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ORIGINAL INVESTIGATIONS

Outcomes 2 Years After Transcatheter Aortic Valve Replacement in Patients at Low Surgical Risk

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ABSTRACT

BACKGROUND In low surgical risk patients with symptomatic severe aortic stenosis, the PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis) trial demonstrated superiority of transcatheter aortic valve replacement (TAVR) versus surgery for the primary endpoint of death, stroke, or re-hospitalization at 1 year.

OBJECTIVES This study determined both clinical and echocardiographic outcomes between 1 and 2 years in the PARTNER 3 trial.

METHODS This study randomly assigned 1,000 patients (1:1) to transfemoral TAVR with the SAPIEN 3 valve versus surgery (mean Society of Thoracic Surgeons score: 1.9%; mean age: 73 years) with clinical and echocardiography follow-up at 30 days and at 1 and 2 years. This study assessed 2-year rates of the primary endpoint and several secondary endpoints (clinical, echocardiography, and quality-of-life measures) in this as-treated analysis.

RESULTS Primary endpoint follow-up at 2 years was available in 96.5% of patients. The 2-year primary endpoint was significantly reduced after TAVR versus surgery (11.5% vs. 17.4%; hazard ratio: 0.63; 95% confidence interval: 0.45 to 0.88; $p = 0.007$). Differences in death and stroke favoring TAVR at 1 year were not statistically significant at 2 years (death: TAVR 2.4% vs. surgery 3.2%; $p = 0.47$; stroke: TAVR 2.4% vs. surgery 3.6%; $p = 0.28$). Valve thrombosis at 2 years was increased after TAVR (2.6%; 13 events) compared with surgery (0.7%; 3 events; $p = 0.02$). Disease-specific health status continued to be better after TAVR versus surgery through 2 years. Echocardiographic findings, including hemodynamic valve deterioration and bioprosthetic valve failure, were similar for TAVR and surgery at 2 years.

CONCLUSIONS At 2 years, the primary endpoint remained significantly lower with TAVR versus surgery, but initial differences in death and stroke favoring TAVR were diminished and patients who underwent TAVR had increased valve thrombosis. (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis [PARTNER 3]; NCT02675114) (J Am Coll Cardiol 2021;77:1149–61) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

BVF = bioprosthetic valve failure

CI = confidence interval

CT = computed tomography

HR = hazards ratio

HVD = hemodynamic valve deterioration

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire–overall summary

LV = left ventricle

MI = myocardial infarction

MR = mitral regurgitation

PVR = paravalvular regurgitation

STS-PROM = Society of Thoracic Surgeons–predicted risk of operative mortality

TAVR = transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

The acceptance of transcatheter aortic valve replacement (TAVR) as a treatment alternative for severe symptomatic aortic stenosis (AS) has been accelerated by multiple randomized clinical trials that have demonstrated similar clinical outcomes and valve hemodynamics, comparing surgery and TAVR in high- and intermediate-risk older adult patients (1–7). Five-year follow-up from these studies has demonstrated sustained clinical benefits and durable mid-term valve performance (8–12). Nevertheless, most patients with AS who undergo surgical aortic valve replacement are younger with low-risk profiles (13). Recently, 2 large, randomized trials in younger and lower surgical risk patients have shown superior or similar clinical outcomes (death and stroke) for TAVR versus surgery at 1 year (6,7). In the low-risk PARTNER 3 (The Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis) (7), the primary endpoint was reduced by 46% at 1 year after TAVR compared with surgery ($p = 0.001$). In this paper, we report 2-year findings from PARTNER 3, emphasizing the clinical outcomes from 1 to 2 years and using new standardized definitions of hemodynamic valve deterioration (HVD) and bioprosthetic valve failure (BVF) (14–16).

SEE PAGE 1162

METHODS

TRIAL DESIGN AND OVERSIGHT. As previously described (7), PARTNER 3 enrolled 1,000 low surgical risk patients with symptomatic severe AS from 71 sites and compared the transfemoral SAPIEN 3 (Edwards Lifesciences, Irvine, California) TAVR versus standard surgical aortic valve replacement. The trial protocol was designed by the sponsor (Edwards Lifesciences) and steering committee and was approved by Institutional Review Boards at each site. The sponsor roles included funding trial-related activities, participation in site selection, data collection and monitoring, and statistical analysis. The principal investigators (M.B.L. and M.J.M.; first 2 authors) and steering committee had unrestricted access to the data, prepared all drafts of the manuscript, and attest to the completeness and accuracy of the data and analyses. Trial administration and management have been previously reported (7).

PATIENTS AND VALVE TECHNOLOGY. Low surgical risk status was determined by a combination of Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) of <4% and/or judgment by the site heart team and trial case review committee. Key anatomic and clinical exclusion criteria were previously reported (7). The study protocol was approved by the Institutional Review Board at each site, and all patients provided written informed consent.

The SAPIEN 3 transcatheter heart valve is a third-generation balloon-expandable valve with an external sealing cuff used to reduce paravalvular regurgitation. It is available in 20-, 23-, 26-, and 29-mm diameter valve sizes (7,17). The expandable transfemoral delivery system has a 14- or 16-F internal diameter.

RANDOMIZATION, PROCEDURES, AND FOLLOW-UP. Patients eligible for randomization were assigned in a 1:1 ratio to be treated with either transfemoral TAVR or surgery. Randomization was conducted using an electronic system and was stratified according to site.

Details of the TAVR procedure have been previously described (7,17). Cerebral embolic protection devices during TAVR were prohibited. Surgeons were encouraged to select a valve size as large as possible; the use of minimally invasive surgery approaches, aortic root enlargement, and other concomitant surgical procedures were at the operator's discretion. Same day or staged concomitant percutaneous coronary intervention procedures (or surgery + coronary artery bypass grafting) were allowed if approved by

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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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the case review committee. Antiplatelet and antithrombotic pharmacological regimens appropriate to the clinical circumstances were recommended in the study protocol (Supplemental Table 1).

Clinical outcomes were assessed at baseline, post-procedure, pre-discharge, at 30 days, 6 months, and 1 and 2 years in all patients. Transthoracic echocardiography was performed at baseline, pre-discharge, 30 days, and at 1 and 2 years.

