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Outcomes of SAPIEN 3 Transcatheter Aortic Valve Replacement Compared With Surgical Valve Replacement in Intermediate-Risk Patients

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ABSTRACT

BACKGROUND Previous studies demonstrated transcatheter aortic valve replacement (TAVR) with an earlier generation balloon-expandable valve to be noninferior to surgical aortic valve replacement (SAVR) for death and disabling stroke in intermediate-risk patients with symptomatic, severe aortic stenosis at 5 years. However, limited long-term data are available with the more contemporary SAPIEN 3 (S3) bioprosthesis.

OBJECTIVES The aim of this study was to compare 5-year risk-adjusted outcomes in intermediate-risk patients undergoing S3 TAVR vs SAVR.

METHODS Propensity score matching was performed to account for baseline differences in intermediate-risk patients undergoing S3 TAVR in the PARTNER 2 (Placement of Aortic Transcatheter Valves) S3 single-arm study and SAVR in the PARTNER 2A randomized clinical trial. The primary composite endpoint consisted of 5-year all-cause death and disabling stroke.

RESULTS A total of 783 matched pairs of intermediate-risk patients with severe aortic stenosis were studied. There were no differences in the primary endpoint between S3 TAVR and SAVR at 5 years (40.2% vs 42.7%; HR: 0.87; 95% CI: 0.74-1.03; $P = 0.10$). The incidence of mild or greater paravalvular regurgitation was more common after S3 TAVR. There were no differences in structural valve deterioration–related stage 2 and 3 hemodynamic valve deterioration or bioprosthetic valve failure.

CONCLUSIONS In this propensity-matched analysis of intermediate-risk patients, 5-year rates of death and disabling stroke were similar between S3 TAVR and SAVR. Rates of structural valve deterioration–related hemodynamic valve deterioration were similar, but paravalvular regurgitation was more common after S3 TAVR. Longer-term follow-up is needed to further evaluate differences in late adverse clinical events and bioprosthetic valve durability. (PII S3i [PARTNER II Trial: Placement of Aortic Transcatheter Valves II – S3 Intermediate], NCT03222128; PII A (PARTNER II Trial: Placement of Aortic Transcatheter Valves II – XT Intermediate and High Risk], NCT01314313) (J Am Coll Cardiol 2023;82:109–123)

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

BVF = bioprosthetic valve failure

HALT = hypoattenuated leaflet thickening

HVD = hemodynamic valve deterioration

PVR = paravalvular regurgitation

S3 = SAPIEN 3

SAVR = surgical aortic valve replacement

SVD = structural valve deterioration

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

Over the past decade, transcatheter aortic valve replacement (TAVR) has evolved to become the preferred therapy for symptomatic severe aortic stenosis (AS). Multiple studies have demonstrated TAVR to be either noninferior or superior to surgical aortic valve replacement (SAVR) across surgical risk profiles.[1-8] Evolution of procedural technique and increased operator experience as well as advances in transcatheter heart valve (THV) design have contributed to improved clinical outcomes.[9,10]

Earlier experience with TAVR demonstrated higher rates of structural valve deterioration (SVD) with the prior generation of balloon-expandable THV, the SAPIEN XT valve (Edwards Lifesciences), compared with SAVR.[11] The SAPIEN 3 (S3) (Edwards Lifesciences) system is a later generation of the original balloon-expandable THV system and was first studied in the PARTNER 2 (Placement of Aortic Transcatheter Valves) S3 high-risk and PARTNER 2 S3 intermediate-risk (P2S3i) single-arm studies.[12,13] Using a propensity score-stratified analysis comparing P2S3i with surgical patients from the PARTNER 2A (P2A) study, the P2S3i study was the first to demonstrate the superiority of TAVR over SAVR at 1 year.[12] Subsequently, the randomized PARTNER 3 trial also demonstrated lower rates of death, stroke, and rehospitalization with transfemoral S3 TAVR compared with SAVR at 1-year follow-up in patients with low surgical risk.[1,2]

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Despite these encouraging early data and widespread adoption of the S3 TAVR platform, long-term clinical and echocardiographic follow-up comparing S3 TAVR with SAVR remains limited. We therefore sought to evaluate and compare 5-year outcomes in intermediate-risk patients from the P2S3i study and the surgical arm of the P2A randomized clinical trial using a propensity-matched analysis.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The present analysis includes TAVR patients from the P2S3i study and SAVR patients from the surgical arm of the P2A randomized clinical trial. The study designs and primary trial findings have been described previously.[4,6,12,13] The P2S3i single-arm study and the P2A randomized trial are registered at ClinicalTrials.gov (P2S3i: NCT03222128; PARTNER 2: NCT01314313), and both studies enrolled patients with symptomatic, severe AS at intermediate risk for operative mortality.

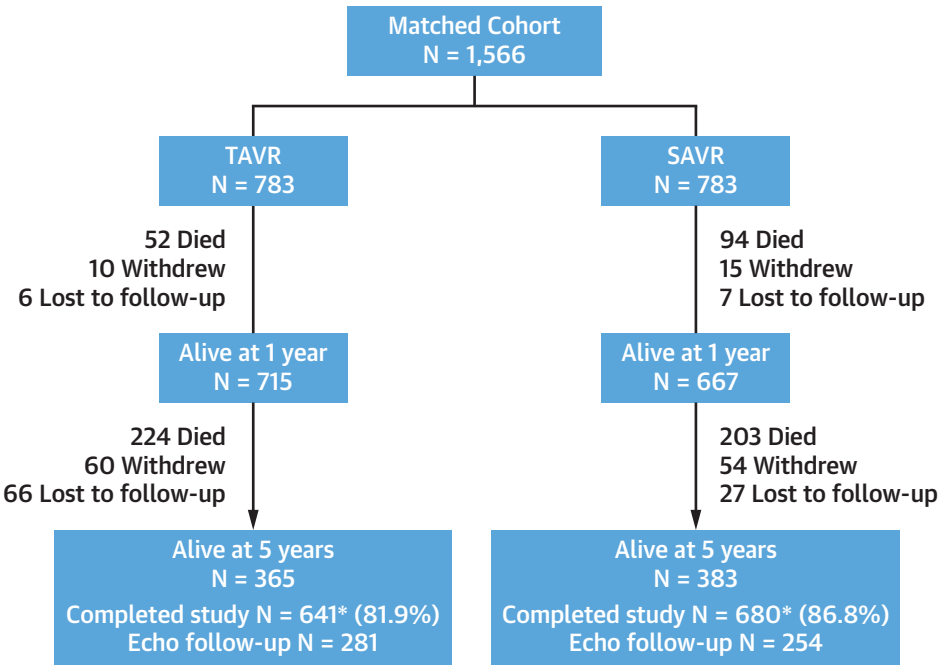
Inclusion and exclusion criteria were similar for the P2S3i study and P2A trial. Key exclusion criteria included a congenitally bicuspid aortic valve, severe aortic regurgitation, left ventricular ejection fraction <20%, untreated severe coronary artery disease, severe renal insufficiency, and estimated life expectancy <2 years. Patients with noncomplex coronary disease requiring revascularization could be enrolled if a treatment plan for the coronary disease (medical therapy or revascularization) was agreed on before enrollment. Both trials were approved by the Institutional Review Board of each participating site, and written informed consent was provided by all patients.

PROCEDURES. Preprocedural TAVR valve sizing was determined using multidetector computed tomography or 3-dimensional transesophageal echocardiography when multidetector computed tomography was unavailable. Multidetector computed tomographic data for the P2S3i substudy were analyzed at a central core laboratory, as previously described.[14,15] Postoperative dual antiplatelet therapy with aspirin and clopidogrel was recommended for at least 1 month, and warfarin was recommended for patients with atrial fibrillation, as indicated.

The studies were designed by the sponsor (Edwards Lifesciences) and the physician executive committee. Executive committee membership was the same for both study cohorts, and the committee attests to the integrity of the data and to protocol adherence. The co-principal investigators and other members of the executive committee had access to the data after the database was locked, in preparation for the present report. An independent clinical events committee adjudicated clinical events through 5 years, and independent echocardiography core laboratories analyzed echocardiograms. The same methods were used for both cohorts. Clinical assessments were performed at baseline, 30 days, 1 year, and yearly up to 5 years. All patients underwent systematic neurologic assessments postprocedure and during follow-up as indicated.

