery patients at 30 days and throughout the follow-up period (**Figure 4C**). At 5 years, 59.1% of surgery patients had RV-PA uncoupling (TAPSE/PASP <0.50 mm/mm Hg) vs 33.9% of TAVR patients ($P < 0.001$). RV dimensions were unchanged after TAVR; however, in surgery patients the basal RV measurements were significantly larger at 30 days and 5 years (4.2 cm vs 3.9 cm; $P < 0.0001$). Tricuspid regurgitation mild to severe was higher following surgery compared to TAVR throughout follow-up ($P < 0.01$) (**Figure 4D**).

ASSOCIATION OF ECHOCARDIOGRAPHIC PARAMETERS AT 30 DAYS WITH 5-YEAR OUTCOMES. Severe, measured PPM at 30 days was low and similar in both arms (TAVR: 4.6% vs surgery: 6.3%) (**Table 1**) and was not associated with the primary composite endpoint for TAVR and surgery combined (**Figure 5A**). Mean gradient ≥20 mm Hg and mild to severe PVR at 30 days were also not associated with the composite endpoint in the combined cohort (**Figures 5B and 5C**), although few patients had moderate to severe PVR. When the analysis was restricted to the TAVR arm, there was no association between mild to severe PVR at 30 days and all-cause mortality at 5 years (only 4 patients had moderate PVR at 30 days and none of them died) (**Figure 5D**).

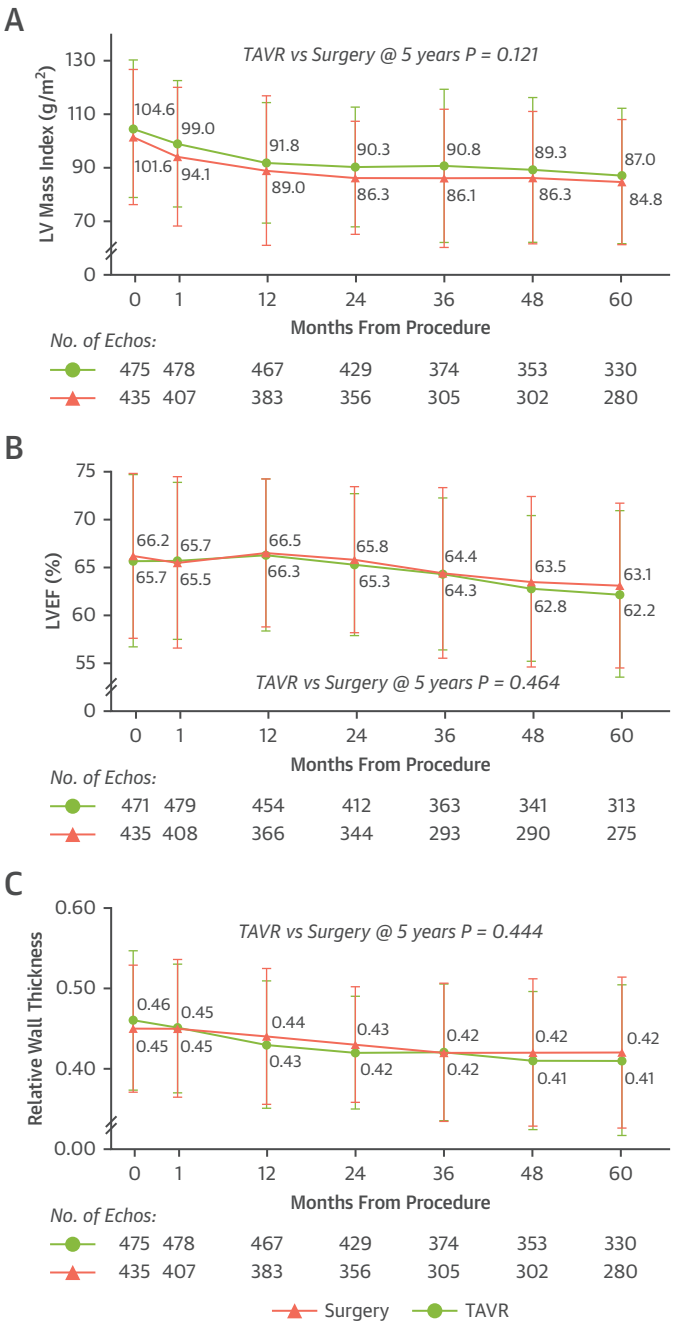
The association between low-flow state (SVi < 35 mL/m^2) at 30 days and the composite outcome was also not significant at 5 years (**Figure 6A**). There was a significant association between Z_{va} ≥4 mm Hg/mL/m^2 and the composite outcome for the combined cohort, consistent with moderately elevated global LV