CLINICAL ENDPOINTS. The primary endpoint of PARTNER 3 was a composite of death from any cause, all stroke (disabling or non-disabling), or cardiovascular rehospitalization at 1 year. Key secondary endpoints for the 2-year follow-up report were acute myocardial infarction (MI), new-onset atrial fibrillation, need for a new pacemaker, new left bundle branch block, coronary obstruction, aortic valve reintervention, aortic valve endocarditis, and valve thrombosis. Valve thrombosis was defined according to Valve Academic Research Consortium (VARC)–2 criteria (18): thrombus associated with an implanted valve that interferes with valve function or warrants treatment (anticoagulation or explantation). Echocardiography or 3-dimensional computed tomography (CT) imaging was used to diagnose valve-related thrombus and restricted leaflet motion (19). Clinical events committee adjudication of 2-year clinical outcomes included all components of the primary endpoint, valve thrombosis, aortic valve reintervention, and aortic valve endocarditis. Other secondary clinical endpoints at 2 years were site-reported with source documentation. Health outcome measures were assessed at 2 years, including the Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ-OS).

ECHOCARDIOGRAPHY FINDINGS. Echocardiograms were analyzed in a core laboratory. Standard hemodynamic parameters were reported in all patients at each time point. Aortic regurgitation was assessed using a multiparameter integrative approach as described previously (20) and was graded according to a 5-class scheme: 0: none or trace; 1: mild; 2: mild to moderate; 3: moderate; 4: moderate to severe; and 5: severe.

Bioprosthetic valve durability was adjudicated by a group of 3 experts and determined using the VARC 3 criteria for HVD and according to recent standards for BVF (14,15,21). The BVF definition used was: 1) stage 3 (severe) HVD; or 2) valve re-intervention or death related to valve dysfunction.

STATISTICAL ANALYSIS. Statistical methods were described in the original publication (7). The primary analysis was performed in the as-treated population; for echocardiography results, analyses were performed using the valve implantation population. Continuous variables, presented as mean ± SD, were compared using Student's *t*-test or the Wilcoxon rank-sum test. Categorical and ordinal variables are presented as proportions and compared using Fisher's exact test or the Wilcoxon rank-sum test. For post-baseline continuous variables, comparisons used analysis of covariance adjusted for the baseline measurement. Comparisons of echocardiographic continuous variables at 1 and 2 years were performed with linear mixed models using baseline value, treatment, visit, and interaction between treatment and visit as predictors. A categorical analysis combining survival and changes in health status (22) was evaluated through 2 years. Time-to-event analyses used Kaplan-Meier estimates and log-rank tests and are presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

Sensitivity analyses of the primary endpoint were performed with: 1) multiple imputation to account for missing data; and 2) an analysis of the hierarchical composite of death, stroke, or rehospitalization with the win ratio method. For the primary endpoint, pre-specified subgroup analyses, with tests for interaction, were also performed. For all analyses, a p value <0.05 was considered statistically significant without adjustment for multiple comparisons.

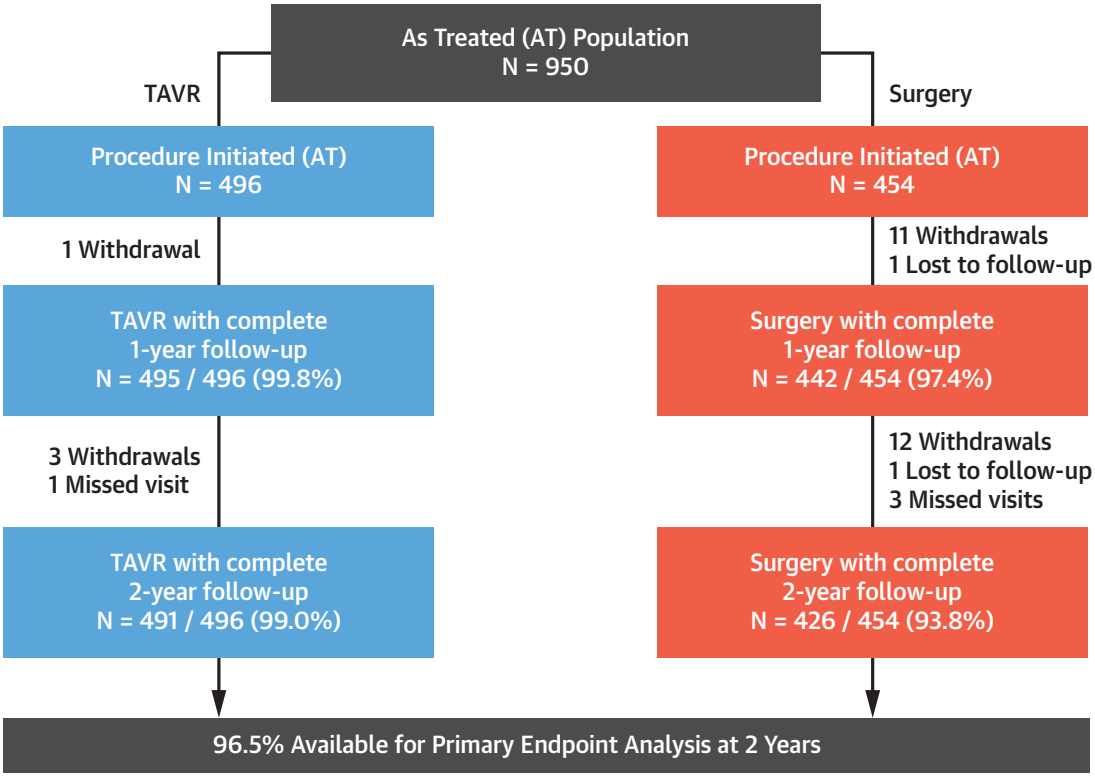
The exposure-adjusted incidence rates of HVD and BVF were reported in both cohorts through 2 years (23). The exposure-adjusted cumulative rate was defined as the number of subjects exposed to the aortic bioprosthetic valve and who experienced an event (HVD or BVF) divided by the total exposure time of all patients at risk for an event (expressed per 100 patient-years).

All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

PATIENTS AND FOLLOW-UP. Baseline patient characteristics are summarized in Supplemental Table 2. There were 950 patients in the as-treated population (496 TAVR and 454 surgery), and the intended valve was implanted in 948. The patients enrolled were younger (mean age: 73 years), included more men (69.3%), had lower STS-PROM scores (mean: 1.9%), fewer severe symptoms (New York Heart Association functional classes III or IV: 27.6%), and fewer co-existing conditions than patients enrolled in

FIGURE 1 Patient Disposition Through 2 Years



This patient flowchart accounts for all patient follow-up at 1 and 2 years, indicating study withdrawals, missed visits, and lost to follow-up. There were disproportionate study withdrawals in surgery versus transcatheter aortic valve replacement (TAVR) (23 vs. 4) over the first 2 years of follow-up, which resulted in a difference in overall follow-up that was lower with surgery (93.8%) versus TAVR (99%) at 2 years.