CLINICAL AND ECHOCARDIOGRAPHIC ENDPOINTS. Prespecified endpoints for the P2S3i and P2A cohorts have been reported previously.[4,6,12,13] The primary endpoint for the present analysis was the composite of death or disabling stroke. Key secondary endpoints included the components of the primary composite endpoint, cardiac death, all strokes, nondisabling strokes, and rehospitalization for symptoms of AS or procedure-related complications. Other clinical

FIGURE 1 Study Flow Diagram



Flow diagram presenting propensity-matched patient population of patients who underwent SAPIEN 3 transcatheter aortic valve replacement (TAVR) or surgery with follow-up data at 1 and 5 years. *Includes patients with 5-year clinical follow-up visit and patients known to be dead. SAVR = surgical aortic valve replacement.

endpoints assessed included incidence of aortic valve reintervention, valve thrombosis, new permanent pacemaker implantation, and endocarditis. Health status assessment was performed using the Kansas City Cardiomyopathy Questionnaire overall summary score.[16] Echocardiographic assessments included aortic valve area, aortic valve gradients, and paravalvular regurgitation (PVR).

As has been previously described,[11] potential hemodynamic valve deterioration (HVD) and bioprosthetic valve failure (BVF) related to SVD were assessed on the basis of changes in echocardiographic hemodynamic valve function parameters from 30-day (or discharge, if 30-day data were not available) echocardiograms and subsequent follow-up echocardiograms. Potential cases were adjudicated by a group of echocardiography experts for presence, stage, and etiology of valve deterioration. Definitions according to the Valve Academic Research Consortium 3 definitions were used[17]; these are summarized in Supplemental Table 1.

PATIENT POPULATION AND STATISTICAL ANALYSIS. The present analysis focuses on outcomes in patients who completed successful TAVR in the P2S3i study or surgical valve replacement procedures from the intention-to-treat cohort of the P2A randomized clinical trial. A propensity-matched analysis was used to account for baseline differences in characteristics between the patients who underwent TAVR in the P2S3i study and SAVR in the P2A randomized clinical trial. A logistic regression model was fitted including 25 baseline covariates: age, sex, body mass index, diabetes mellitus, hypertension, coronary artery disease, prior myocardial infarction, prior coronary artery bypass graft surgery, prior percutaneous coronary intervention, NYHA functional class, angina class, prior stroke, peripheral vascular disease, previous or current smoker, chronic obstructive pulmonary disease, renal insufficiency (ie, creatinine ≥2 mg/dL), porcelain aorta, cardiomyopathy, carotid disease, pre-existing permanent pacemaker requirement, prior aortic valvuloplasty, annular diameter, baseline left ventricular ejection fraction, moderate to severe mitral regurgitation, and baseline Society of Thoracic Surgeons score. Aortic valve replacement treatment modality (S3 TAVR vs SAVR) was entered into the model as the dependent variable. Missing baseline data were imputed using the Markov-chain

TABLE 1 Baseline Characteristics in the Unmatched and Propensity-Matched Patient Cohorts

	All Patients			Propensity-Matched Patients		
	TAVR (n = 1,078)	SAVR (n =1,021)	*P* Value	TAVR (n = 783)	SAVR (n =783)	*P* Value
Age, y	81.9 ± 6.60 (1,078)	81.7 ± 6.71 (1,021)	0.35	81.7 ± 6.71 (783)	81.5 ± 6.77 (783)	0.60
Male	61.8 (666/1,078)	54.8 (560/1,021)	0.001	57.9 (453/783)	57.2 (448/783)	0.80
Body mass index, kg/m^2	28.7 ± 6.05 (1,078)	28.3 ± 6.21 (1,021)	0.17	28.6 ± 6.11 (783)	28.6 ± 6.08 (783)	0.84
STS score, %	5.3 ± 1.29 (1,078)	5.8 ± 1.87 (1,020)	<0.0001	5.5 ± 1.30 (783)	5.5 ± 1.54 (782)	0.74
NYHA functional class III/IV	72.5 (781/1,077)	76.1 (776/1,020)	0.06	74.5 (583/783)	74.6 (584/783)	0.95
Angina class ≥III	6.6 (71/1,073)	6.4 (65/1,017)	0.86	7.8 (61/781)	6.6 (51/779)	0.38
Previous or current smoker	50.3 (542/1,078)	48.7 (497/1,021)	0.48	48.8 (382/783)	49.3 (386/783)	0.88
Hypertension	92.1 (993/1,078)	94.8 (968/1,021)	0.01	93.5 (732/783)	93.9 (735/783)	0.84
Diabetes mellitus	34.0 (367/1,078)	34.2 (349/1,021)	0.96	35.3 (276/783)	34.6 (271/783)	0.83
Coronary artery disease	69.7 (751/1,078)	66.5 (679/1,021)	0.12	68.6 (537/783)	67.6 (529/783)	0.66
Prior myocardial infarction	16.0 (172/1,078)	17.5 (179/1,021)	0.33	16.1 (126/783)	16.1 (126/783)	1.00
Prior CABG	27.9 (301/1,078)	25.6 (261/1,021)	0.22	27.01 (212/783)	25.9 (203/783)	0.61
Prior PCI	32.0 (345/1,078)	27.6 (282/1,021)	0.03	28.7 (225/783)	27.7 (217/783)	0.65
Prior aortic valvuloplasty	5.1 (55/1,078)	4.9 (50/1,021)	0.83	5.2 (41/783)	5.1 (40/783)	0.91
Cerebrovascular disease	9.0 (97/1,078)	10.2 (104/1,021)	0.36	9.8 (77/783)	9.3 (73/783)	0.73
Peripheral vascular disease	28.2 (304/1,078)	32.9 (336/1,021)	0.02	29.9 (234/783)	29.5 (231/783)	0.87
Carotid disease	23.0 (248/1,078)	20.1 (205/1,021)	0.11	21.2 (166/783)	20.3 (159/783)	0.71
Renal insufficiency	7.6 (82/1,078)	5.2 (53//1,021)	0.03	6.0 (47/783)	6.0 (47/783)	1.00
Cardiomyopathy	8.4 (90/1,078)	11.0 (112/1,021)	0.046	9.6 (75/783)	9.8 (77/783)	0.93
COPD						
Any	29.9 (322/1,076)	30.2 (306/1,014)	0.90	28.7 (224/781)	29.0 (225/777)	0.90
Oxygen dependent	5.0 (54/1,076)	3.2 (32/1,007)	0.03	5.0 (39/778)	2.5 (19/770)	0.008
Atrial fibrillation	36.1 (389/1,078)	35.2 (359/1,021)	0.66	35.1 (275/783)	34.0 (266/783)	0.63
Permanent pacemaker	13.3 (143/1,078)	12.0 (123/1,021)	0.40	11.5 (90/783)	12.4 (97/783)	0.59
Frailty assessment						
15-ft walk time >7 s	41.4 (435/1,051)	46.4 (418/901)	0.03	41.9 (319/762)	43.3 (307/709)	0.58
Albumin <3.5 g/dL	13.1 (138/1,057)	14.7 (140/951)	0.28	13.2 (102/770)	13.7 (105/768)	0.81
Aortic valve area, cm^2	0.70 ± 0.17 (1,016)	0.69 ± 0.20 (861)	0.45	0.69 ± 0.17 (744)	0.71 ± 0.21 (722)	0.03
Annular diameter, mm	21.9 ± 2.22 (1,077)	21.5 ± 2.05 (1,018)	<0.0001	21.7 ± 2.21 (783)	21.7 ± 2.09 (781)	0.69
Mean gradient, mm Hg	46.1 ± 12.63 (1,049)	44.7 ± 12.55 (916)	0.01	45.9 ± 12.85 (769)	44.7 ± 12.42 (767)	0.06
Left ventricular ejection fraction, %	58.5 ± 13.36 (925)	55.4 ± 11.75 (629)	<0.0001	57.3 ± 14.00 (682)	57.0 ± 10.66 (512)	0.66
Left ventricular mass index, g/m^2	118.1 ± 33.96 (936)	120.6 ± 32.61 (830)	0.11	118.3 ± 34.55 (679)	119.3 ± 32.03 (690)	0.57
Moderate/severe MR	8.8 (92/1,042)	19.1 (171/894)	<0.0001	11.6 (88/757)	12.5 (88/706)	0.62
Porcelain aorta	0.1 (1/1,078)	0.1 (1/1,019)	1.00	0.0 (0/783)	0.0 (0/783)	–

Values are mean ± SD (n) or % (n/N).

CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; MR = mitral regurgitation; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

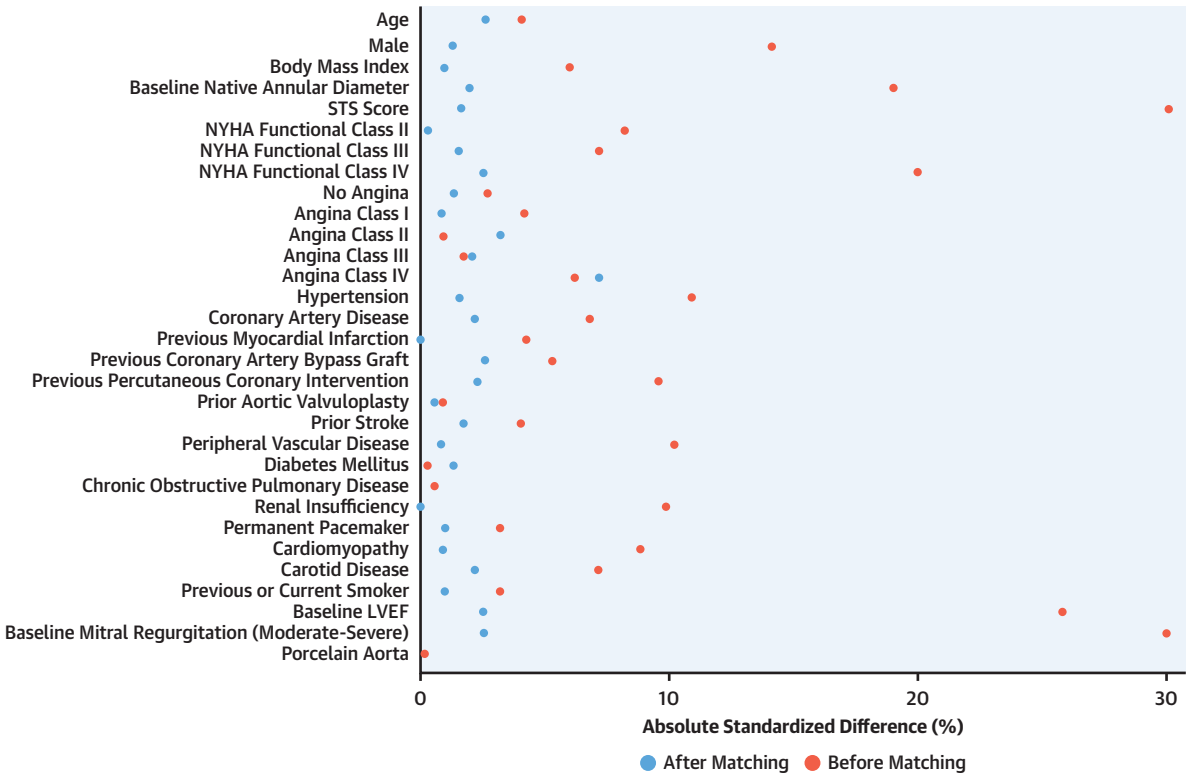
Monte Carlo method prior to modeling. On the basis of the propensity score, each P2S3i patient was matched to a P2A SAVR patient (1:1) to create 2 balanced cohorts, using a greedy matching strategy with caliper of width equal to 0.02 of the SD of the logit of the propensity score.

Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate, and continuous variables using Student's *t*-test. Kaplan-Meier estimates were calculated for adjudicated time-to-event data and compared using HRs and the log-rank test. Incidence rates were calculated for site-reported data. In addition, we performed a sensitivity analysis to assess the consistency of the results obtained using the present propensity-matching methodology with the results obtained using the original propensity-scoring methodology.[12] The methodologic details of this analysis are presented in the Supplemental Appendix. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS OF PROPENSITY-MATCHED COHORTS. A total of 1,078 patients underwent S3 TAVR and 1,021 patients underwent SAVR in the P2S3i TAVR study and P2A randomized clinical trial, respectively. Of these patients, 1,566 patients (n = 783 in each group) were included in the analytical cohort. Median follow-up duration for the matched cohort

FIGURE 2 Plot of Standardized Mean Differences



Absolute mean standardized differences presented as percentages before and after propensity matching. LVEF = left ventricular ejection fraction; STS = Society of Thoracic Surgeons.

was 4.70 years (IQR: 2.56-5.06 years). Follow-up data were available at 5 years for 641 patients with S3 TAVR (81.9%) and 680 patients with SAVR (86.8%) (**Figure 1**). Baseline patient characteristics of the unmatched and propensity-matched cohorts are presented in **Table 1**, and standardized mean differences are presented in **Figure 2**. The majority of patient baseline clinical characteristics were similar between the matched groups. An exception was a statistically significant difference in baseline aortic valve area (0.69 ± 0.17 cm^2 vs 0.71 ± 0.21 cm^2; $P = 0.03$) between the S3 TAVR and SAVR groups. Transfemoral TAVR was performed in 868 patients (87.6%) who underwent S3 TAVR in this cohort.

1-YEAR ADVERSE CLINICAL EVENTS. Adjudicated adverse clinical event rates at 1 year are presented in Supplemental Table 2. Rates of the composite endpoint of all-cause death or disabling stroke were significantly lower after S3 TAVR than after SAVR after 1-year follow-up (7.6% vs 15.4%; HR: 0.47; 95% CI: 0.34-0.64; $P < 0.0001$).

Site-reported outcomes for the propensity-matched cohort at 1 year are presented in Supplemental Table 3. At 1 year, rates of new atrial

TABLE 2 5-Year Adverse Clinical Event Rates in the Propensity-Matched Cohort

	TAVR (n = 783)	SAVR (n = 783)	HR (95% CI)	*P* Value
Death or disabling stroke	40.2 (285)	42.7 (310)	0.87 (0.74-1.03)	0.10
All-cause mortality	39.2 (276)	41.4 (297)	0.90 (0.76-1.06)	0.21
Cardiac death	26.4 (171)	27.6 (180)	0.92 (0.75-1.13)	0.44
Noncardiac death	17.1 (103)	19.0 (117)	0.85 (0.65-1.11)	0.23
Stroke	13.4 (87)	11.4 (77)	1.09 (0.80-1.48)	0.58
Disabling stroke	5.8 (37)	7.9 (54)	0.66 (0.43-1.00)	0.046
Nondisabling stroke	6.4 (41)	3.5 (24)	1.67 (1.01-2.76)	0.045
TIA	3.9 (26)	4.5 (28)	0.89 (0.52-1.51)	0.66
Rehospitalization	26.6 (171)	25.3 (173)	0.94 (0.76-1.16)	0.54
Death or rehospitalization	50.9 (365)	50.3 (370)	0.94 (0.81-1.09)	0.41
Death or stroke	44.8 (321)	44.3 (322)	0.97 (0.83-1.13)	0.66
Death, stroke, or rehospitalization	55.4 (401)	52.9 (392)	0.97 (0.85-1.12)	0.70

Values are Kaplan-Meier estimates presented as % (n) unless otherwise indicated.
TIA = transient ischemic attack; other abbreviations as in **Table 1**.