FIGURE 2 Aortic Valve Regurgitation



Aortic regurgitation severity (3-class) assessed as total aortic regurgitation (A); transvalvular aortic regurgitation (B); and paravalvular aortic regurgitation (C). Abbreviation as in Figure 1.

FIGURE 3 LV Function



Left ventricular (LV) size and function from baseline to 5 years, assessed by LV mass index (A); left ventricular ejection fraction (LVEF) (B); relative wall thickness (C); and valvulo-arterial impedance (Z_{va}). MG = mean gradient; SBP = systolic blood pressure; other abbreviations as in Figure 1.

Continued on the next page

hemodynamic load (Figure 6B). The curves separated by 1 year and appear to diverge further over time. The association between Z_{va} at 30 days and the composite outcome at 5 years was driven mainly by differences in the rate of rehospitalization (Table 3). After adjusting for select covariates such as STS (Society of Thoracic Surgeons) score, high Z_{va} (≥4 mm Hg/mL/m^2) remained independently associated with a higher risk of the primary outcome (HR: 1.45; 95% CI: 1.06-1.98) (Supplemental Table 3). Whereas the associations remained similar, the result was no longer significant in regard to the composite endpoint when Z_{va} was treated as a continuous variable (Supplemental Table 4).

RV-PA uncoupling (TAPSE/PASP <0.50 mm/mm Hg) was also significantly associated with the composite endpoint at 5 years (FIGURE 6C), which appears to be driven by cardiac mortality and stroke (Table 3). With respect to the composite endpoint, this finding remained significant after adjusting for select covariates (HR: 1.50; 95% CI: 1.03-2.18) (Supplemental Table 5) but not when TAPSE/PASP was treated as a continuous variable (Supplemental Table 6).

DISCUSSION

The PARTNER 3 low-risk trial recently reported no significant difference in the composite primary endpoint at 5 years between TAVR and surgery.[7] In this report of the echocardiographic findings, we present the evolution of cardiac chamber geometry and function and determine associations with 30-day and 5-year clinical outcomes. The key findings were: 1) transprosthetic gradients, AVAs, regression of LV hypertrophy, and evolution of LV systolic function were similar in TAVR and surgery patients, although mild to severe PVR was higher after TAVR; 2) there was no association between mild to severe PVR or moderate to severe PPM and clinical outcomes after TAVR or surgery; 3) surgery was associated with significantly worse RV function (TAPSE), larger RV dimensions, and greater severity of TR compared to TAVR; 4) ventricular-arterial hemodynamics characterized by Z_{va} and RV-PA coupling favored TAVR vs surgery over time; and 5) high Z_{va} and RV-PA uncoupling at 30 days were associated with adverse clinical outcomes for the combined cohort.

TAVR is an effective treatment option for patients with severe, symptomatic AS,[15,16] and current guidelines recommend TAVR for those aged ≥65 years after

shared decision-making to balance expected patient longevity and valve durability.[15] TAVR outcomes and valve durability to 5 years and beyond have been shown across risk categories.[1-4,7,17-21] Deciding between surgery and TAVR may require more detailed evaluation of the relative benefits for each therapy. The current analysis provides a comprehensive evaluation of the echocardiographic results of PARTNER 3, showing a similar and sustained improvement in mean gradient, AVA, and Doppler velocity index. The approximately 1-mm Hg difference in mean gradients, higher in the TAVR cohort, did not translate to a difference in the calculated AVA. This can be explained by the larger LVOT diameter (with no difference in LVOT velocity-time integral) with TAVR, a finding in other trials thought to be related to the absence of a sewing ring. A 5-year analysis of the PARTNER 2 S3i (SAPIEN Intermediate-risk) Registry and the surgical arm of the PARTNER 2A trial reported not only smaller LVOT diameters post surgery, but a significantly smaller valve area compared to post TAVR.[22] The absence of a difference in AVA in the current study may be related to improvements in surgical technique and the greater number of 25-29 mm surgical valves implanted: 43.2% in PARTNER 3 compared to 20% in the PARTNER 2A trial.