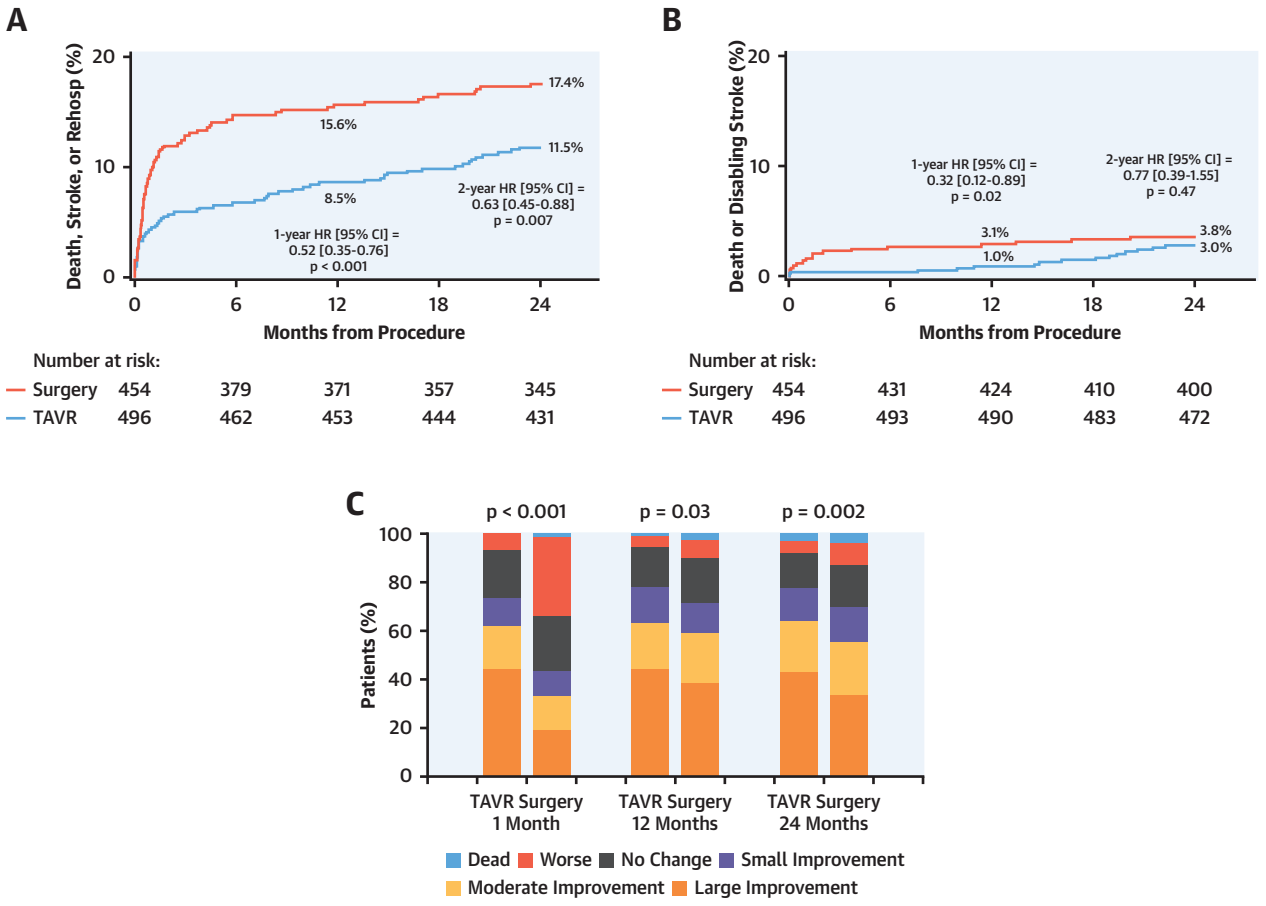
previous TAVR trials with higher surgical risk populations (1-5).

Patient disposition through 2 years is shown in **Figure 1**. Overall, complete primary endpoint follow-up through 2 years was 96.5% (TAVR: 99.0% and surgery: 93.8%).

PRIMARY ENDPOINT EVENTS. At 2 years, the composite of death from any cause, all stroke, or cardiovascular rehospitalization occurred in 57 patients (11.5%) after TAVR and 78 patients (17.4%) after surgery (HR: 0.63; 95% CI: 0.45 to 0.88; p = 0.007) (**Central Illustration**). The results using the hierarchical win ratio method were consistent with the primary analysis (win ratio: 1.59; 95% CI: 1.13 to 2,23; p = 0.008) (Supplemental Table 3). A sensitivity analysis using multiple imputation for missing data through 2 years was also consistent (Supplemental Table 3). Similarly, the restricted mean event-free survival time at 2 years improved with TAVR versus surgery (670 days vs. 622 days; p < 0.001) (Supplemental Table 4). Subgroup analyses for the primary endpoint at 2 years showed no heterogeneity of treatment effect for any of the subgroups examined (Supplemental Figure 1).

Components of the primary composite endpoint are shown in **Table 1 and Figures 2A to 2C**. At 2 years, the event rates for TAVR compared with surgery were 2.4% versus 3.2% (HR: 0.75; 95% CI: 0.35, 1.63; p = 0.47) for death from any cause; 2.4% versus 3.6% (HR: 0.66; 95% CI: 0.31 to 1.40; p = 0.28) for stroke; and 8.5% versus 12.5% (HR: 0.67; 95% CI: 0.45 to 1.00; p = 0.046) for rehospitalization. Between 1 and 2 years, TAVR was associated with more deaths than surgery (7 vs. 3), more strokes (6 vs. 1), and a similar number of rehospitalizations (10 vs. 8). Specific causes of deaths, strokes, and rehospitalizations between 1 and 2 years are shown in Supplemental Tables 5 to 7. The combined endpoint of death or disabling stroke at 2 years for TAVR was 3.0% compared with 3.8% for surgery (HR: 0.77; 95% CI: 0.39 to 1.55; p = 0.47) (**Table 1, Central Illustration**).

CENTRAL ILLUSTRATION **Time-to-Event Curves and Disease-Specific Health Status in TAVR Versus Surgery Through 2 Years**



Leon, M.B. et al. J Am Coll Cardiol. 2021;77(9):1149–61.