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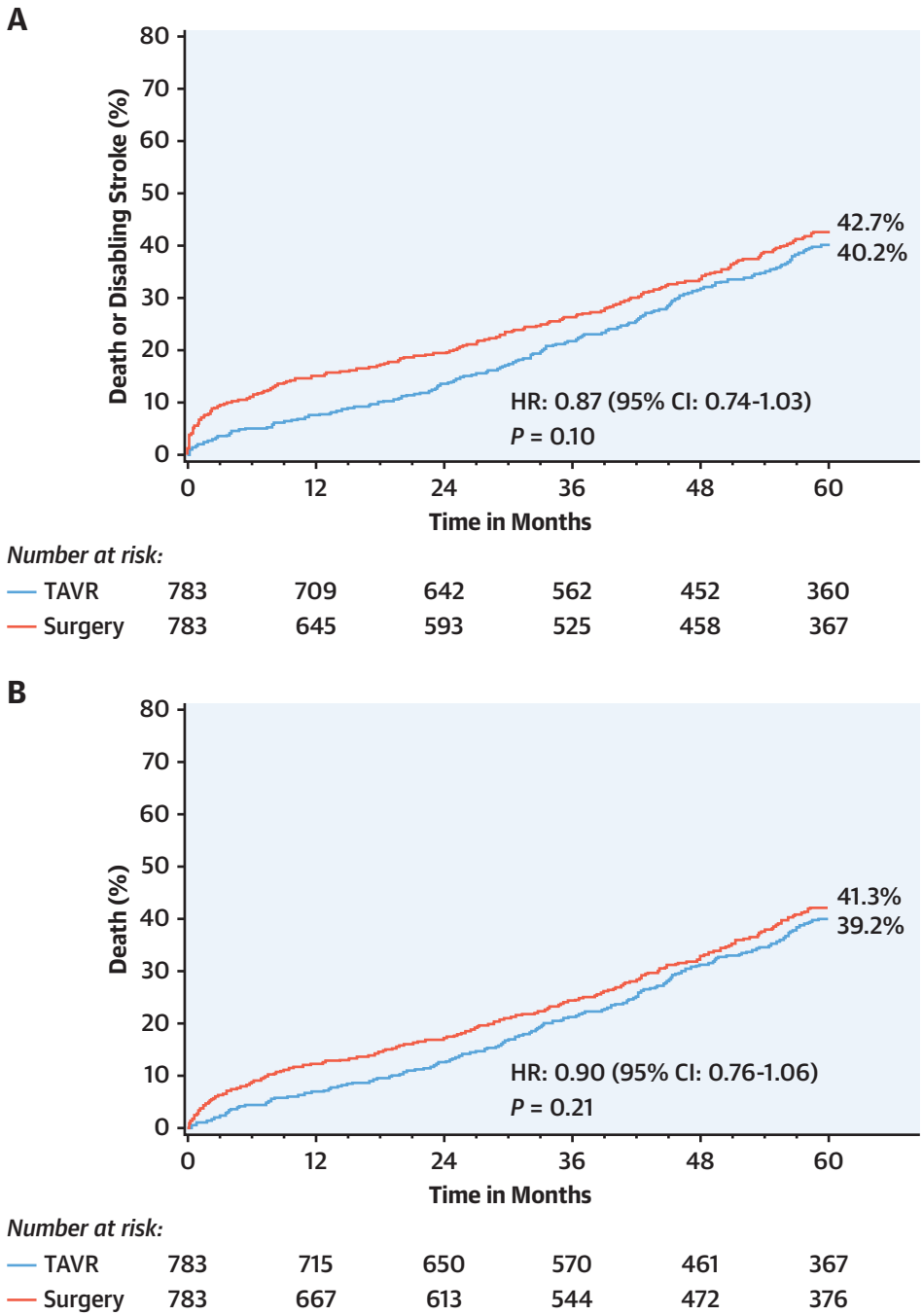
CENTRAL ILLUSTRATION **Time-to-Event Curves for the Primary Composite Endpoint by Treatment Strategy**



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5-year rates of the primary composite endpoint of death or disabling stroke **(A)** and components including death **(B)** and disabling stroke **(C)** by SAPIEN 3 transcatheter aortic valve replacement (TAVR) or surgery.

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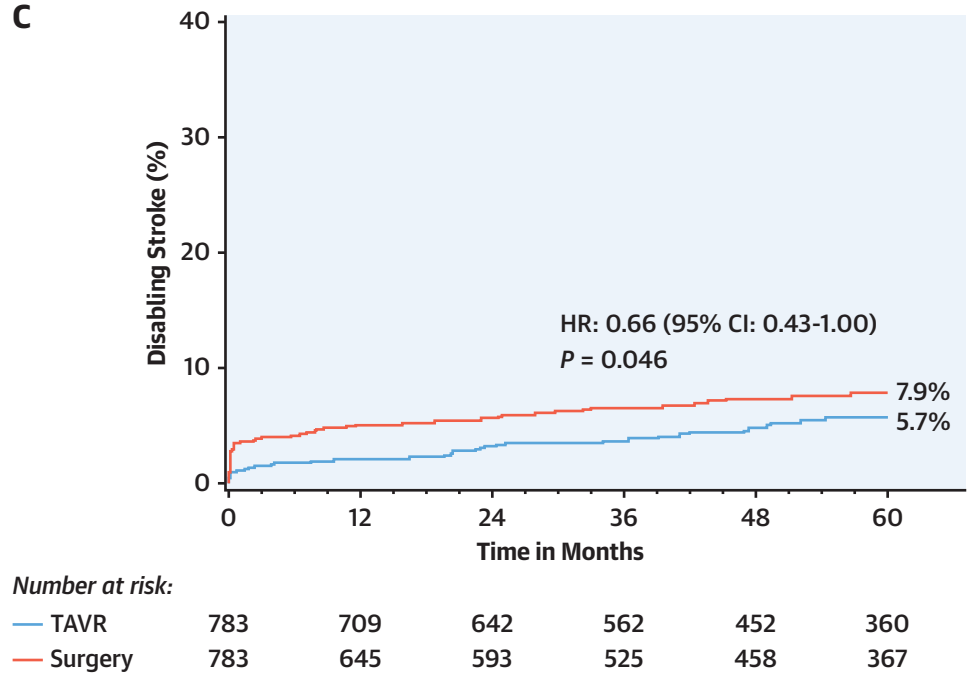
CENTRAL ILLUSTRATION Continued



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fibrillation were 6.1% following S3 TAVR and 30.1% following SAVR ($P < 0.0001$), with the majority occurring within 30 days of the procedure (>80% after S3 TAVR vs >98% after SAVR). One-year rates of new pacemakers were higher following S3 TAVR compared with SAVR (12.3% vs 8.9%, respectively; $P = 0.03$).

5-YEAR ADVERSE CLINICAL EVENTS. Rates of adjudicated adverse clinical events for the propensity-matched cohort at 5 years are presented in **Table 2**. Kaplan-Meier curves for the rates of the primary composite endpoint of death or disabling stroke and its components are presented in the **Central Illustration**. Rates of the primary composite endpoint of death or disabling stroke were not significantly different between S3 TAVR and SAVR in the propensity-matched cohort at 5-year follow-up (40.2% vs 42.7%; HR: 0.87; 95% CI: 0.74-1.03; $P = 0.10$). Rates of all-cause death were similar between groups at 5-year follow-up (39.2% vs 41.4%; HR: 0.90; 95% CI: 0.76-1.06; $P = 0.21$), while disabling stroke occurred less frequently after S3 TAVR than after SAVR (5.8% vs 7.9%; HR: 0.66; 95% CI: 0.43-1.00; $P = 0.0046$).

Kaplan-Meier curves for the rates of all stroke and nondisabling stroke are presented in **Figure 3**. Overall stroke rates were similar between groups at 5-year follow-up (13.4% vs 11.4%; HR: 1.09; 95% CI: 0.80-1.48; $P = 0.58$). Nondisabling stroke was more common after S3 TAVR than after SAVR at 5-year follow-up. Rates of cardiac death; noncardiac death; transient ischemic attack; rehospitalization; death or rehospitalization; and the composite of death, stroke, or rehospitalization did not differ significantly between groups at 5-year follow-up. Supplemental Table 4 presents adjudicated causes of cardiovascular death at 5 years.

A landmark analysis of clinical events before 1 year and from 1 to 5 years for the propensity-matched cohort is presented in Supplemental Table 5. Rates of late death or disabling stroke were not significantly different between S3 TAVR and SAVR (35.5% vs 33.4%; HR: 1.10; 95% CI: 0.91-1.31; $P = 0.34$). There were no differences in late all-cause death between groups. Late stroke (between 1 and 5 years) was significantly more common after S3 TAVR than after SAVR (9.3% vs 5.1%; HR: 1.97; 95% CI: 1.24-3.13; $P = 0.003$), driven primarily by increased rates of late nondisabling stroke after S3 TAVR. Rates of late disabling stroke did not differ significantly between groups. Supplemental Tables 6 and 7 present the association between baseline characteristics with late

(after 1 year) all, disabling, and nondisabling stroke with S3 TAVR and SAVR, respectively.

Site-reported outcomes at 5 years are presented in Table 3. Higher rates of new pacemaker requirement after S3 TAVR persisted at 5-year follow-up. Although rates of aortic valve reintervention were similar between the 2 groups, the S3 TAVR group underwent valve-in-valve reintervention more frequently compared with SAVR. Rates of endocarditis and clinical valve thrombosis between the 2 groups remained similar at 5-year follow-up.

PROPENSITY SCORE SENSITIVITY ANALYSIS. Results of the sensitivity analysis using the original propensity-scoring methodology are presented in Supplemental Table 8. In each of the propensity score-stratified quintiles, patients who underwent S3 TAVR had a similar rate of the primary endpoint of death or disabling stroke at 5 years compared with individuals who underwent SAVR. The pooled weighted difference was −2.28% (95% CI: −12.74% to 8.17%) and was not significantly different between S3 TAVR and SAVR ($P = 0.67$).