LV forward flow was significantly greater in TAVR patients, with SVi diverging at 1 month following AVR and remaining significantly different throughout follow-up. This may be explained in part by better RV function and less tricuspid regurgitation, favoring TAVR. Although more PVR was observed in the TAVR group compared to surgery, there was no significant association with outcomes, and moderate PVR was only seen in 4 TAVR patients.

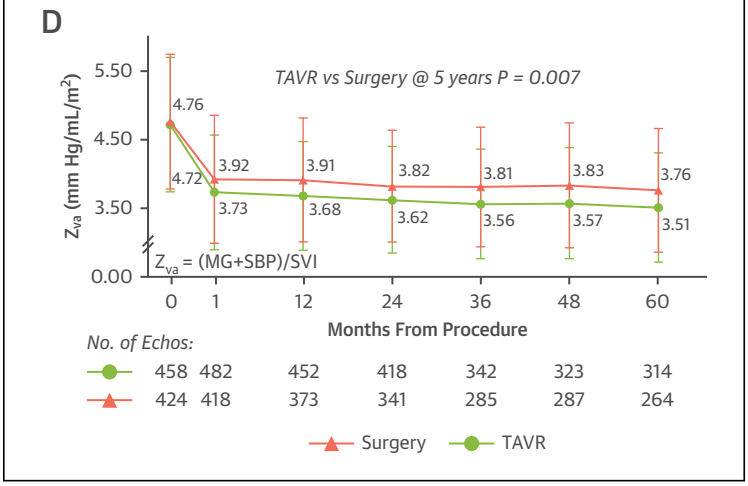
PPM and residual postimplant mean gradients ≥20 mm Hg were not associated with adverse outcomes in the current study. This finding is supported by the recent analysis of the Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapy registry comparing 20-mm to ≥23-mm balloon-expandable valves, which showed that lower gradients (<10 mm Hg) were associated with lower flow, lower LV ejection fraction, and worse clinical outcomes compared to intermediate gradients (10-30 mm Hg) or gradients >30 mm Hg, indicating that the clinical impact of gradients is nonlinear and highly dependent on cardiac function and LV forward flow.[23]

With regard to left heart remodeling and function, LV mass regression and LV ejection fraction were similar for TAVR and surgery. Notably, whereas LV ejection fraction remained in the normal range at 5 years, both cohorts exhibited a nonsignificant decline, which may be more reflective of LV mass regression and changes in LV geometry than structural changes in LV function. Prior studies have suggested that higher Z_{va} post-TAVR is associated with worse LV function,[24] less LV mass regression,[25] and worse quality of life,[26] but not with mortality.[27] In this study, a higher Z_{va} was only associated with increased risk of rehospitalization but not with all-cause mortality or stroke.

Z_{va} provides an estimate of the global LV hemodynamic load that results from the summation of the valvular and vascular loads indexed to the forward flow, reflecting the hemodynamic burden and thus the energy cost of blood ejected by the heart. Although subgroup analysis is only hypothesis-generating, Z_{va} was higher in the surgical cohort compared to TAVR despite slightly lower blood pressure and mean transvalvular gradients, in the setting of lower SVi. Both LV ejection fraction and estimates of diastolic function (E/e' ratio, LA volume index, and tricuspid regurgitation velocities) were not different between the TAVR and surgical AVR cohorts. Thus, in the absence of obvious differences in left heart/valve function, differences in right heart/valve function likely play a large role in the lower SVi in the surgical patients. Postsurgical loss of RV function (ie, TAPSE and RV-PA coupling), greater incidence of significant tricuspid regurgitation, and adverse RV remodeling likely contribute to lower SVi for the surgical cohort.

