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ORIGINAL INVESTIGATIONS

# 3-Year Outcomes After Valve-in-Valve Transcatheter Aortic Valve Replacement for Degenerated Bioprostheses

## The PARTNER 2 Registry

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ABSTRACT

**BACKGROUND** Transcatheter aortic valve replacement (TAVR) for degenerated surgical bioprosthetic aortic valves is associated with favorable early outcomes. However, little is known about the durability and longer-term outcomes associated with this therapy.

**OBJECTIVES** The aim of this study was to examine late outcomes after valve-in-valve TAVR.

**METHODS** Patients with symptomatic degeneration of surgical aortic bioprostheses at high risk (≥50% major morbidity or mortality) for reoperative surgery were prospectively enrolled in the multicenter PARTNER (Placement of Aortic Transcatheter Valves) 2 valve-in-valve and continued access registries. Three-year clinical and echocardiographic follow-up was obtained.

**RESULTS** Valve-in-valve procedures were performed in 365 patients. The mean age was 78.9 ± 10.2 years, and the mean Society of Thoracic Surgeons score was 9.1 ± 4.7%. At 3 years, the overall Kaplan-Meier estimate of all-cause mortality was 32.7%. Aortic valve re-replacement was required in 1.9%. Mean transaortic gradient was 35.0 mm Hg at baseline, decreasing to 17.8 mm Hg at 30-day follow-up and 16.6 mm Hg at 3-year follow-up. Baseline effective orifice area was 0.93 $cm^2$, increasing to 1.13 and 1.15 $cm^2$ at 30 days and 3 years, respectively. Moderate to severe aortic regurgitation was reduced from 45.1% at pre-TAVR baseline to 2.5% at 3 years. Importantly, moderate or severe mitral and tricuspid regurgitation also decreased (33.7% vs. 8.6% [$p < 0.0001$] and 29.7% vs. 18.8% [$p = 0.002$], respectively). Baseline left ventricular ejection fraction was 50.7%, increasing to 54.7% at 3 years ($p < 0.0001$), while left ventricular mass index was 136.4 $g/m^2$, decreasing to 109.1 $g/m^2$ at 3 years ($p < 0.0001$). New York Heart Association functional class improved, with 90.4% in class III or IV at baseline and 14.1% at 3 years ($p < 0.0001$), and Kansas City Cardiomyopathy Questionnaire overall score increased (43.1 to 73.1; $p < 0.0001$).

**CONCLUSIONS** At 3-year follow-up, TAVR for bioprosthetic aortic valve failure was associated with favorable survival, sustained improved hemodynamic status, and excellent functional and quality-of-life outcomes. (The PARTNER II Trial: Placement of Aortic Transcatheter Valves II - PARTNER II - Nested Registry 3/Valve-in-Valve [PII NR3/ViV]; NCT03225001) (J Am Coll Cardiol 2019;73:2647–55) © 2019 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**EOA** = effective orifice area

**STS** = Society of Thoracic Surgeons

**TAVR** = transcatheter aortic valve replacement

**THV** = transcatheter heart valve

**VIV** = valve-in-valve

Early experience with transcatheter aortic valve replacement (TAVR) within failed bioprosthetic surgical aortic valves has shown that valve-in-valve (VIV) TAVR is a feasible therapeutic option with acceptable acute procedural results (1-4). The PARTNER 2 (Placement of Aortic Transcatheter Valves) VIV and continued access registries examined 30-day and 1-year outcomes in a large cohort of patients at high-risk for reoperative surgery (1). At 30 days and 1 year, VIV TAVR was associated with relatively low rates of mortality and major complications, improved hemodynamic status, and excellent improvement in functional and quality-of-life outcomes. Few studies have reported VIV TAVR outcomes beyond 1 year (5).

SEE PAGE 2656

## METHODS

The PARTNER 2 trial was a prospective, multicenter study that enrolled patients with severe aortic stenosis. This study included a nested registry of patients with degenerated surgical aortic bioprostheses who were at high surgical risk (mortality or major morbidity 50%). Following the enrollment of a maximum of 100 patients in the nested registry, additional patients were enrolled in a continued access registry. The trial was approved by the Institutional Review Boards of all participating sites, and written, informed consent was provided by all patients.

Patients were required to have symptomatic severe dysfunction of a bioprosthesis suitable for VIV treatment with either a 23-mm or a 26-mm SAPIEN XT transcatheter heart valve (THV) (Edwards Lifesciences, Irvine, California). The diagnosis of severe dysfunction required the presence of severe stenosis, severe regurgitation, or the combination of at least moderate stenosis and at least moderate regurgitation by standard echocardiographic criteria. Key exclusion criteria included a bioprosthetic valve with a labeled size <21 mm. The THV used consisted of a balloon-expandable cobalt chromium frame with bovine pericardial leaflets and a polyethylene terephthalate internal seal.