ECHOCARDIOGRAPHIC FOLLOW-UP. Figure 4 presents baseline and follow-up echocardiographic measurements of aortic valve area and mean gradient. After adjusting for baseline values, aortic valve area remained greater after S3 TAVR compared with SAVR at all follow-up time points up to 5 years (Figure 4A). Similarly, after adjusting for baseline values, improvements in aortic valve mean gradient persisted after both S3 TAVR and SAVR at 5-year follow-up, and no differences were noted between groups.

Figure 5 shows baseline and follow-up measurements of total aortic regurgitation and PVR for patients in the propensity-matched cohort with available follow-up echocardiography. When analyzed as a 3-level variable, S3 TAVR was associated with greater rates of aortic regurgitation at baseline and all follow-up points. Similarly, PVR was greater after S3 TAVR at all follow-up points up to 5 years. However, no significant differences in moderate to severe aortic regurgitation (0.7% vs 1.2%; $P = 0.67$) or PVR (0.7% vs 0.4%; $P = 1.00$) were noted between groups in patients with available echocardiographic follow-up data at 5 years. Of the patients with moderate to severe PVR at 30 days after S3 TAVR, 10 of 30 patients (33.3%) experienced improvements in PVR grade, 11 patients (36.7%) died, and 8 patients (25.8%) had missing data at 5-year follow-up. Rates of mild PVR were significantly higher after S3 TAVR compared with SAVR at 5 years (28.7% vs 6.8%; $P < 0.0001$).

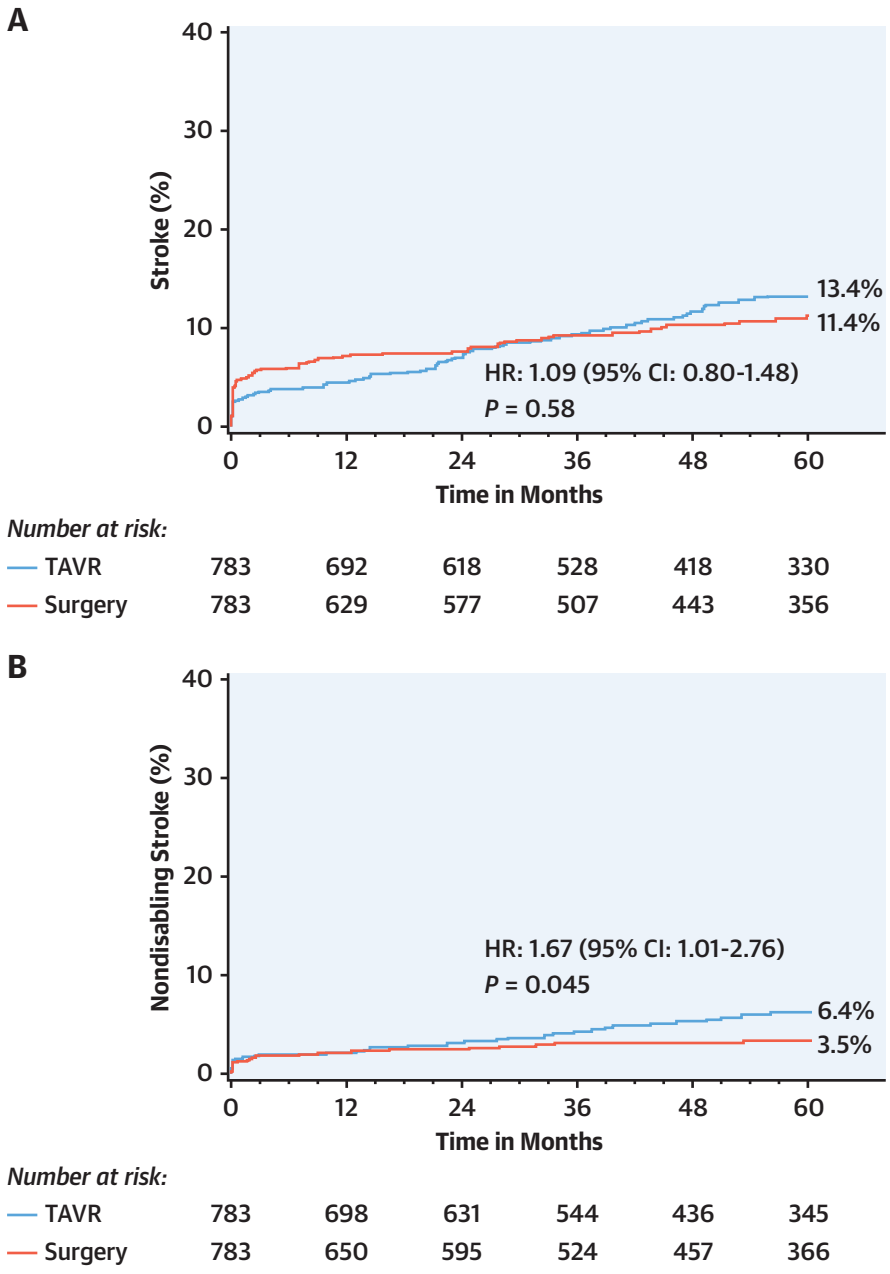
Figure 6 presents 5-year rates of SVD-related HVD and BVF per 100 exposure years. No significant differences were noted between the S3 TAVR and SAVR groups with regard to SVD-related stage 2 and 3 HVD ($P = 0.86$) or SVD-related BVF ($P = 0.22$) at 5-year follow-up.

DISCUSSION

The present analysis of 783 propensity-matched pairs of patients undergoing S3 TAVR in the single-arm P2S3i study compared with the SAVR arm of the randomized P2A trial presents the longest-term follow-up to date with the contemporary S3 THV. The principal findings of this propensity-matched analysis are as follows: 1) rates of the primary endpoint of death or disabling stroke were similar after S3 TAVR vs SAVR in intermediate-risk patients with severe AS at 5 years; 2) although overall stroke rates were comparable between both aortic valve replacement modalities, early disabling strokes were more common after SAVR, and late nondisabling strokes were more common after S3 TAVR; 3) rates of other key endpoints, including all-cause mortality and rehospitalization, were not significantly different between S3 TAVR and SAVR at 5 years; and 4) in line with previous findings, the incidence of moderate or greater SVD-related HVD and BVF was similar between S3 TAVR and SAVR at 5 years.

One of the key questions evaluated in this study is whether the initial benefits observed with S3 TAVR over SAVR are maintained over longer-term follow-up.[12] In the present study of well-matched cohorts drawn from the P2S3i (TAVR) and P2A (SAVR) studies, the initial differences in all-cause mortality rates favoring TAVR were less evident by 5 years, thus contributing to similar rates of the primary composite endpoint of death or disabling stroke with longer follow-up. One obvious question is whether this represents an increase in event rates after 1 year with TAVR compared with SAVR. Importantly, the landmark analysis did not demonstrate a significant increase in death or disabling stroke between 1 and 5 years. Notably, results obtained using the original prespecified propensity-scoring methodology as a sensitivity analysis were consistent with the overall results of the propensity-matched analysis. These results are also similar to the mid-term follow-up in the P2A randomized trial, which did not demonstrate any difference in mortality at 5 years between TAVR with the prior generation SAPIEN XT vs SAVR.[6] Similarly, in the low-risk patients studied in the PARTNER 3 randomized clinical trial, lower rates of death and stroke that favored S3 TAVR over SAVR at 1

FIGURE 3 Time-to-Event Curves for Stroke and Nondisabling Stroke by Treatment Strategy



5-year rates of all stroke **(A)** and nondisabling stroke **(B)** by SAPIEN 3 transcatheter aortic valve replacement (TAVR) or surgery.

year did not meet statistical significance at 2-year follow-up,[1,2] though the composite of death, stroke, and rehospitalization remained lower with S3 TAVR at 2 years. Longer-term follow-up of these patients is still ongoing.