The lower SVi in the surgical cohort may also be affected by procedural and clinical factors. Approximately 26% of surgical patients had concomitant procedures (eg, coronary artery bypass graft, root

FIGURE 3 Continued



CENTRAL ILLUSTRATION Key Echocardiographic Outcomes of the PARTNER 3 Low-Risk Trial at 5 Years

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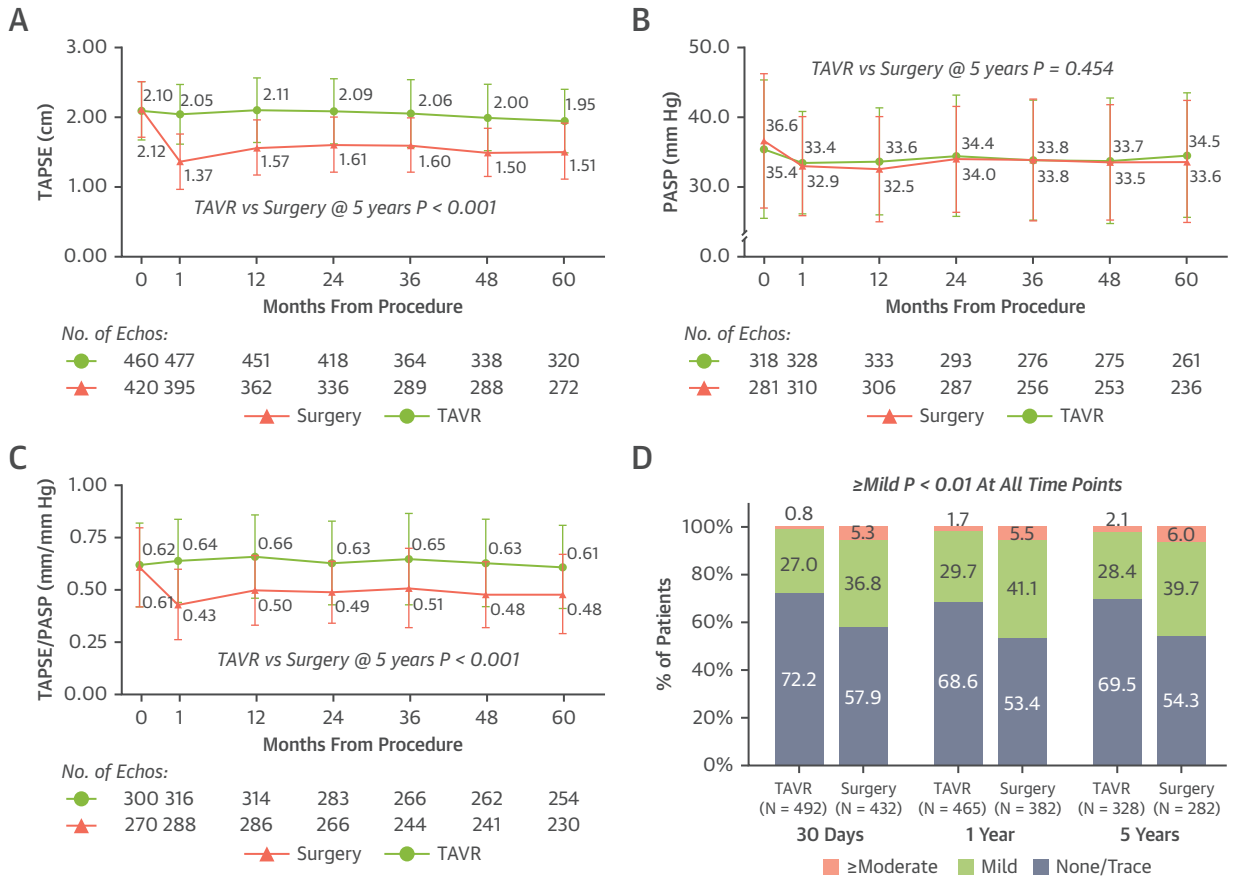
Valve hemodynamics and left- and right-heart function in low-risk patients with severe aortic stenosis through 5 years are described. Key echocardiographic parameters at 30 days and their association with 5-year clinical outcomes (composite of all-cause death, stroke, and rehospitalization related to the valve, procedure, or heart failure) are also provided. AVA = aortic valve area; LV = left ventricular; MG = mean gradient; PARTNER 3 = Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis; PPM = patient-prosthesis mismatch; PVR = paravalvular regurgitation; RV-PA = right ventricular-to-pulmonary artery; SBP = systolic blood pressure; SVi = stroke volume index; TAPSE/PASP = tricuspid annular plane systolic excursion divided by pulmonary arterial systolic pressure; TAVR = transcatheter aortic valve replacement; T/P = TAPSE/PASP; Z_{va} = valvulo-arterial impedance.