**TABLE 1 Kaplan-Meier Estimate of Events at 3 Years**

| | |
|---|---|
| Composite endpoints | |
| Death or stroke | 35.6 (125) |
| Death | |
| All-cause | 32.7 (114) |
| Cardiovascular | 20.5 (69) |
| Noncardiovascular | 15.4 (45) |
| Neurological event | |
| Stroke or TIA | 7.8 (26) |
| Stroke | 6.2 (21) |
| TIA | 3.0 (9) |
| Repeat aortic valve replacement | |
| Any | 1.9 (5) |

Values are % (n).
TIA = transient ischemic attack.

Clinical assessments were performed at baseline and at all subsequent follow-up time points (baseline, discharge, 30 days, 1 year, 2 years, and 3 years). Serial echocardiograms were analyzed independently by a core laboratory. Outcomes up to the 1-year protocol-specified primary endpoint were adjudicated by an independent clinical events committee, and those beyond 1 year were site reported.

The primary endpoint for the present analysis was all-cause mortality at 3 years. Secondary endpoints included cardiac mortality, stroke, aortic valve reintervention, major vascular complications, acute kidney injury (Valve Academic Research Consortium-2 criteria), new permanent pacemaker, myocardial infarction, hemodynamic valve deterioration, as defined in a 2018 consensus document (6) and clinical alleviation of symptoms, as assessed by New York Heart Association functional status, and quality of life (Kansas City Cardiomyopathy Questionnaire). Endpoints are defined in Online Table 1.

The statistical analysis was based on a valve implantation population that included all patients who underwent treatment with the study device. All statistical tests were carried out at a 2-sided 0.05 level of significance, and all p values are presented as 2-sided p values. Continuous variables are expressed as mean ± SD and were compared using the Student's *t*-test. Categorical variables are reported as percentage and were compared using the chi-square test or

for Edwards Lifesciences. Dr. Herrmann has received grants from and is a consultant for Edwards Lifesciences. Dr. Blanke is a consultant for Edwards Lifesciences. Drs. Blanke and Leipsic provide computed tomographic core laboratory services for Edwards Lifesciences. Dr. Pibarot provides echocardiography core laboratory services for Edwards Lifesciences. Dr. Kodali has received grants from Edwards Lifesciences; and is a member of the PARTNER trial executive committee. Drs. Miller and Leon are members of the PARTNER trial executive committee. Dr. Wood has served as a consultant to Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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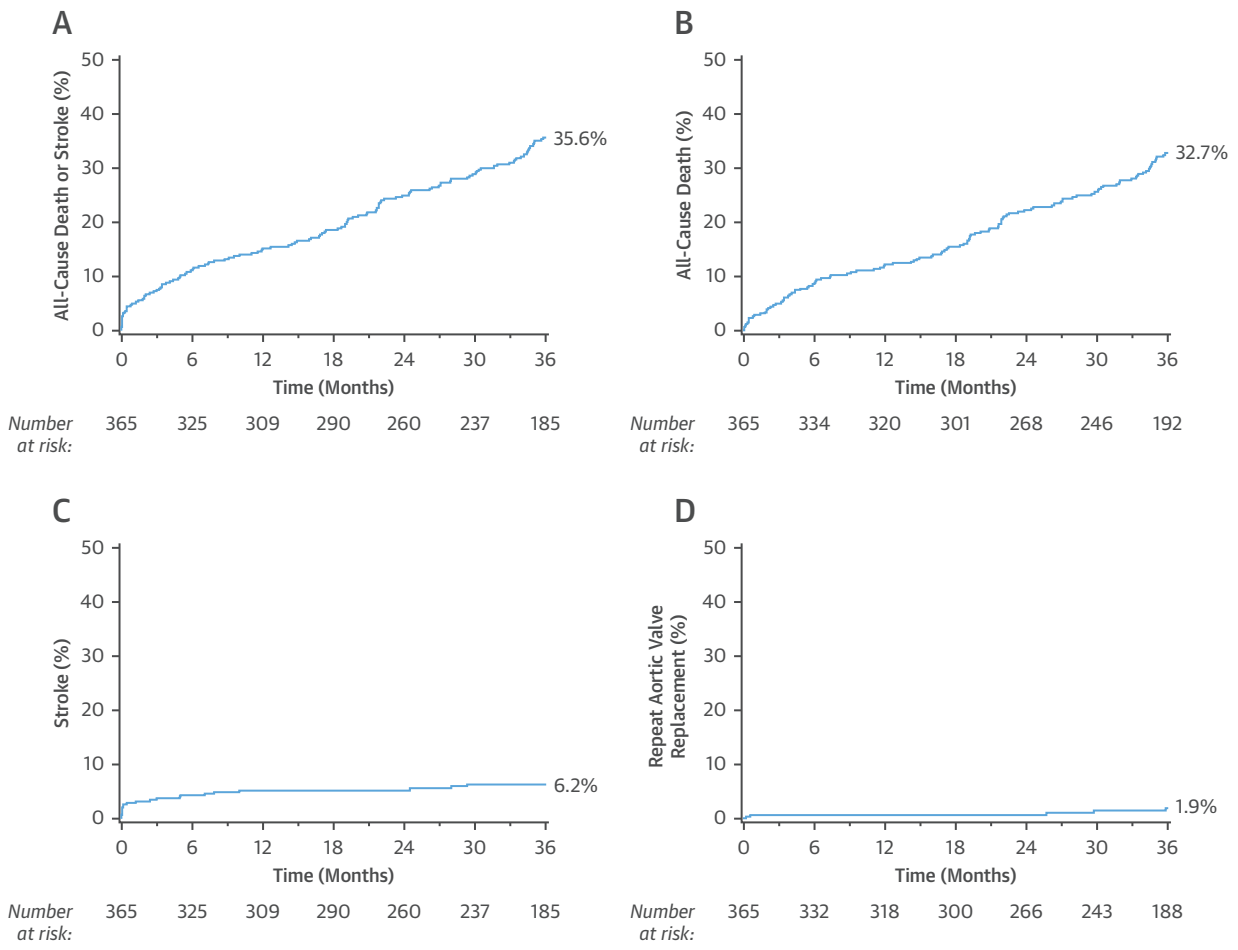
**FIGURE 1 Kaplan-Meier Time-to-Event Rates**