Although overall stroke rates were not significantly different at 5 years, there were important differences in stroke severity. The initial benefit in disabling stroke favoring TAVR was maintained at 5-year follow-up. However, this was driven by the early events in the SAVR group, with no further difference in rates of disabling stroke between 1 and 5 years. In contrast, late (>1-year) nondisabling strokes were more frequent after TAVR. The mechanism behind

TABLE 3 5-Year Incidence Rates of Site-Reported Adverse Clinical Events in the Propensity-Matched Cohort

	TAVR (n = 783)	SAVR (n = 783)	OR (95% CI)	*P* Value
New permanent pacemaker	127/783 (16.2)	92/783 (11.7)	1.38 (1.08-1.77)	0.01
Endocarditis	17/783 (2.2)	19/783 (2.4)	0.89 (0.47-1.71)	0.74
Aortic valve reintervention	10/783 (1.3)	6/783 (0.8)	1.67 (0.61-4.56)	0.31
Surgical reintervention	2/783 (0.3)	6/783 (0.8)	0.33 (0.07-1.65)	0.29
BAV	1/783 (0.1)	0/783 (0.0)	—	1.00
Valve-in-valve	8/783 (1.0)	0/783 (0.0)	—	0.008
Valve thrombosis	6/783 (0.8)	1/783 (0.1)	6.00 (0.72-49.72)	0.12

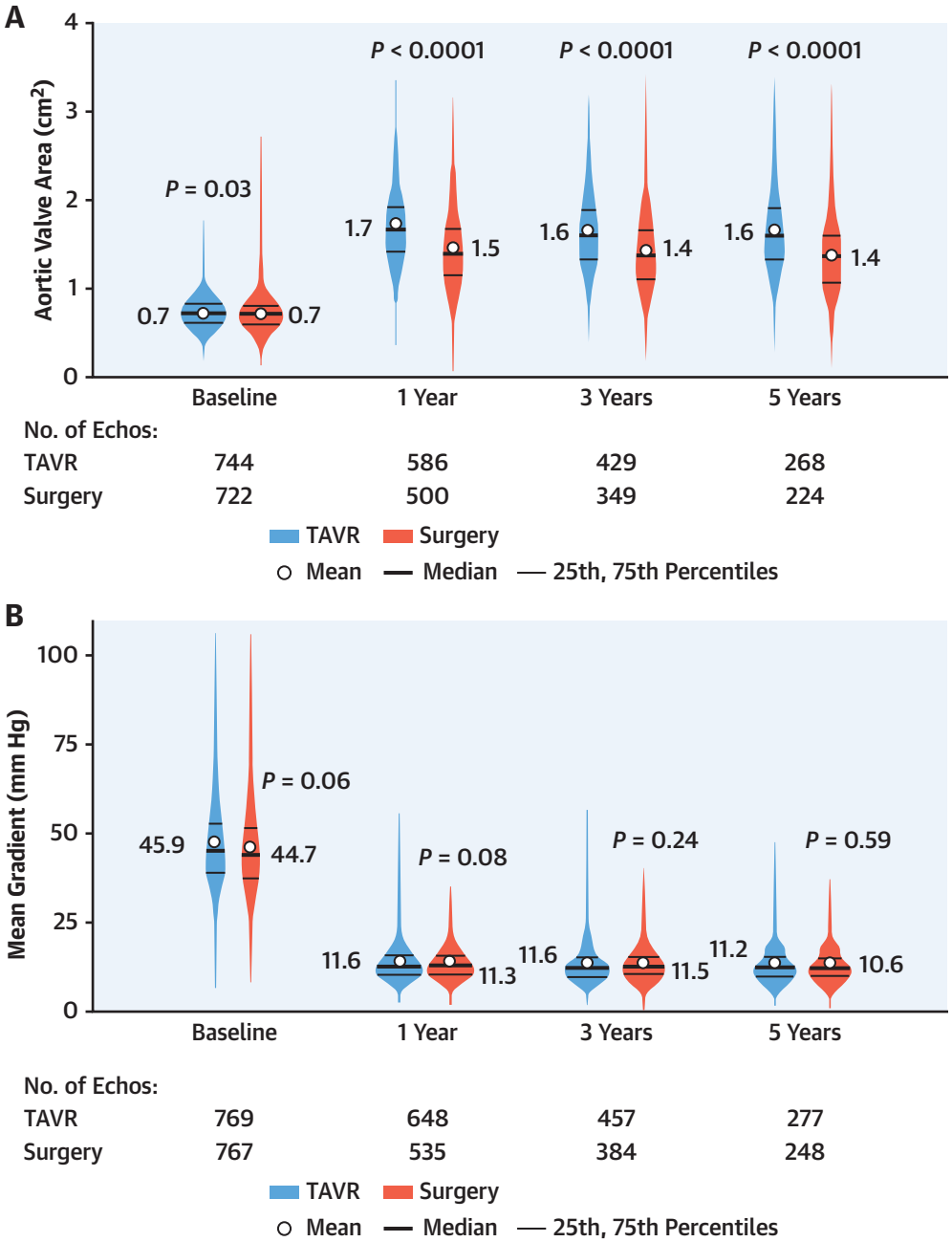
Values are n/N (%) unless otherwise indicated.
BAV = bicuspid aortic valve; other abbreviations as in Table 1.

these events remains unclear. One potential concern is the presence of hypoattenuated leaflet thickening (HALT), which has been described after both TAVR and SAVR, with numerically higher rates after TAVR.[18] A recent meta-analysis of the initial observational studies describing this phenomenon showed an association between HALT and adverse neurologic events.[19] On the basis of concerns raised from these initial studies, computed tomographic surveillance substudies evaluating the incidence of HALT were included in recent low-risk TAVR trials.[20,21] The PARTNER 3 computed tomographic substudy evaluating 435 patients undergoing S3 TAVR or SAVR demonstrated a significantly higher rate of HALT at 30 days following TAVR. The presence of HALT at 30 days was associated with a higher rate of stroke, transient ischemic attack, or thromboembolism at 1 year, suggesting an association between its presence and clinical events. However, at 1 year, although numerically higher with TAVR, the difference in the rates of HALT was no longer significant between the 2 groups.[20] A comparable study in the Evolut Low Risk randomized trial similarly demonstrated HALT to be a dynamic process, with similar rates between TAVR and SAVR at 1 year. In that study, however, there was no association between HALT and neurologic events.[21] More recently, 2-year data from the PARTNER 3 low-risk study suggest that rates of valve thrombosis were higher with S3 TAVR in low-risk patients compared with SAVR[2]; however, most thromboses were not associated with clinical events. In the present analysis, there were no differences in incidence of detected clinical valve thrombosis between groups on the basis of an older (Valve Academic Research Consortium 2) definition, and none of the patients with clinical valve thrombosis developed stroke in this matched cohort. Therefore, whether nondisabling stroke rates in patients who underwent S3 TAVR may be related to late valve-associated microthrombi due to HALT or other mechanisms after valve replacement requires further investigation.

Adjunctive medication regimens and treatment practices may have the potential to alter risk for thrombotic complications after aortic valve replacement. For example, treatment with direct-acting oral anticoagulant agents after TAVR has been demonstrated to reduce rates of subclinical leaflet thickening and motion abnormalities and bioprosthetic valve thrombosis; however, to date, no reduction in clinical endpoints, such as stroke or thromboembolic events,[22,23] has been observed with such a strategy. Importantly, in the present analysis, more patients in the SAVR group developed new-onset atrial fibrillation after aortic valve replacement by 1-year follow-up, with most within 30 days (30.1% vs 6.1%; $P < 0.0001$), and this may have contributed to early hazard of disabling stroke in patients who underwent SAVR. Higher rates of atrial fibrillation after SAVR have previously been described in large patient-level clinical data sets.[24] Although higher rates of new-onset atrial fibrillation after SAVR compared with S3 TAVR could have resulted in differential practices in antithrombotic treatments providing a protective effect against late stroke favoring surgery, it is unlikely, as the majority of postoperative atrial fibrillation is transient after cardiac surgery.[25] Data regarding rates of conversion back to sinus rhythm or differences in antithrombotic regimens were not assessed in this study. In addition to medical therapy, there is potential to further reduce rates of stroke after TAVR and SAVR with left atrial appendage occlusion. It was previously demonstrated in the LAAOS III (Left Atrial Appendage Occlusion Study) that left atrial appendage occlusion during cardiac surgery was associated with substantially lower rates of ischemic stroke or systemic embolism compared with the control group.[26] Efforts are currently under way to assess the impact on prophylactic left atrial appendage closure on stroke risk after SAVR,[27] and similarly, prophylactic percutaneous left atrial appendage occlusion after TAVR in patients with atrial fibrillation is also being studied.