(A) Kaplan-Meier rates of the primary endpoint composite (death, stroke, or rehospitalization) at 1 and 2 years in patients receiving transcatheter aortic valve replacement (TAVR) or surgery. This time-to-event analysis of the primary composite endpoint for the as-treated patient population indicates that the significant difference favoring TAVR at 1 year ($p < 0.001$) was sustained at 2-year follow-up ($p = 0.007$). **(B)** Kaplan-Meier rates of the composite of death or disabling stroke at 1 and 2 years in patients who underwent TAVR or surgery. This time-to-event analysis of death or disabling stroke indicates that important differences favoring TAVR at 1 year ($p = 0.02$) were diminished between 1 and 2 years, such that at 2 years the rates of death or disabling stroke were similar (p+0.47). **(C)** Proportion of patients who achieved specific levels of change in the Kansas City Cardiomyopathy Questionnaire-overall summary (KCCQ-OS) after TAVR or surgery. A large improvement in KCCQ-OS was defined as a ≥20 point increase from baseline, moderate improvement as an increase between 10 and <20 points; small improvement as an increase between 5 and <10 points, no change as between −5 and <5 points, and worse as a >5 point decrease from baseline. p Values were derived from ordinal logistic regression models. This ordinal categorical variable analysis incorporating mortality as the worst outcome compared TAVR versus surgery at 1, 12, and 24 months. The findings indicated that TAVR resulted in a marked improvement in quality-of-life indexes at 1 month ($p < 0.001$) compared with surgery, and the difference was diminished but still significant at 12 ($p = 0.03$) and 24 months ($p = 0.002$). CI = confidence interval; HR = hazard ratio.

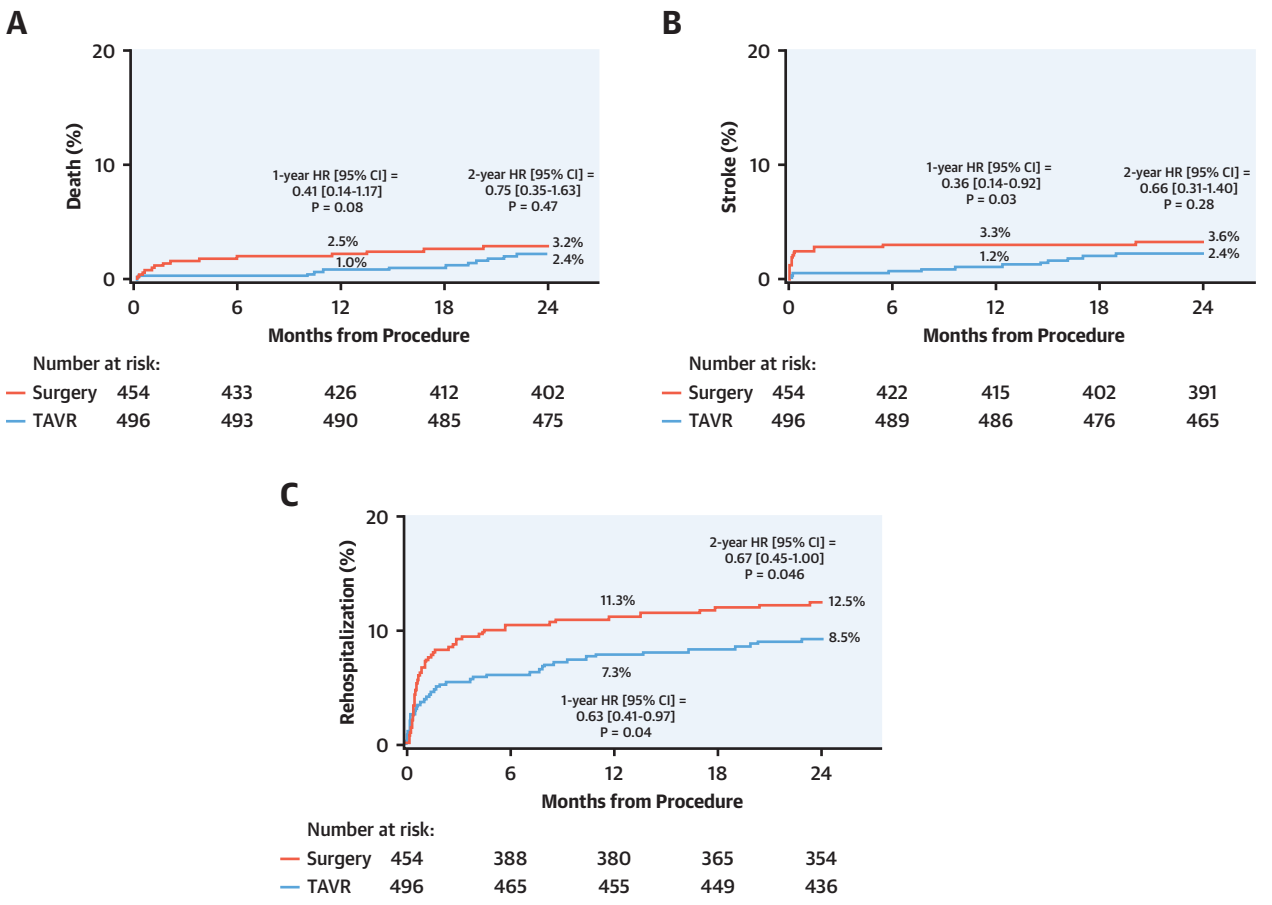
SECONDARY ENDPOINTS. Secondary endpoint results at 1 and 2 years are listed in Table 2. There were small changes between 1 and 2 years for both TAVR and surgery in most secondary endpoints, including aortic valve re-intervention and endocarditis. However, the rates of valve thrombosis, which were numerically higher at 1 year after TAVR (1.0%) compared with those of surgery (0.2%; p = 0.13), continued to diverge through 2 years (TAVR: 2.6%; surgery: 0.7%; p = 0.02). Among the patients with valve thrombosis at 2 years, 7 of 13 (54%) patients who underwent TAVR and 0 of 3 patients who underwent surgery had an echocardiographic aortic valve mean gradient >20 mm Hg, with an increase from post-treatment of >10 mm Hg (Table 3). Clinical events possibly related to valve thrombosis occurred in 4 patients (3 TAVR and 1 surgery), including 2 of the 3 disabling strokes that occurred between 1