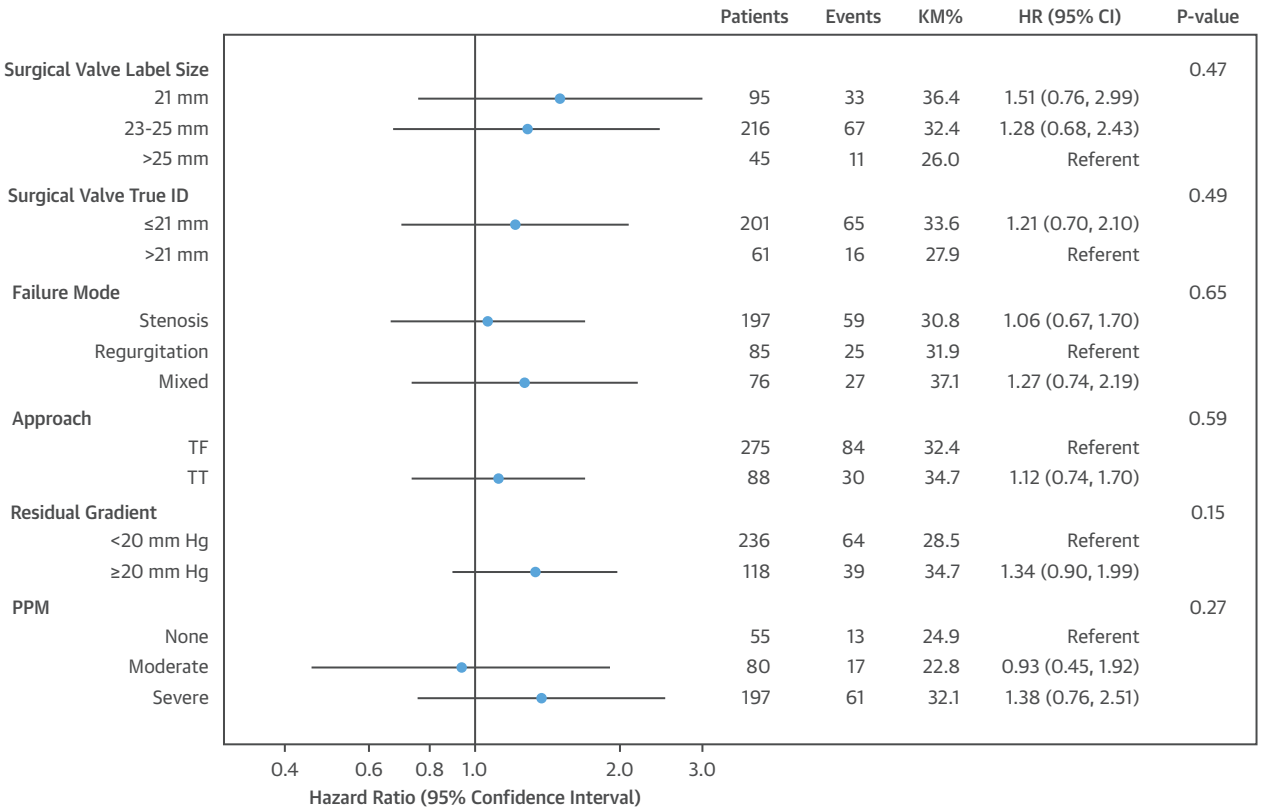

Curves depict Kaplan-Meier time-to-event rates for **(A)** all-cause mortality or any stroke, **(B)** all-cause mortality, **(C)** stroke, and **(D)** repeat aortic valve replacement.

Fisher exact test as appropriate. Clinical outcomes were summarized using Kaplan-Meier event rates and visualized using cumulative incidence curves. A multivariate Cox proportional hazards regression model was used to assess the adjusted association between mortality and risk factors (Society of Thoracic Surgeons [STS] score, mode of valve failure, access route, surgical valve size, and moderate or severe prosthesis-patient mismatch). Longitudinal outcomes were modeled using a linear mixed-effects model, which included data from all available time points (baseline, discharge/30 days, 1 year, 2 years, and 3 years). The analyses included time as a fixed effect and patient as a random effect to adjust for repeated measures within each patient. These models are more robust than simple paired analyses to missing data because of loss to follow-up and mortality. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, North Carolina).