The present assessment of long-term outcomes in intermediate-risk patients who underwent TAVR with the S3 balloon-expandable valve system is paralleled by recently published 5-year follow-up data with self-expanding TAVR valves in the SURTAVI (Surgical or Transcatheter Aortic Valve Replacement) trial.[5,28] This modified intention-to-treat analysis demonstrated similar rates of the primary composite endpoint of 5-year all-cause mortality or disabling stroke in 1,660 intermediate-risk patients who were randomized to treatment with TAVR using 1 of 2 self-

FIGURE 4 Aortic Stenosis Severity by Treatment Strategy

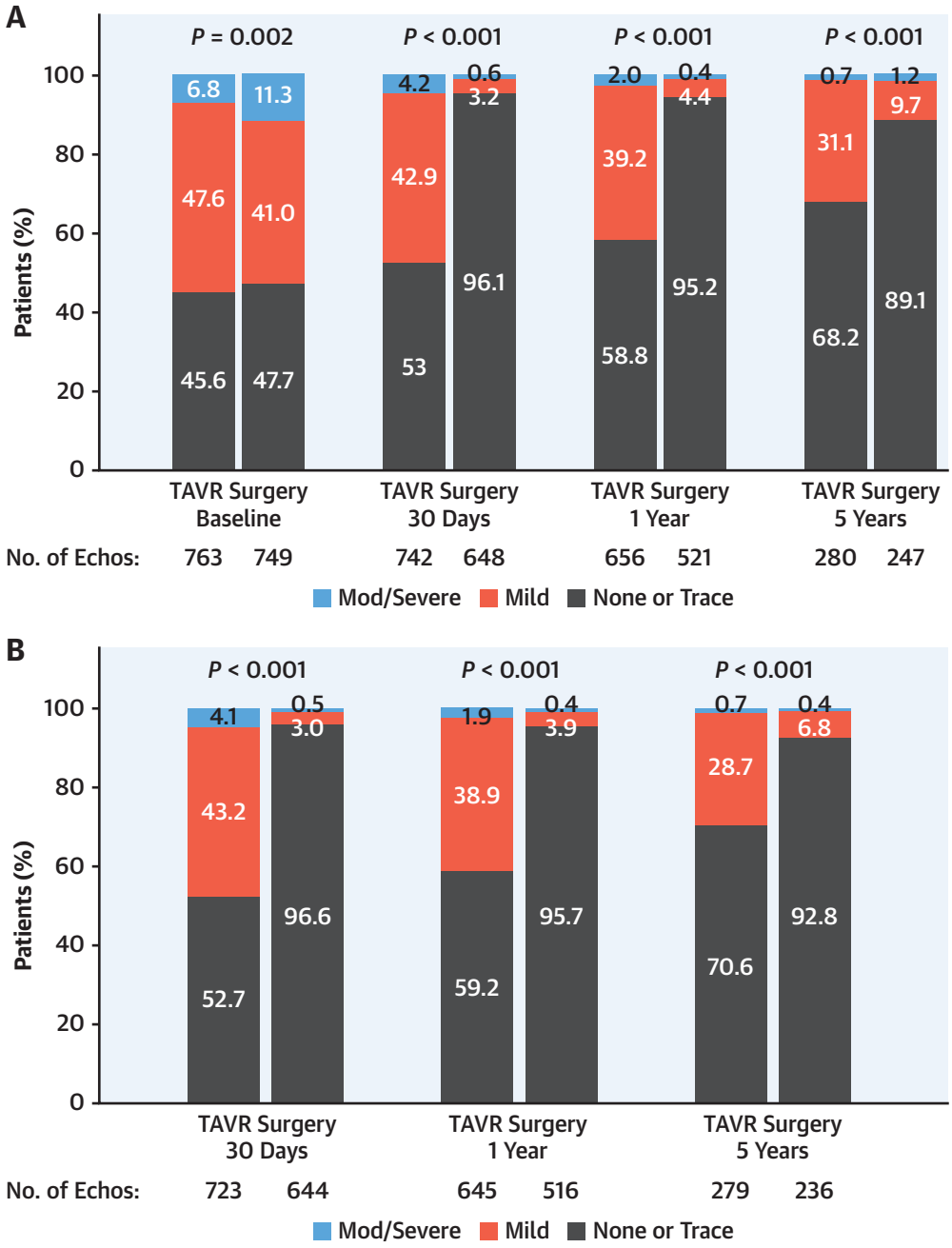


Comparisons of aortic valve area **(A)** and mean gradient **(B)** assessed by echocardiography between SAPIEN 3 transcatheter aortic valve replacement (TAVR) and surgery after adjusting for baseline values at 5-year follow-up.

expanding valve systems (CoreValve [84%] or Evolut R [16%], Medtronic) or SAVR (31.3% vs 30.8%; HR: 1.02; 95% CI: 0.85-1.22; $P = 0.85$).[28] Thus, available data suggest that the risk for death or disabling stroke between both balloon-expandable and self-expanding THV platforms and SAVR is similar at 5-year follow-up.

Given the steadily increasing number of TAVR procedures,[9] durability is a crucial consideration when assessing THVs. Recent bench data

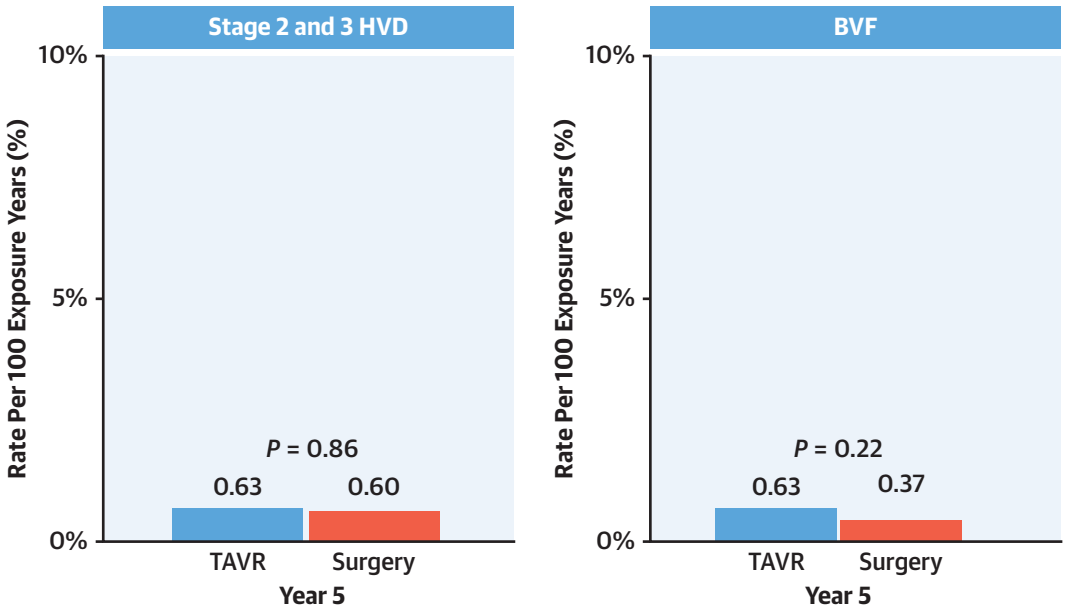
FIGURE 5 Aortic Valve and Paravalvular Regurgitation by Treatment Strategy



Comparisons of severity of aortic regurgitation **(A)** and paravalvular regurgitation **(B)** assessed by echocardiography between SAPIEN 3 transcatheter aortic valve replacement (TAVR) and surgery at 5-year follow-up. Mod = moderate.

demonstrated that the S3 THV has durability equivalent to 25 years and comparable with surgical heart valves.[29] The present study reiterates the comparable 5-year durability of the S3 TAVR system compared with SAVR previously reported by Pibarot et al.[11] In the present analysis, rates of aortic regurgitation and PVR were higher with S3 TAVR compared with SAVR at all follow-up periods up to 5 years. However, this was driven largely by rates of mild aortic regurgitation and PVR, as there were no significant differences

FIGURE 6 Durability of Aortic Valve Replacement by Treatment Strategy



Incidence of heart valve deterioration (HVD) (stages 2 and 3) and bioprosthetic valve failure (BVF) related to structural valve deterioration are presented as rates per 100 exposure years. TAVR = transcatheter aortic valve replacement.

in moderate to severe aortic regurgitation or PVR between groups at 5 years. Given the conflicting evidence regarding the impact of mild PVR on prognosis,[30,31] further long-term study focused on the mechanisms and degree of PVR and the relationship with clinical outcomes after more contemporary THV devices is needed.