TABLE 1 Primary Endpoint Events at 1 and 2 Years

	KM Rate at 1 Year				KM Rate at 2 Years			
	TAVR (n = 496)	SAVR (n = 454)	Hazard Ratio (95% CI)	p Value	TAVR (n = 496)	SAVR (n = 454)	Hazard Ratio (95% CI)	p Value
Death, stroke, or rehospitalization*	42 (8.5)	70 (15.6)	0.52 (0.35–0.76)	<0.001	57 (11.5)	78 (17.4)	0.63 (0.45–0.88)	0.007
Death	5 (1.0)	11 (2.5)	0.41 (0.14–1.17)	0.08	12 (2.5)	14 (3.2)	0.75 (0.35–1.63)	0.47
Cardiovascular	4 (0.8)	9 (2.0)	0.40 (0.12–1.30)	0.11	8 (1.6)	12 (2.7)	0.59 (0.24–1.44)	0.24
Noncardiovascular	1 (0.2)	2 (0.5)	0.44 (0.04–4.86)	0.49	4 (0.8)	2 (0.5)	1.74 (0.32–9.50)	0.52
Stroke	6 (1.2)	15 (3.3)	0.36 (0.14–0.92)	0.03	12 (2.5)	16 (3.6)	0.66 (0.31–1.40)	0.28
Disabling	1 (0.2)	5 (1.1)	0.18 (0.02–1.53)	0.08	4 (0.8)	5 (1.1)	0.71 (0.19–2.63)	0.60
Nondisabling	5 (1.0)	10 (2.2)	0.45 (0.15,1.31)	0.13	8 (1.6)	11 (2.5)	0.65 (0.26–1.61)	0.34
TIA	5 (1.0)	5 (1.1)	0.88 (0.26–3.05)	0.85	5 (1.0)	7 (1.6)	0.63 (0.02–1.98)	0.42
Death or disabling stroke	5 (1.0)	14 (3.1)	0.32 (0.11–0.89)	0.02	15 (3.1)	17 (3.8)	0.78 (0.39–1.55)	0.47
Rehospitalization*	36 (7.3)	50 (11.3)	0.63 (0.41–0.97)	0.04	42 (8.5)	55 (12.5)	0.67 (0.45–1.00)	0.046

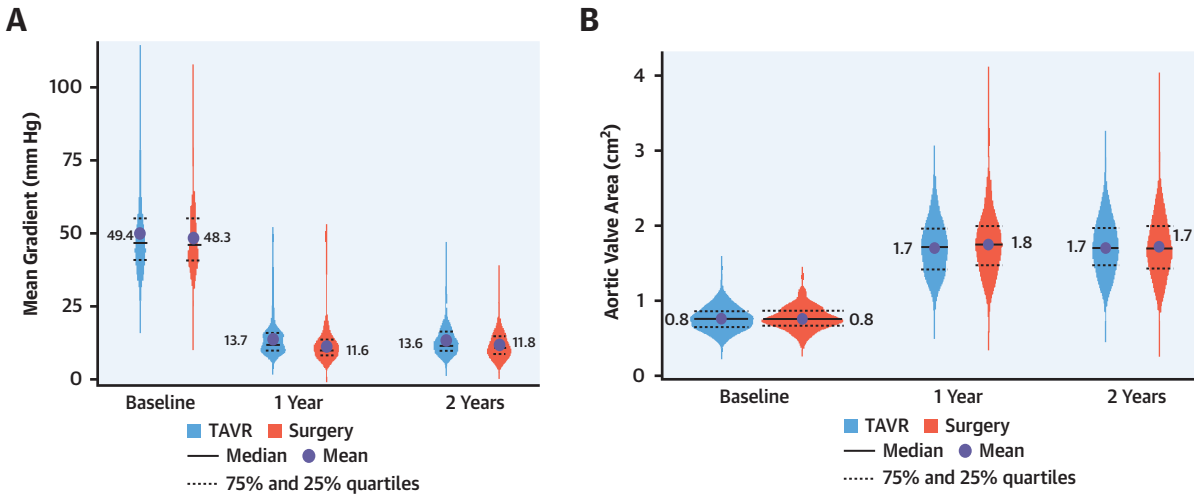
Values are n (%) according to Kaplan-Meier (KM) estimate. The p values are based on log-rank test. *Rehospitalization: valve- or procedure-related and including heart failure.
CI = confidence interval; HR = hazard ratio; SAVR = surgical aortic valve replacement; TAVR = transaortic valve replacement; TIA = transient ischemic attack.

FIGURE 2 Kaplan-Meier Rates of the Components of the Primary Endpoint Through 2 Years in Patients Who Underwent TAVR or Surgery



(A) All-cause mortality. This time-to-event analysis of mortality indicates that trends favoring TAVR with lower mortality compared with surgery at 1 year (p = 0.08) were diminished at 2 years, such that TAVR and surgery were not significantly different (p = 0.47). **(B)** All strokes: This time-to-event analysis of strokes indicates that reduced stroke rates at 1 year with TAVR versus surgery (p = 0.03) were diminished at 2 years, such that there were no longer significant differences between TAVR and surgery (p = 0.28). **(C)** Re-hospitalizations: This time-to-event analysis of re-hospitalizations showed a reduced rate with TAVR versus surgery at both 1 year (p = 0.04) and 2 years p = 0.046) follow-up. CI = confidence interval; HR = hazard ratio; other abbreviation as in Figure 1.

FIGURE 3 Echocardiography: Hemodynamic Findings Through 2 Years



The data are represented as density distribution plots with indications of the mean values **(circles)**, median values **(solid lines)**, and 75% and 25% quartile values **(dashed lines)** for patients who underwent TAVR **(blue)** and surgery **(red)**. **(A)** Mean gradients: the results indicate a dramatic and similar reduction in mean gradients from baseline to 1 year for both TAVR and surgery groups, which was maintained at 2 years. **(B)** Effective orifice areas: the results indicate a dramatic and similar increase in mean effective orifice areas from baseline to 1 year for both TAVR and surgery groups, which was maintained at 2 years. Abbreviation as in **Figure 1**.

and 2 years in patients who underwent TAVR (Supplemental Table 8). Bleeding events possibly related to anticoagulation in patients with valve thrombosis occurred in 2 patients who underwent TAVR (Supplemental Table 8).

FUNCTIONAL STATUS AND HEALTH OUTCOME MEASURES. New York Heart Association functional class and disease-specific health status, assessed by the KCCQ-OS, was substantially improved from baseline in both groups (Supplemental Figures 2 and 3). Between-group comparisons demonstrated a small, but statistically significant difference in the KCCQ-OS at 2 years. Finally, when changes in the KCCQ-OS were analyzed as an ordinal categorical variable that incorporated mortality as the worst outcome, TAVR outcomes were superior to surgery at 1 month and at 1 and 2 years (**Central Illustration**).