## RESULTS

Between June 2012 and December 2014, 365 patients underwent VIV procedures at 34 sites (96 initial registry, 269 continued access patients). Baseline characteristics have been previously reported (1). Briefly, mean age was 78.9 ± 10.2 years, mean STS score was 9.1 ± 4.7%, 64.1% were men, and 90.4% were in New York Heart Association functional class III or IV. Comorbidities included prior percutaneous coronary intervention or coronary artery bypass graft in 57.3%, atrial fibrillation in 46.8%, pulmonary disease in 43%,

**FIGURE 2 Subgroup Analyses of All-Cause Mortality to 3 Years**




Shown are the rates of all-cause mortality during 3-year follow-up within various subgroups. The **blue dots** represent the hazard ratio, and **horizontal lines** are corresponding 95% confidence intervals; p values compare event rates between the subgroups on the basis of the log-rank test. ID = internal diameter; KM = Kaplan Meier; PPM = patient-prosthesis mismatch; TF = transfemoral; TT = transthoracic.

prior or current cancer in 40.3%, diabetes in 31.2%, frailty in 26.6%, renal insufficiency in 12.3%, prior stroke in 12.1%, hostile chest in 11.8%, and liver disease in 7.4%. Access was transfemoral in 75.8% and either transapical or direct aortic in 24.2%.

Initial registry patients, compared with continued access, had similar STS scores but higher mean logistic European System for Cardiac Operative Risk Evaluation scores (15.7 vs. 11.1; p = 0.002) and were more often frail (37.5% vs. 22.8%; p = 0.005). There were no other significant differences.

**OUTCOMES AT 3 YEARS.** Three-year clinical outcomes are shown in Table 1 and Figure 1. Follow-up at 3 years was complete in 337 patients (92.3%), while 28 patients (7.7%) were either withdrawn from the study or were lost to follow-up at 3 years. The overall 3-year Kaplan-Meier estimate of mortality was 32.7%, of cardiac mortality was 20.5%, of stroke was 6.2%, and of repeat aortic valve replacement was 1.9%.

**PREDICTORS OF 3-YEAR MORTALITY.** At 3-year follow-up, no increased mortality was observed in patients stratified according to mode of valve failure, access route, 21-mm versus >21-mm surgical valve, or moderate or severe prosthesis-patient mismatch (Figure 2). Multivariate analyses adjusting for these variables and baseline STS risk score revealed no significant associations with 3-year mortality.

**REPEAT AORTIC VALVE REPLACEMENT.** There were 5 repeat aortic valve replacements (1.9%) for aortic valve dysfunction at a median of 783 days post-VIV TAVR. Four patients were treated with redo surgery and 1 with repeat VIV TAVR for stenosis. No patients died within 30 days of reintervention.

**ECHOCARDIOGRAPHIC FOLLOW-UP AT 3 YEARS.** Three-year echocardiographic follow-up is shown in Table 2 and Figures 3 and 4. There were 158 patients with evaluable echocardiograms at 3-year follow-up. At 3 years, the mean gradient was 16.6 ± 9.0 mm Hg, mean effective orifice area (EOA) was

**TABLE 2 Echocardiographic Outcomes**

| | Baseline (n = 350) | Discharge/30 Days (n = 347) | 1 Year (n = 262) | 2 Years (n = 217) | 3 Years (n = 158) | Difference, 3 Years vs. Baseline (95% CI) | p Value* |
|---|---|---|---|---|---|---|---|
| EOA, $cm^2$ | 0.93 ± 0.43 | 1.17 ± 0.39 | 1.15 ± 0.41 | 1.11 ± 0.38 | 1.15 ± 0.42 | 0.22 (0.16 to 0.28) | <0.0001 |
| EOA index, $cm^2/m^2$ | 0.49 ± 0.21 | 0.62 ± 0.21 | 0.59 ± 0.21 | 0.58 ± 0.19 | 0.60 ± 0.24 | 0.12 (0.09 to 0.15) | <0.0001 |
| Mean gradient, mm Hg | 35.0 ± 15.6 | 17.7 ± 7.8 | 17.8 ± 7.9 | 17.5 ± 7.7 | 16.6 ± 9.0 | −18.81 (−20.49 to −17.13) | <0.0001 |
| LVEF, % | 50.7 ± 13.1 | 49.3 ± 13.1 | 53.8 ± 11.3 | 53.4 ± 11.7 | 54.7 ± 11.1 | 4.64 (2.64 to 6.64) | 0.0001 |
| LV mass, g | 263.2 ± 82.5 | 255.9 ± 78.7 | 228.2 ± 77.3 | 227.5 ± 82.1 | 211.3 ± 65.0 | −51.01 (−59.37 to −42.65) | <0.0001 |
| LV mass index, $g/m^2$ | 136.4 ± 37.4 | 132.5 ± 35.7 | 118.0 ± 33.3 | 116.7 ± 36.5 | 109.1 ± 28.2 | −26.76 (−31.08 to −22.44) | <0.0001 |
| Total AR | | | | | | | |
| None to mild | 54.9 (192/350) | 97.1 (337/347) | 98.1 (257/262) | 99.1 (215/217) | 97.5 (154/158) | NA | NA |
| Moderate | 28.9 (101/350) | 2.3 (8/347) | 1.9 (5/262) | 0.9 (2/217) | 2.5 (4/158) | NA | NA |
| Severe | 16.3 (57/350) | 0.6 (2/347) | 0.0 (0/262) | 0.0 (0/217) | 0.0 (0/158) | NA | NA |
| Moderate or severe | 45.1 (158/350) | 2.9 (10/347) | 1.9 (5/262) | 0.9 (2/217) | 2.5 (4/158) | NA | NA |
| MR and TR | | | | | | | |
| Moderate or severe MR | 33.7 (115/341) | 17.2 (59/343) | 11.2 (28/251) | 10.4 (22/212) | 8.6 (13/152) | NA | <0.0001 |
| Moderate or severe TR | 29.7 (94/316) | 21.8 (74/340) | 16.7 (41/245) | 14.2 (29/204) | 18.8 (28/149) | NA | 0.002 |