enlargement), and there was a higher incidence of new-onset atrial fibrillation in surgery vs TAVR (42.4% vs 13.7%, respectively[7]), which is known to influence the SVi. Eleid et al[28] indeed reported that atrial fibrillation is the main determinant of low-flow state in patients with native AS. Hence, we believe the main factors underlying the lower SVi and, thus, lower Z_{va} in surgery vs TAVR are the higher incidence of atrial fibrillation, worse RV systolic function, and more prevalent tricuspid regurgitation in surgery.

A low 30-day TAPSE/PASP (using a cutoff of 0.50 mm/mm Hg) was significantly associated with the composite primary outcome, with an approximately 3-fold increase in cardiovascular death and 2-fold increase in stroke. The association with cardiovascular death suggests that an RV-PA coupling ratio characterizes the physiologic burden to the right heart in a way that TAPSE or PASP alone cannot. Recent studies have shown that the echo-measured TAPSE/PASP was a strong predictor of the invasively measured ratio of end-systolic elastance and effective arterial elastance in patients with pulmonary hypertension.[29] RV-PA coupling assessed by echocardiographic TAPSE/PASP ratio appears to be an independent outcome predictor for heart failure patients,[30] and multiple studies have shown an association between TAPSE/PASP and outcomes for AS patients.[31] Baseline uncoupling measured by TAPSE/PASP predicts outcomes following transcatheter or surgical valve replacement[12] and the presence of either persistent or new-onset RV-PA uncoupling following TAVR has been associated with an increased mortality risk.[31] Our results contribute to the published reports suggesting that RV-PA coupling using TAPSE/PASP may be an important measure of outcomes in low-risk patients undergoing intervention.