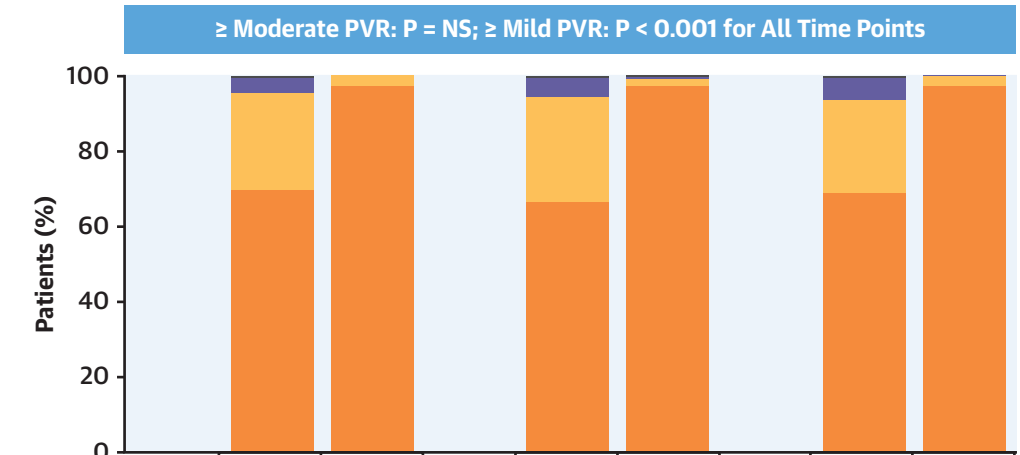
ECHOCARDIOGRAPHY FINDINGS. Hemodynamic findings and LV function changes showed small changes from 1 to 2 years (**Figure 3**, Supplemental Table 9). At 2 years, the mean gradients were slightly higher after TAVR versus surgery (13.6 ± 5.53 vs. 11.8 ± 4.82; $p = 0.06$) and effective orifice areas were similar with TAVR versus surgery (1.7 ± 0.37 vs. 1.7 ± 0.42; $p = 0.34$). At 2 years, there were still important differences in mild and mild to moderate paravalvular regurgitation (PVR) favoring surgery, but there were no differences in moderate or greater PVR (**Figure 4**).

Moderate or severe HVD and BVF were infrequent, and there were no differences between TAVR and surgery through 2 years (**Figure 5**).

DISCUSSION

An abundance of clinical evidence has supported the appropriate use of TAVR as an important new therapy in patients with symptomatic severe AS. The primary endpoints of the clinical trials were meant to establish initial safety and efficacy through 1 or 2 years (1-7). There have been many ≥5-year follow-up reports in patients with extreme, high, and intermediate surgical risk, treated with either balloon-expandable or self-expanding TAVR (8-12). These studies have provided reassurance that the early favorable clinical and hemodynamic outcomes after TAVR are sustained and comparable to surgery (8,10-12). Lower surgical risk and younger patients, like those enrolled in the PARTNER 3 trial, represent the most challenging cohort, because actuarial life expectancy stresses the limits of bioprosthetic valve durability, rendering patients more likely candidates for multiple valve replacement procedures during a lifetime with aortic valve disease. Therefore, the assiduous reporting of clinical and echocardiography

FIGURE 4 **Echocardiography: PVR Through 2 Years**



	30 Days		1 Year		2 Years	
	TAVR N = 487	Surgery N = 421	TAVR N = 470	Surgery N = 382	TAVR N = 431	Surgery N = 354
Severe	0	0	0	0	0	0
Moderate-Severe	0.2	0	0.2	0	0	0
Moderate	0.6	0	0.6	0.5	0.5	0
Mild-Moderate	3.7	0	5.1	0.3	6.0	0.3
Mild	25.1	2.9	24.3	1.8	20.0	2.0
None/Trace	70.4	97.1	69.8	97.4	73.5	97.7

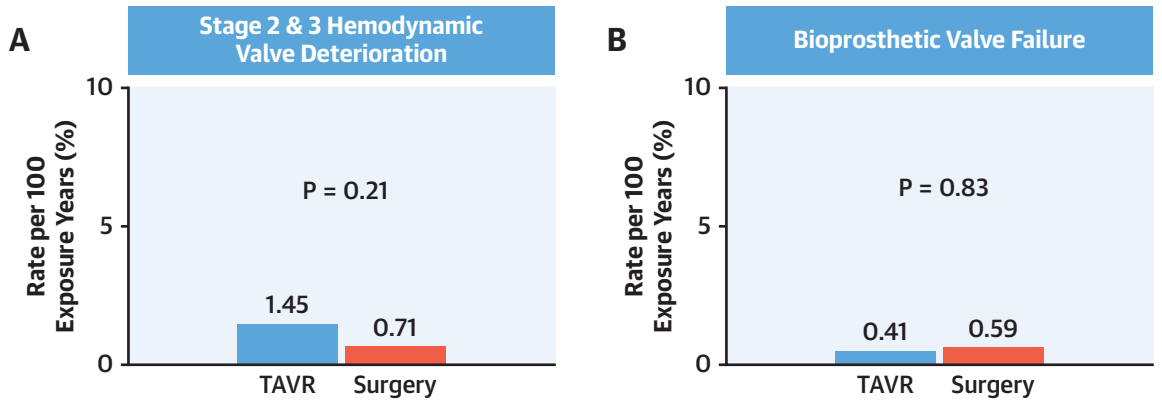
The data are represented as stacked bars for TAVR and surgery at 30 days and at 1- and 2-year follow-up. Each stacked bar includes 100% of patients with evaluable echos and are divided into the 6 categories of paravalvular regurgitation (PVR) which are color-coded: none-trace, mild, mild-moderate, moderate, moderate-severe, and severe. The results indicate no changes in moderate or greater PVR between surgery and TAVR for all time points but a highly significant difference for mild or greater PVR favoring less PVR for surgery versus TAVR ($p < 0.001$) for all time points. Abbreviation as in Figure 1.

follow-up beyond the initial assigned primary endpoint is mandatory in the low-risk TAVR trials.

The main findings from the 2-year follow-up of PARTNER 3 can be summarized as follows: 1) the primary endpoint was significantly reduced by 37% after TAVR compared with surgery; 2) death from all causes and strokes were more frequent with TAVR between 1 and 2 years, such that cumulative event rates through 2 years were similar to surgery; 3) valve thrombosis was more frequent after TAVR versus surgery through 2 years and was associated with an increase in aortic valve gradients in 54% of TAVR cases; 4) a categorical analysis of health outcomes incorporating survival and health status indicated significant benefits with TAVR compared with surgery through 2 years; 5) echocardiography findings were similar at 1 and 2 years, with no differences in moderate or severe PVR, but surgery continued to show less mild PVR; and 6) VARC-3 endpoint assessment of bioprosthetic valve durability indicated infrequent HVD at 2 years with no significant differences in patients who underwent TAVR versus patients who underwent surgery.