Values are mean ± SD or % (n/N), unless otherwise indicated. *Echocardiographic parameters were modeled using a linear mixed-effects model. All available data from baseline, discharge/30 days, 1 year, 2 years, and 3 years are included in the model for robust estimation. Mean differences are estimated and comparisons are performed using the mixed model. These models are superior to paired analyses when the amount of missing data due to mortality or loss to follow-up is appreciable. Change over time.

AR = aortic regurgitation; CI = confidence interval; EOA = effective orifice area; LV = left ventricular; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NA = not applicable; TR = tricuspid regurgitation.

1.15 ± 0.42 $cm^2$, and mean indexed EOA was 0.60 ± 0.24 $cm^2/m^2$. When 30-day and 3-year echocardiographic data were compared using linear mixed-effects models, no significant differences in mean EOA (1.17 $cm^2$ vs. 1.15 $cm^2$; p = 0.45) or mean gradient (17.7 mm Hg vs. 16.6 mm Hg; p = 0.13) were seen. At 3 years, total aortic regurgitation was less than mild in 97.5% and moderate in 2.5%. No patients had severe aortic regurgitation.

Stage 2 (moderate) hemodynamic valve deterioration occurred in 2 of 160 patients (1.3%), and stage 3 (severe) hemodynamic valve deterioration also occurred in 2 of 160 patients (1.3%) at 3 years. Mean left ventricular ejection fraction by the Simpson biplane method increased from 50.7 ± 13.1% at baseline to 54.7 ± 11.1% at 3 years (p < 0.0001). Overall, mean left ventricular mass index decreased from 136.4 ± 37.4 $g/m^2$ at baseline to 125.0 ± 34.0 $g/m^2$ at 30 days and 109.1 ± 28.2 $g/m^2$ at 3 years (p < 0.0001). From baseline to 3 years, the rates of moderate or severe mitral (33.7% vs. 8.6%; p < 0.0001) and tricuspid regurgitation (29.7% vs. 18.8%; p = 0.002) both decreased.