FIGURE 4 Right Ventricular Function

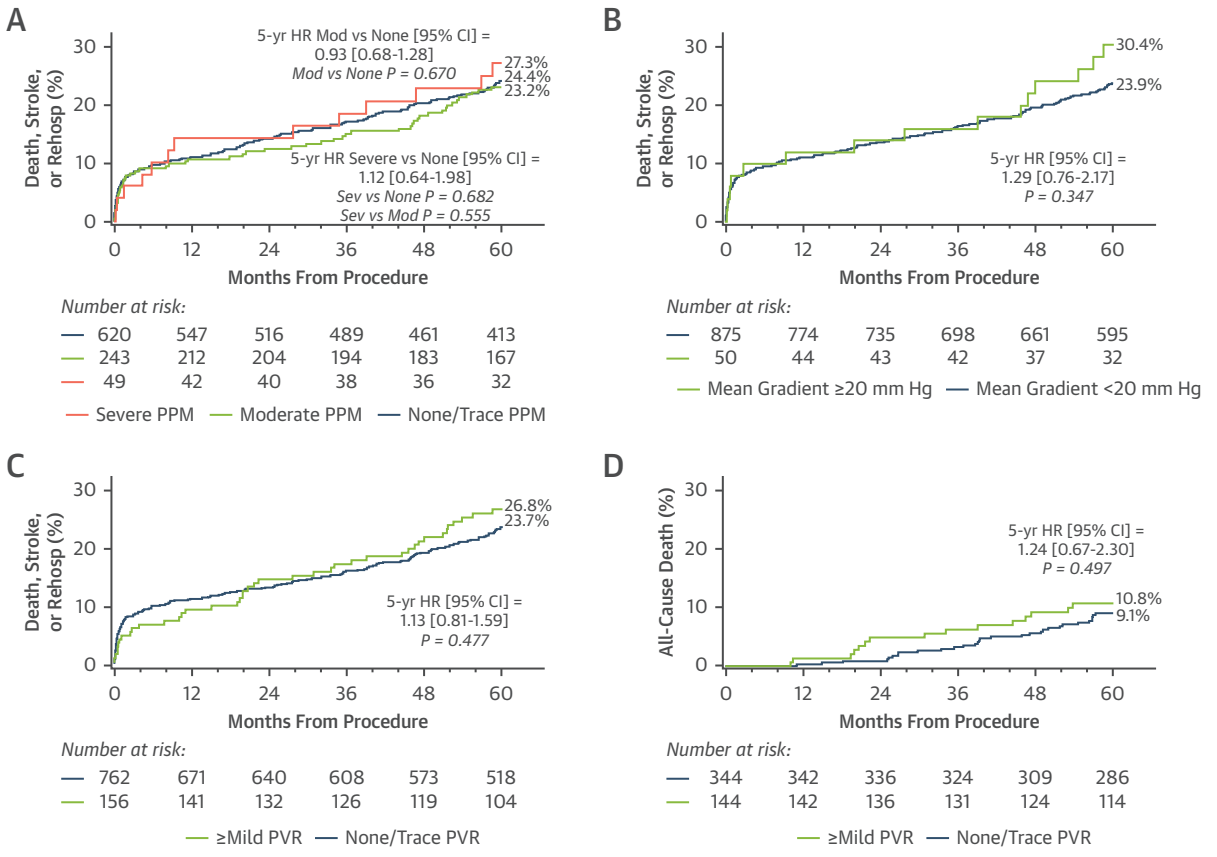


Right-heart parameters from baseline to 5 years, assessed by TAPSE (A); PASP (B); TAPSE divided by PASP (TAPSE/PASP) (C); and tricuspid regurgitation (D). PASP = pulmonary arterial systolic pressure; TAPSE = tricuspid annular plane systolic excursion; other abbreviation as in Figure 1.

Although RV-PA coupling was not significantly associated with stroke when analyzed as a continuous variable, the higher rates of stroke at 5 years in patients with TAPSE/PASP <0.50 mm/mm Hg may reflect a patient population with baseline comorbidities that inherently increase their stroke risk, because baseline RV dysfunction or high PA pressures both indicate a more advanced "stage" of AS.[32] For the surgical cohort, the role of atrial fibrillation or concomitant procedures may increase the risk of stroke in patients experiencing a decrease in RV-PA coupling. There is a possibility that compensatory mechanisms of RV function following open pericardiectomy may have influenced overall RV function, thus reducing the impact of TAPSE as a measure of RV function in the surgical cohort. In addition, the effect of significant tricuspid regurgitation, which was more frequent in the surgical cohort, may result in an increase in TAPSE that consequently dilutes the impact of longitudinal function measures.

Given these findings, it is possible that a high Z_{va} or low TAPSE/PASP seen at 30 days warrants closer follow-up and possible improvement in medical management. Better blood pressure control or aggressive management of comorbidities could potentially improve Z_{va}, but this requires further study. Similarly, whether management of RV congestion or improvement in pre- or postcapillary pulmonary hypertension can change the risk of a low 30-day TAPSE/PASP is currently unknown; although, an improvement in RV-PA coupling following TAVR has been associated with improved outcomes.[31] Whether measures of LV- or RV-arterial interaction may be novel endpoints or define longer-term outcomes in future trials deserves continued study. Follow-up is planned for 10 years in the PARTNER 3 trial.