STUDY LIMITATIONS. Although the P2S3i cohort was a part of the PARTNER 2 trial and therefore included the same study leadership and a similar design (ie, endpoint adjudication, evaluation, and follow-up) as the P2A SAVR arm, intermediate-risk patients were not randomized between S3 TAVR and SAVR in the present analysis. However, we adjusted for 25 important covariates as part of this propensity-matched analysis. Nonetheless, some degree of unmeasured confounding is still possible. Although this study represents the longest-term follow-up available after TAVR with the S3 valve system, with >80% of patients included in the 5-year analysis, higher loss to follow-up in the S3 TAVR arm was observed compared with patients in the SAVR arm. Last, information regarding postprocedural medication regimens (eg, antithrombotic treatments) was not systematically studied in PARTNER 2, so the impact of these therapies on outcomes after aortic valve replacement could not be determined.

CONCLUSIONS

In this propensity-matched analysis of 783 matched pairs of intermediate-risk patients with severe, symptomatic AS who underwent aortic valve replacement, rates of death and disabling stroke were similar between S3 TAVR and SAVR at 5 years. Early disabling stroke was more common after SAVR, whereas late nondisabling stroke occurred more frequently after S3 TAVR. Additional studies with longer-term follow-up are required to provide better mechanistic insights regarding adverse clinical outcomes and bioprosthetic valve durability after aortic valve replacement with S3 TAVR compared with SAVR.

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CryoLife, JenaValve, Shockwave, and Boston Scientific. Dr Makkar has received grant support from and has research contracts with Edwards Lifesciences and St Jude Medical; and has received consulting fees and honoraria from and is a Speakers Bureau member for Abbott Vascular, Cordis Corporation, and Medtronic. Dr Mack has served as co-primary investigator for the PARTNER trial for Edwards Lifesciences and the COAPT trial for Abbott; and has served as study chair for the APOLLO trial for Medtronic (all activities unpaid). Dr Webb is a consultant for Edwards Lifesciences. Dr Herrmann has received institutional research funding from Abbott Vascular, Ancora, Boston Scientific, Edwards Lifesciences, and Medtronic; and has received consulting fees from Abbott Vascular, Edwards Lifesciences, and Medtronic; and holds equity in Micro Interventional Devices. Dr Cohen has received institutional research grants from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott Vascular; and has received consulting fees from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott Vascular. Dr Pibarot has received funding from Edwards Lifesciences, Medtronic, Pi-Cardia, and Cardiac Phoenix for echocardiography core laboratory analyses and research studies in the field of transcatheter valve therapies, for which he received no personal compensation. Dr Hahn has received speaker fees from Abbott Vascular, Baylis Medical, and Edwards Lifesciences; has institutional consulting agreements for which she receives no direct compensation with Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and Novartis; holds equity with Navigate; and is the Chief Scientific Officer for the echocardiography core laboratory at the Cardiovascular Research Foundation. Dr Xu is an employee of Edwards Lifesciences. Dr Alu has received institutional funding (no direct compensation) from Edwards Lifesciences and Abbott. Dr Leon serves on the PARTNER trial executive committee for Edwards Lifesciences (unpaid); has received institutional research grants from and is an unpaid adviser for Abbott, Boston Scientific, and Medtronic; is an unpaid adviser for Sinomed; and holds equity in Medinol. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In propensity-matched intermediate-risk patients, 5-year incidence rates of death, disabling stroke, SVD, and BVF were similar after TAVR with the S3 prosthesis and SAVR, but PVR was more frequent after TAVR.

TRANSLATIONAL OUTLOOK: Longer-term follow-up will better characterize clinical outcomes and prosthetic valve durability after TAVR and SAVR.

REFERENCES

1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med*. 2019;380:1695–1705.

2. Leon MB, Mack MJ, Hahn RT, et al. Outcomes 2 years after transcatheter aortic valve replacement in patients at low surgical risk. *J Am Coll Cardiol*. 2021;77:1149–1161.

3. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med*. 2019;380:1706–1715.

4. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2016;374:1609–1620.

5. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med*. 2017;376:1321–1331.

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

7. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–2491.

8. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. *J Am Coll Cardiol*. 2014;63:1972–1981.

9. Carroll JD, Mack MJ, Vemulapalli S, et al. STS-ACC TVT Registry of transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2020;76:2492–2516.

10. Beohar N, Kirtane AJ, Blackstone E, et al. Trends in complications and outcomes of patients undergoing transfemoral transcatheter aortic valve replacement: experience from the PARTNER Continued Access Registry. *J Am Coll Cardiol Intv*. 2016;9:355–363.

11. Pibarot P, Ternacle J, Jaber WA, et al. Structural deterioration of transcatheter versus surgical aortic valve bioprostheses in the PARTNER-2 trial. *J Am Coll Cardiol*. 2020;76:1830–1843.

12. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. *Lancet*. 2016;387:2218–2225.

13. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J*. 2016;37:2252–2262.

14. Hahn RT, Pibarot P, Leipsic J, et al. The Effect of post-dilatation on outcomes in the PARTNER 2 SAPIEN 3 registry. *J Am Coll Cardiol Intv*. 2018;11:1710–1718.

15. Mooney J, Sellers SL, Blanke P, et al. CT-defined prosthesis-patient mismatch downgrades frequency and severity, and demonstrates no association with adverse outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol Intv*. 2017;10:1578–1587.

16. Baron SJ, Arnold SV, Wang K, et al. Health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial. *JAMA Cardiol*. 2017;2:837–845.

17. VARC-3 Writing Committee, Généreux P, Piazza N, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77(21):2717–2746.

18. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med*. 2015;373:2015–2024.

19. Rashid HN, Gooley RP, Nerlekar N, et al. Bioprosthetic aortic valve leaflet thrombosis detected by multidetector computed tomography is associated with adverse cerebrovascular events: a meta-analysis of observational studies. *EuroIntervention*. 2018;13:e1748–e1755.

20. Makkar RR, Blanke P, Leipsic J, et al. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol*. 2020;75:3003–3015.

21. Blanke P, Leipsic JA, Popma JJ, et al. Bioprosthetic aortic valve leaflet thickening in the evolut low risk sub-study. *J Am Coll Cardiol*. 2020;75:2430–2442.

22. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382:130–139.

23. Collet J-P. Oral anti-Xa anticoagulation after trans-aortic valve implantation for aortic stenosis: the randomized ATLANTIS trial. Presented at: ACC 2021; May 15, 2021.

24. Kalra R, Patel N, Doshi R, et al. Evaluation of the incidence of new-onset atrial fibrillation after aortic valve replacement. *JAMA Intern Med*. 2019;179:1122–1130.

25. Charitos EI, Herrmann FEM, Ziegler PD. Atrial fibrillation recurrence and spontaneous conversion to sinus rhythm after cardiac surgery: insights from 426 patients with continuous rhythm monitoring. *J Cardiovasc Electrophysiol*. 2021;32:2171–2178.

26. Whitlock RP, Belley-Cote EP, Paparella D, et al. Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med*. 2021;384:2081–2091.

27. Kiviniemi T, Bustamante-Munguira J, Olsson C, et al. A randomized prospective multicenter trial for stroke prevention by prophylactic surgical closure of the left atrial appendage in patients undergoing bioprosthetic aortic valve surgery—LAA-CLOSURE trial protocol. *Am Heart J*. 2021;237:127–134.

28. Van Mieghem NM, Deeb GM, Sondergaard L, et al. Self-expanding transcatheter vs surgical aortic valve replacement in intermediate-risk patients: 5-year outcomes of the SURTAVI randomized clinical trial. *JAMA Cardiol*. 2022;7(10):1000–1008.

29. Sathananthan J, Hensey M, Landes U, et al. Long-term durability of transcatheter heart valves: insights from bench testing to 25 years. *J Am Coll Cardiol Intv*. 2020;13:235–249.

30. Chau KH, Chen S, Crowley A, et al. Paravalvular regurgitation after transcatheter aortic valve replacement in intermediate-risk patients: a pooled PARTNER 2 study. *EuroIntervention*. 2022;17:1053–1060.

31. Okuno T, Tomii D, Heg D, et al. Five-year outcomes of mild paravalvular regurgitation after transcatheter aortic valve implantation. *EuroIntervention*. 2022;18:33–42.

KEY WORDS aortic stenosis, aortic valve replacement, surgical aortic valve replacement, transcatheter aortic valve replacement

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