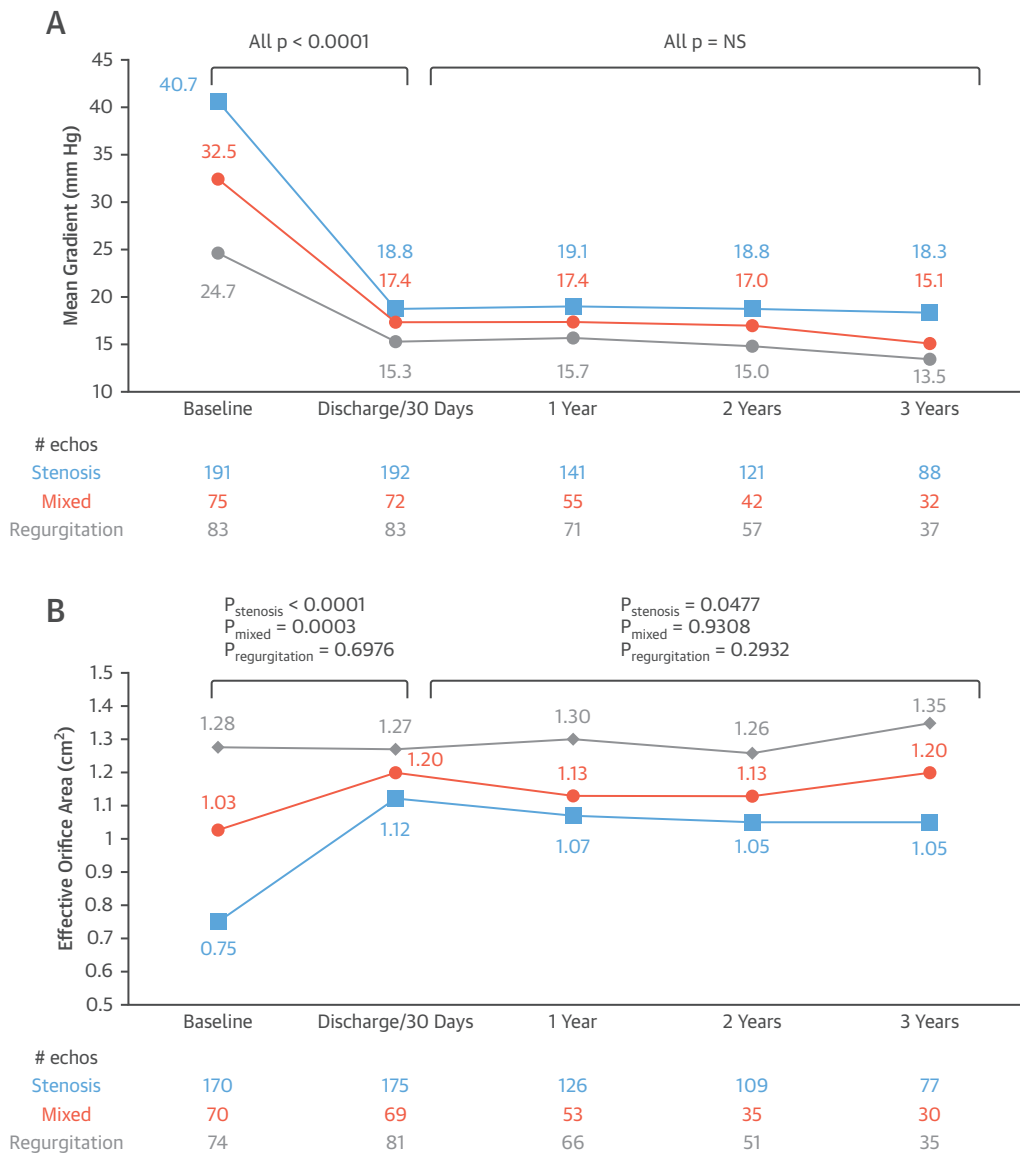
**SYMPTOMS, FUNCTION, AND QUALITY-OF-LIFE OUTCOMES.** Three-year outcomes are shown in the Central Illustration. Patient symptoms decreased from baseline to 30-day, 1-year, 2-year, and 3-year follow-up. At baseline, 90.4% of patients were in New York Heart Association functional class III or IV, decreasing to 10.4% at 30 days (p < 0.0001) and remaining similar thereafter (11.6%, 13.0%, and 14.1% at 1, 2, and 3 years, respectively). The mean overall summary Kansas City Cardiomyopathy Questionnaire score was 43.0 ± 22.0 at baseline, increasing to 70.8 ± 22.9 at 30 days (p < 0.0001), with sustained improvement at 3 years (p < 0.0001) compared with baseline. No reductions in Kansas City Cardiomyopathy Questionnaire scores were seen when patients were stratified according to small bioprosthesis size, elevated residual gradient, or the presence of moderate or severe prosthesis-patient mismatch.

## DISCUSSION

Long-term follow-up data in the PARTNER 2 VIV registry demonstrate sustained valve performance, with no change in transvalvular gradients, indexed EOA, or total aortic regurgitation between 30 days and 3 years. Important left ventricular indexes continued to improve significantly. Mitral and tricuspid regurgitation also improved, as assessed by a robust linear mixed-effects analysis. Remarkable early improvements in functional status and quality-of-life indexes were maintained at 2- and 3-year follow-up.

Prior reports of long-term follow-up post-VIV TAVR are limited, and no prior prospective studies with echocardiography core laboratory follow-up have reported outcomes beyond 1 year. Ye et al. (7) reported median survival of 4.5 years in 42 patients, and that survival was reduced in patients with small surgical valves (21-mm labeled size). In the VIVID