The overall composite primary endpoint continued to favor TAVR at 2 years, largely due to a continued higher rate of cardiovascular re-hospitalization events after surgery, which usually occurred within 6 months of the procedure. Death and stroke were more frequent with TAVR between 1 and 2 years, although cumulative rates remained lower with TAVR. The excess deaths between 1 and 2 years were largely due to higher noncardiovascular mortality in patients who underwent TAVR, and the excess strokes included 3 disabling strokes, 2 of which occurred in patients after a diagnosis of valve thrombosis. In other TAVR versus surgery randomized trials with >1-year follow-up (11,12,16), there were consistent trends of reduced TAVR mortality during the first year that diminished in subsequent years, resulting in similar long-term cumulative mortality. It is possible that more vulnerable patients had earlier mortality with surgery and later delayed

FIGURE 5 **HVD and BVF Through 2 Years**



Bioprosthetic valve durability was adjudicated by a group of 3 experts and determined using the Valve Academic Research Consortium (VARC 3) criteria for hemodynamic valve deterioration (HVD) and bioprosthetic valve failure (BVF). HVD stage 2 (or moderate) was defined as an increase in the mean gradient of ≥10 mm Hg and <20 mm Hg, with a final mean gradient of ≥20 mm Hg and any of: 1) a decrease in aortic valve area ≥0.3 cm^2 or ≥ 25%; and 2) a decrease in the Doppler velocity index (DVI) ≥0.1 or ≥20%; and/or ≥1 grade new-onset or worsening transvalvular aortic regurgitation with a final grade of moderate or more. HVD stage 3 (or severe) required an increase in the mean gradient of ≥20 mm Hg with a final mean gradient of ≥30 mm Hg and any of: 1) decrease in aortic valve area ≥0.6 cm^2 or ≥50%; and 2) decrease in DVI ≥0.2 or ≥40%; and/or ≥2 grades of new-onset or worsening transvalvular aortic regurgitation with a final grade of severe. BVF was defined according to recently published VARC-3 standardized definitions: 1) stage 3 (severe) HVD related to permanent structural changes to the prosthetic valve; or 2) valve re-intervention or death related to valve dysfunction. The exposure-adjusted cumulative rate was defined as the number of subjects exposed to the device (i.e., the aortic bioprosthetic valve) and who experienced an event (HVD or BVF) divided by the total exposure time of all patients who were at risk of an event and is expressed per 100 patient-years. **(A)** HVD: compares TAVR **(blue)** versus surgery **(red)** through 2 years and indicates no significant differences between the groups; **(B)** BVF compares TAVR **(blue)** versus surgery **(red)** through 2 years and indicates no significant differences between the groups. Abbreviation as in Figure 1.

events with less invasive TAVR. Alternatively, more frequent coronary revascularization in patients with concomitant coronary disease in the surgery cohort compared with the TAVR cohort might have resulted in fewer late deaths.

The concepts of clinical valve thrombosis and subclinical valve leaflet thickening after bioprosthetic valve implantation are controversial and rapidly evolving (14,16,24-31). In PARTNER 3, the VARC-2 definitions of valve thrombosis were applied (7,19). Clinical events committee adjudication of valve thrombosis according to this definition required the appearance of valve-related thrombus during imaging assessments (echocardiography or CT) that either interfered with valve function or warranted treatment (anticoagulation or valve explantation). Among the 16 valve thrombosis cases through 2 years (13 TAVR and 3 surgery), 63% occurred between 1 and 2 years, and all had evidence of thrombus confirmed on imaging studies. In addition, 7 patients had >10 mm Hg increases in aortic valve gradients, and 7 were treated with anticoagulation therapy. Importantly, 75% of the patients with clinical events committee–adjudicated valve thrombosis were without symptoms, and the diagnosis was driven by interval-mandated echocardiograms that showed hemodynamic changes, often followed by CT studies that detected hypoattenuated leaflet thickening and restricted leaflet motion. Moreover, embedded within the PARTNER 3 trial was a serial CT substudy requested by the U.S. Food and Drug Administration (30) for the purpose of studying the natural history and consequences of CT abnormalities after TAVR and surgery. Clearly, there was a heightened awareness in PARTNER 3 on identifying serial aortic valve gradient changes on echocardiograms, which resulted in more frequent CT studies in asymptomatic patients and might have inflated the frequency of valve thrombosis events. The VARC-3 consensus document (14), currently in press, attempted to address these issues by separating clinically significant valve thrombosis from valve leaflet thickening and reduced leaflet motion detected on imaging, with revised definitions for both entities. Thus, although a greater number of valve thrombosis cases were seen after TAVR compared with surgery, most were not associated with clinical events. The consequences of clinically silent small increases in aortic valve gradients remains uncertain.

TABLE 2 Key Secondary Endpoints

	KM Rate at 1 Year			KM Rate at 2 Years		
	TAVR (n = 496)	SAVR (n = 454)	p Value	TAVR (n = 496)	SAVR (n = 454)	p Value
MI	6 (1.2)	10 (2.2)	0.23	9 (1.8)	12 (2.7)	0.36
New-onset atrial fibrillation	30 (7.2)	150 (40.9)	<0.001	33 (7.9)	153 (41.8)	<0.001
New PPM (excluding baseline)	38 (7.9)	25 (5.8)	0.18	44 (9.1)	30 (7.0)	0.21
New PPM (including baseline)	38 (7.7)	25 (5.6)	0.18	44 (8.9)	30 (6.8)	0.20
New LBBB (excluding baseline)	98 (20.4)	35 (8.0)	<0.001	100 (20.8)	42 (9.7)	<0.001
New LBBB (including baseline)	98 (19.8)	35 (7.7)	<0.001	100 (20.2)	42 (9.4)	<0.001
Coronary obstruction	1 (0.2)	3 (0.7)	0.28	1 (0.2)	3 (0.7)	0.28
AV re-intervention	3 (0.6)	2 (0.5)	0.76	4 (0.8)	4 (0.9)	0.85
Endocarditis	1 (0.2)	2 (0.5)	0.49	1 (0.2)	4 (0.9)	0.13
Valve thrombosis*	5 (1.0)	1 (0.2)	0.13	13 (2.6)	3 (0.7)	0.02

Values are n (%) according to KM estimate. The p values are based on the log-rank test. *Valve thrombosis according to Valve Academic Research Consortium (VARC 2) definition (thrombus associated with an implanted valve that interferes with valve function or warrants treatment [e.g., anticoagulation or explantation]).

LBBB = left bundle branch block; MI = myocardial infarction; PPM = permanent pacemaker; other abbreviations as in Table 1.