FIGURE 5 Clinical Endpoints for TAVR and Surgery by 30-Day Echocardiographic Parameters



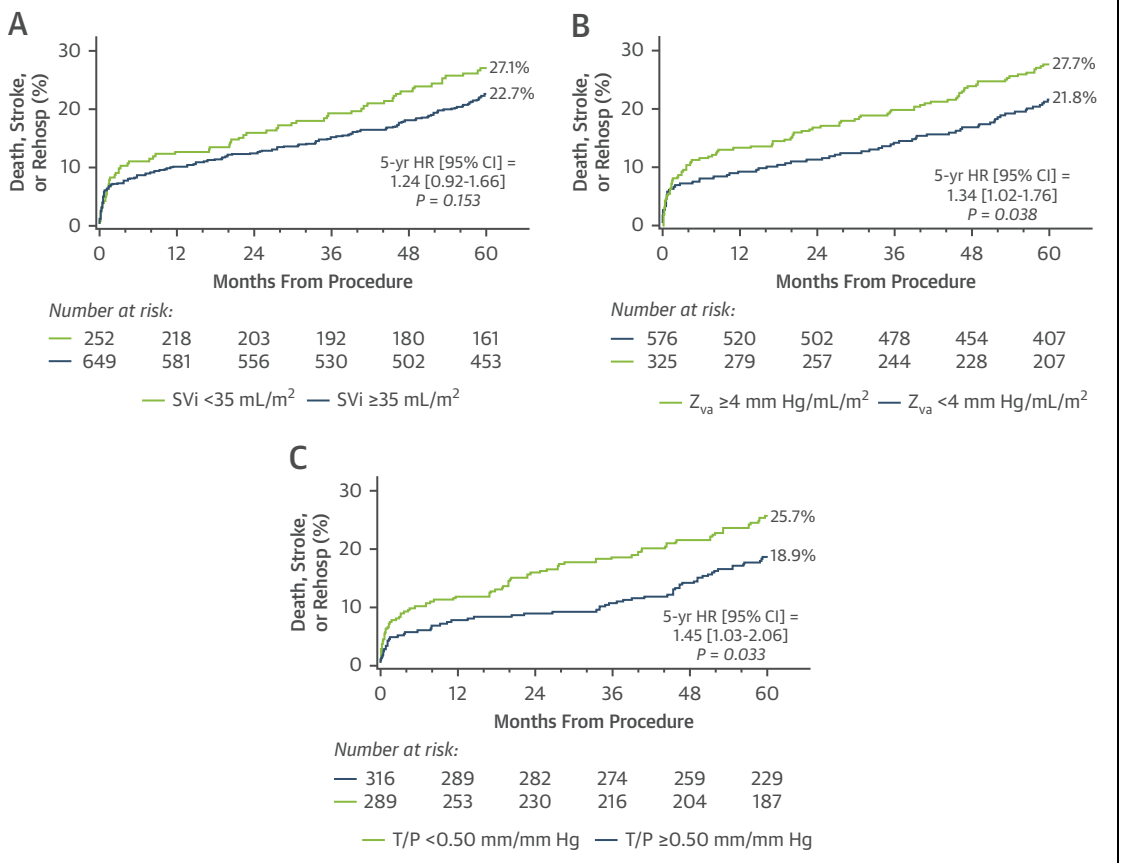
Time-to-event curves for the composite primary endpoint of all-cause mortality, stroke, or rehospitalization (related to the procedure, valve, or heart failure) to 5 years following TAVR or surgery according to the following echo parameters measured at 30 days: PPM (A); high residual mean gradient (mean gradient ≥20 mm Hg) (B); and paravalvular aortic regurgitation (C). (D) All-cause mortality by paravalvular regurgitation (PVR) for TAVR only. PPM = patient-prosthesis mismatch; Rehosp = Rehospitalization; other abbreviation as in Figure 1.

STUDY LIMITATIONS. The main limitations of this trial have been discussed previously.[5,7,33] Importantly, these results may not be generalizable given the well-defined trial population, which excluded those with poor transfemoral access, bicuspid aortic valves, or other anatomic or clinical factors that increased the risk of complications associated with either TAVR or surgery. Additionally, the results may not apply to other transcatheter valve systems. Whereas the percentage of missing data was low for most echocardiographic variables, another limitation is that for a few variables (eg, TAPSE/PASP), the rate of missing data was higher, likely due to unevaluable imaging. Adjudication of outcomes and echocardiographic assessments of valve function could not be blinded, which may have introduced bias, particularly in the measurement of LVOT diameters (and thus the quantification of SVi). Finally, findings using site-reported instead of core lab-adjudicated analyses may differ.