**FIGURE 3 Change in Effective Orifice Area and Mean Gradient**

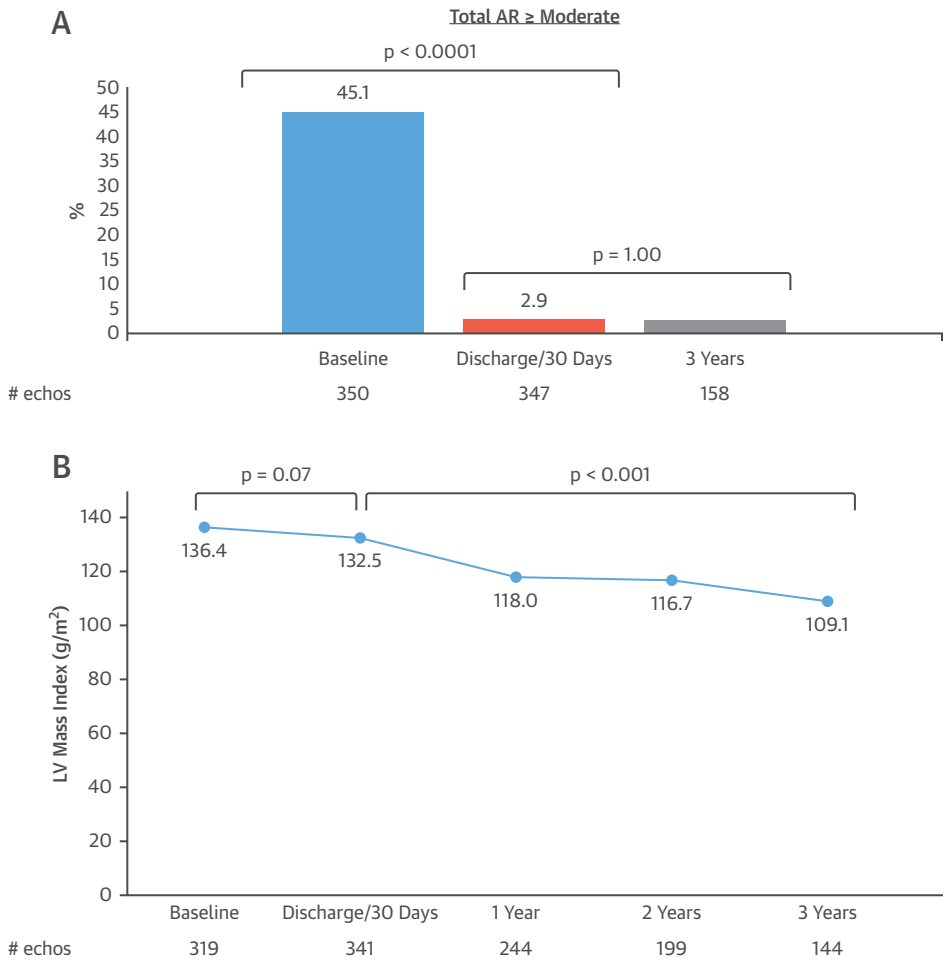



Graph depicts **(A)** mean gradient (MG) by mode of failure (stenosis, regurgitation, or mixed) and **(B)** effective orifice area (EOA) by mode of failure (stenosis, regurgitation, or mixed). MG improved significantly by 30 days regardless of failure mode, while EOA improved significantly by 30 days for patients presenting with stenosis or mixed etiology. Hemodynamic improvements were maintained between 30 days and 1 year.

(Valve-in-Valve International Data) registry, severe pre-existing prosthesis-patient mismatch of the failed surgical bioprosthesis was independently and strongly associated with increased risk for mortality following VIV (8). Recently, a multicenter study of balloon-expandable and self-expanding valves found no increase in late cumulative mortality related to surgical valve size, gradient at discharge, or the presence of severe prosthesis-patient mismatch (5). Multivariate analysis in our study did not find an increase in mortality with 21-mm labeled surgical valves or those with true internal diameter of 21 mm, noting that those labeled <21 mm were excluded.

Higher than desirable residual transvalvular gradients after VIV TAVR may be related to incomplete THV expansion. Although a post-VIV mean transaortic gradient of 20 mm Hg in this cohort was found to be a predictor of all-cause mortality at 1 year, there