Health status is especially relevant in younger lower risk patients, and a comprehensive analysis of PARTNER 3 health status results through 1 year was recently reported (22). Despite relatively high KCCQ-OS scores at baseline, both TAVR and surgery led to substantial improvement by 1 year, which was sustained at 2 years. Moreover, even at 2-year follow-up, disease-specific health status was better after TAVR than surgery. A comprehensive analysis of serial echocardiographic findings in PARTNER 3 through 1 year was also recently published (32). Extending the echocardiography follow-up assessments to 2 years demonstrated no significant interval changes; mean transvalvular gradients trended slightly higher after TAVR, effective orifice areas were similar in both groups, greater than moderate PVR was rare, and similar in both groups, and mild PVR was lower after surgery. Using the 5-class PVR grading scheme, most of PVR falling between the moderate and none or trace categories was mild and not mild to moderate PVR (Figure 4). The 1.8 mm Hg higher mean gradients after TAVR compared with surgery in PARTNER 3 at 2 years was probably multifactorial. First, the surgical valve size distribution in PARTNER 3 demonstrated larger implanted valves compared with previous PARTNER trials, which was most likely driven by trial-specific guidance to the surgical operators. Second, the LV stroke volume index was significantly greater after TAVR versus surgery (32), which might partially account for the observed differences in gradients. Differences in echo imaging and pressure recovery of transcatheter versus surgical valves might have been contributed to small systematic differences in gradient measurements (32,33). Finally, an increased stroke volume and gradient might have been seen in the presence of mild aortic regurgitation without affecting the calculation for aortic valve area by the continuity equation. The calculated aortic valve areas for TAVR and surgical valves were not significantly different in this study. The robust obliteration of significant PVR after TAVR with the SAPIEN 3 valve persisted through 2 years in PARTNER 3. Only 2 of 431 patients who underwent TAVR had moderate PVR, and no patient had either moderate to severe or severe PVR. These results most likely reflected a combination of improved valve sizing with CT guidance and enhanced efficacy of the external cuff in providing flush apposition of the valve with the aortic valvar complex. The long-term consequences, if any, of the higher rate of mild PVR with TAVR remain to be determined; mild PVR has not been associated with clinical sequelae at 2 years.

TABLE 3 Valve Thrombosis Hemodynamic Changes

	TAVR (n = 496)	Surgery (n = 454)	p Value
Valve thrombosis*	13 (2.6)	3 (0.7)	0.02
Mean gradient >20 mm Hg and increase >10 mm Hg	7 (53.8)	0 (0)	
Mean gradient >20 mm Hg and increase <10 mm Hg	4 (30.7)	3 (100.0)	
Increased transvalvular AR (mild) with no change in mean gradient	1 (7.7)	0 (0)	
CT findings (thrombus) with no change in hemodynamics	1 (7.7)	0 (0)	

Values are n (%). *Clinical events committee–adjudicated valve thrombosis per VARC 2 (all patients received anticoagulation). The p value is based on the log-rank test.

AR = aortic regurgitation; CT = computed tomography; other abbreviations as in Tables 1 and 2.

The area of greatest controversy and uncertainty concerning expanded use of TAVR in low-risk and younger patients relates to the possibility of reduced

durability of transcatheter bioprosthetic valves (34). PARTNER 3 adopted the VARC-3 revised definitions of HVD and BVF for both TAVR and surgery, which had been applied to 5-year serial echocardiographic follow-up in the PARTNER 2A trial and in the SAPIEN 3 registry (both intermediate-risk studies) (12,16,35). These analyses with 5-year echo follow-up discerned differences in echo-derived hemodynamics in specific TAVR systems versus surgical valves before changes in symptoms or the appearance of clinical events (16,35). The more rigorous standardized definitions were applied to PARTNER 3 low-risk patients though 2 years, and thus far, we have not observed differences in moderate or severe HVD or BVF comparing SAPIEN 3 TAVR with surgery.

STUDY LIMITATIONS. The main limitations of this study were described previously (7). This report was intended to focus on interval clinical events and echocardiographic findings between 1 and 2 years; major outcomes associated with valve durability are not expected to occur until at least 5 years after the index procedure. Clearly, ongoing assessment of clinical and echocardiographic findings is needed in younger and low-risk patients and planned follow-up in PARTNER 3 will continue through at least 10 years. It should be emphasized that because PARTNER 3 excluded patients with specific anatomic features suboptimal for TAVR, bicuspid aortic valve disease, and patients without acceptable transfemoral access, the reported results cannot be generalized to all patients and apply only to the enrolled study population. Trial logistic issues, including disproportionate study withdrawal in the surgery cohort and missing follow-up data or lack of formal adjudication of some secondary endpoints are study limitations being managed with sensitivity analyses and other statistical adjustments.

A concern regarding PARTNER 3 (7) was the appropriateness of making practice-changing recommendations based upon a single randomized trial not powered to address individual clinical endpoints and without long-term follow-up (36). The response to this suggested limitation is the following. First, there has been more than a decade of PARTNER randomized trials and registries in progressively lower surgical risk strata, beginning with patients who were not candidates for surgery and concluding with the present PARTNER 3 low-risk trial. In these studies, which involved 3 generations of balloon-expandable transcatheter valves and approximately 10,000 patients, the hard clinical endpoints of all-cause mortality and stroke were consistently noninferior to surgery, with approximately one-half of the patients already reaching ≥5 year follow-up (1,2,4,8,9,12,16,17,35). Second, there were a total of 3,661 patients who were low risk for surgery in 4 randomized trials that used both balloon-expandable and self-expanding TAVR systems (6,7,11,37), and the primary endpoint outcomes (mortality and stroke) again consistently showed that TAVR was either superior or noninferior to surgery. Third, the restricted mean survival time in this study favored TAVR (670 days vs. 622 days; $p < 0.001$) at 2 years. Finally, there have been numerous surgical aortic valves, including the current generation of suture-less valves (38–40), which are being widely used in clinical practice with less rigorous serial echocardiography and clinical durability assessments.

CONCLUSIONS

The 2-year follow-up from the PARTNER 3 low-risk trial showed continued superiority of the primary endpoint favoring TAVR versus surgery, but more frequent deaths, strokes, and valve thrombosis events in the TAVR group between 1 and 2 years. Disease-specific health status at 2 years was better after TAVR than surgery. Echocardiographic findings through 2 years indicated stable valve hemodynamics and no differences in valve durability parameters.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with surgical aortic valve replacement in low-risk patients, balloon-expandable TAVR was associated with a lower incidence of the composite endpoint of death, stroke, or rehospitalization at 2 years, but between 1 and 2 years after TAVR, there were more deaths, strokes, and episodes of valve thrombosis.

TRANSLATIONAL OUTLOOK: Longer-term follow-up is needed to determine the value of TAVR as an alternative to surgery in patients with aortic stenosis.

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

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