CONCLUSIONS

In low-risk patients with severe AS, compared with surgery, TAVR was associated with similar and stable bioprosthetic valve hemodynamics through 5-year follow-up. TAVR was also associated with lower Z_{va} and higher RV-PA coupling, indicating improved hemodynamic burden on the LV and RV function, respectively. In both treatment groups, RV-PA uncoupling and high Z_{va} at 30 days were associated with an increased risk of the composite endpoint at 5-years, whereas there was no association between any degree of aortic

FIGURE 6 Composite Primary Endpoint for TAVR and Surgery by 30-Day Echocardiographic Parameters



Time-to-event curves for the composite primary endpoint of all-cause mortality, stroke, or rehospitalization (related to the procedure, valve, or heart failure) to 5 years following aortic valve replacement according to the following echo parameters measured at 30 days: low SVi (<35 mL/m^2) (A); increased Z_{va} (≥4 mm Hg/mL/m^2) (B); and right ventricular-to-pulmonary artery coupling (TAPSE/PASP [T/P] ≤0.50 mm/mm Hg) (C). Abbreviations as in Figures 1, 3, and 5.

TABLE 3 30-Day Parameters That Had a Significant Association With Clinical Outcomes at 5 Years for TAVR + Surgery

	Kaplan-Meier Estimate at 5 Years % (SE)		HR (95% CI)	*P* Value
Valvulo-arterial impedance (Z_{va})	Z_{va} ≥4 mm Hg/mL/m^2	Z_{va} <4 mm Hg/mL/m^2		
All-cause death	9.9 (1.72)	7.7 (1.14)	1.31 (0.82-2.09)	0.260
CV death	5.7 (1.34)	4.1 (0.85)	1.41 (0.75-2.66)	0.281
Stroke	5.5 (1.30)	6.1 (1.03)	0.93 (0.52-1.67)	0.814
Rehospitalization[a]	19.9 (2.28)	12.5 (1.41)	1.67 (1.19-2.36)	0.003
RV-PA coupling	TAPSE/PASP <0.50 mm/mm Hg	TAPSE/PASP ≥0.50 mm/mm Hg		
All-cause death	9.0 (1.76)	5.6 (1.33)	1.67 (0.90-3.11)	0.101
CV death	6.8 (1.56)	2.4 (0.88)	3.03 (1.26-7.25)	0.009
Stroke	7.8 (1.65)	3.7 (1.08)	2.24 (1.08-4.64)	0.026
Rehospitalization[a]	15.7 (2.21)	11.7 (1.84)	1.38 (0.88-2.15)	0.155

[a]Rehospitalization defined as related to the valve, procedure, or heart failure.
CV = cardiovascular; other abbreviations as in Tables 1 and 2.

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JUNE 2025:625–640

regurgitation or PPM at 30-day and 5-year clinical outcomes.

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ADDRESS FOR CORRESPONDENCE: Dr Rebecca T. Hahn, Columbia University Medical Center, New York-Presbyterian Hospital, 177 Fort Washington Avenue, New York, New York 10032, USA. E-mail: rth2@columbia.edu. X handle: @hahn_rt.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with severe AS and low surgical risk, TAVR is associated with a higher percentage of mild PVR compared to surgery and no difference in PPM; neither parameter is associated with adverse clinical outcomes at 5 years. Transprosthetic gradients, AVAs, regression of LV hypertrophy, and evolution of LV systolic function are similar in TAVR vs surgery through 5 years. Ventricular-arterial hemodynamics, characterized by Z_{va} for the left heart and RV-PA coupling for the right heart, favors TAVR vs surgery. High Z_{va} and worse RV-PA coupling are associated with 5-year clinical outcomes.

TRANSLATIONAL OUTLOOK 1: In the low surgical risk population with severe AS, TAVR achieves similar valve hemodynamic performance and durability at 5 years compared to surgery.

TRANSLATIONAL OUTLOOK 2: Longer-term echocardiographic follow-up is needed to confirm stable and comparable valve hemodynamic function in TAVR vs surgery and the impact of valvular-arterial interaction and RV-PA coupling beyond 5 years.

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KEY WORDS aortic stenosis, echocardiography, hemodynamics, TAVR, transcatheter aortic valve replacement

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