**FIGURE 4 Other Echocardiographic Changes**



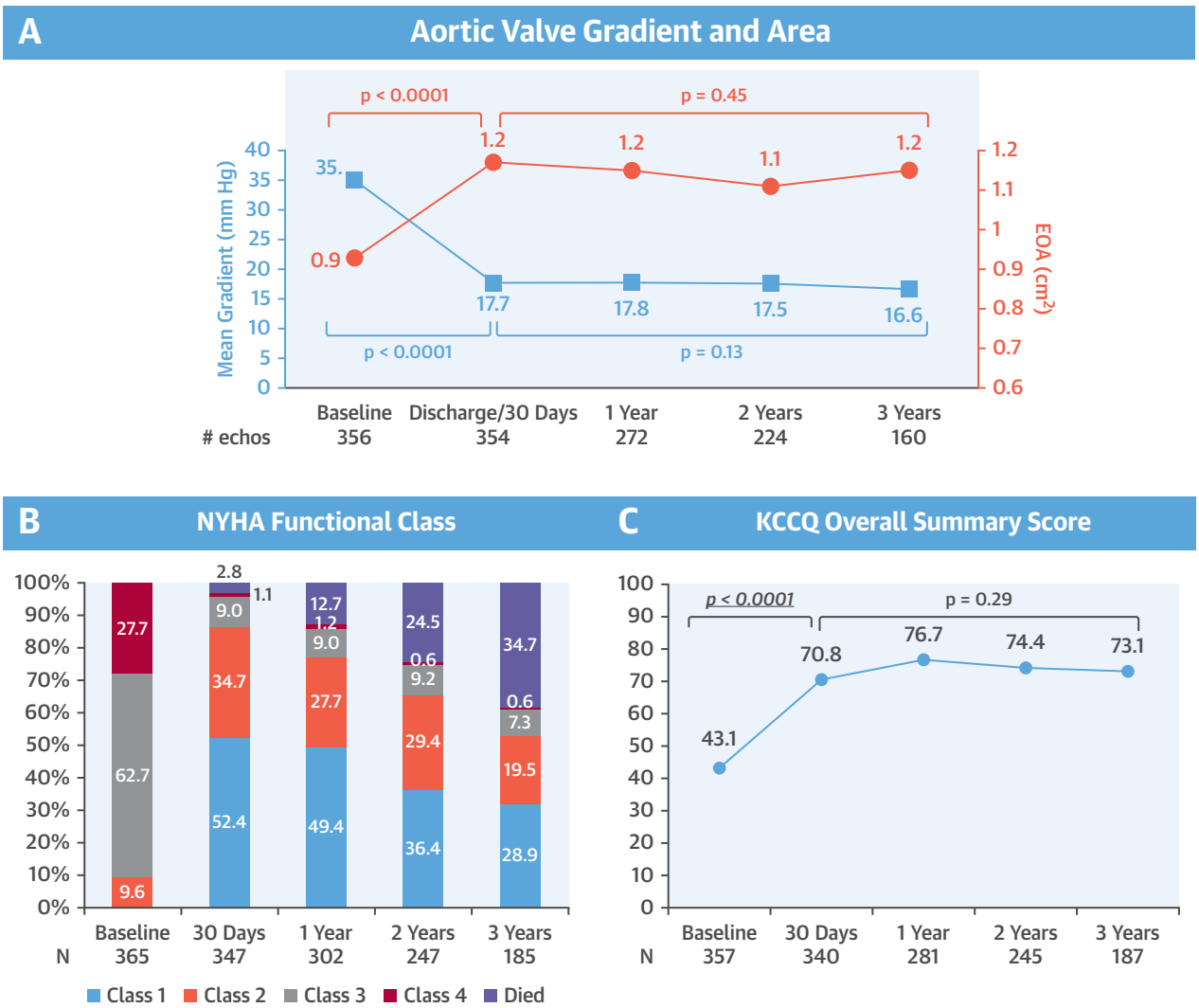

Significant improvements in **(A)** total aortic regurgitation (AR) and **(B)** left ventricular (LV) mass index were observed.

was no significant difference at 3 years. In a cohort of >900 patients in the VIVID registry, severe patient-prosthesis mismatch and transaortic gradient of 20 mm Hg was not found to be a predictor of adverse outcomes or 1-year mortality (9,10). Similarly, in a recent study of 62,1125 patients from the TVT (Transcatheter Valve Therapy) registry only severe, not moderate, prosthesis-patient mismatch was found to predict adverse outcomes (11). A recent study suggests that Doppler echocardiography may substantially overestimate the transaortic gradient in the context of VIV (12), which may also contribute to the lack of association between high residual gradient and mid-term mortality observed in this study.

An apparent inflection of the Kaplan-Meier survival curve after 1 year may reflect the background mortality rate in this high-risk cohort. As expected, late mortality was substantial in this high-risk and multicomorbid cohort. Despite this, 3-year mortality compares favorably with high-risk patients treated with either TAVR or surgery in the PARTNER Cohort A randomized trial of native aortic stenosis (32.5% [VIV TAVR] vs. 44.2% [TAVR] vs. 44.8% [surgery]) (13).

Repeat aortic valve replacement was uncommon in this cohort (1.9% at 3 years), as was hemodynamic valve deterioration (1.3% at 3 years). This occurred despite frequent fluoroscopic underexpansion of the THV frame. Therefore, this study provides further reassurance that rapid structural valve deterioration is rare, at least within the first 3 years post-VIV TAVR, and that early clinical benefits are maintained during this time frame (14).

**CENTRAL ILLUSTRATION Hemodynamic Status, Functional Status, and Quality of Life Following Valve-in-Valve Transcatheter Aortic Valve Replacement**




**Webb, J.G. et al. J Am Coll Cardiol. 2019;73(21):2647–55.**

Valve-in-valve transcatheter aortic valve replacement resulted in early improvements in **(A)** effective orifice area (EOA) and mean gradient and **(B)** function and quality of life that were maintained throughout 3 years of follow-up. KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

**STUDY LIMITATIONS.** Limitations include the lack of a randomized comparator arm. Coupled with the lack of blinding in the study, it is possible that a placebo effect may have contributed to the magnitude of patient-reported symptomatic improvement. Follow-up beyond 1 year was limited to site-collected data and not adjudicated by a clinical events committee, although the study was conducted at carefully selected sites with extensive oversight. The available THV sizes (23 and 26 mm) did not allow inclusion of patients with the smallest or largest of surgical bioprostheses. Clinical and hemodynamic outcomes may vary with different THV devices.

## CONCLUSIONS

At 3-year follow-up, TAVR for bioprosthetic aortic valve failure was associated with favorable survival,

improved hemodynamic status, and sustained excellent functional and quality-of-life outcomes. Reintervention for THV dysfunction was uncommon. The early improvements associated with VIV TAVR are maintained through 3 years, supporting the value of VIV TAVR as an important alternative therapy in appropriate patients with aortic bioprosthetic valve failure.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** TAVR for degenerated surgical bioprosthetic aortic valves is associated with favorable survival, hemodynamic status, ventricular function, functional class, and quality-of-life measures after 3 years.

**TRANSLATIONAL OUTLOOK:** Further studies are needed to define the clinical and echocardiographic characteristics of patients most likely to gain sustained benefit from TAVR among those with degenerated surgical bioprostheses.

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**KEY WORDS** 6-min walk distance, aortic stenosis, mortality, registry, regurgitation

**APPENDIX** For a supplemental table, please see the online version of this paper.