# Clinical Summary
# TAVI in Low-Risk Patients at 5 Years
# PARTNER 3 Trial

Mack MJ, et al. Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years. N Engl J Med. 2023 Oct 24. doi: 10.1056/NEJMoa2307447

## Study aim

To compare the 5-year outcomes of TAVI with SAPIEN 3 valve and SAVR in patients with ssAS in low surgical risk.

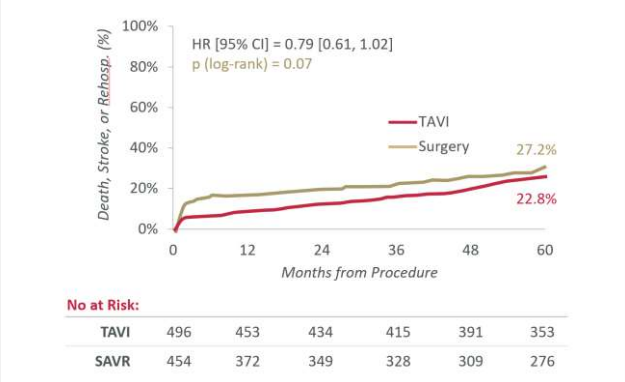
THE PARTNER 3 TRIAL

## Methodology

- **PARTNER 3:** 5 years data; Randomized Clinical Trial - patients treated with TF-TAVI or SAVR
- **1000 low surgical risk** patients with ssAS - Average age 73 y.o. – STS score 1.9
- **At 5 years:** 469 patients with SAPIEN 3 valves, 401 patients with surgical valves (70% Edwards)

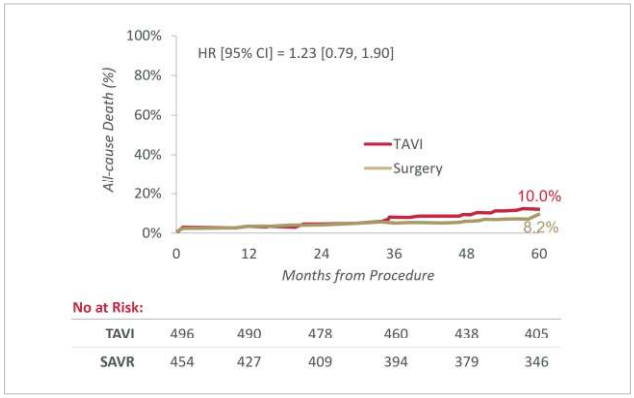
## Results

### Primary Endpoints:




- **Death, stroke, or rehospitalization*** composite: No significant difference between TAVI and SAVR.
  - **Event-free survival was longer by 103 days in the TAVI cohort.**
- **Win ratio§** - hierarchical composite of death, disabling stroke, non-disabling stroke, and rehosp. days: 1.17 - **22.1% of wins for TAVI and 19% wins for SAVR.** No significant difference.

### Mortality:




- **All-cause mortality: No significant difference** between TAVI (10.0%) and SAVR (8.2%).
  - **Vital status sweep$** reduced the gap between TAVI and SAVR. **TAVI 10.2% vs. SAVR 9.0%.**
  - Mortality differences mainly due to **non-CV deaths** – e.g., Cancers, Covid-19, and Sepsis deaths.

* related to the valve, the procedure, or heart failure / $ vital status sweep: conducted to obtain information about the patients who withdrew or were lost to follow-up § Win ratio: NT × NC paired comparisons - Test (TAVI) or Control (SAVR) wins when specific endpoints happen first over the same follow-up time– the ratio represented n of wins divided by n of loses".

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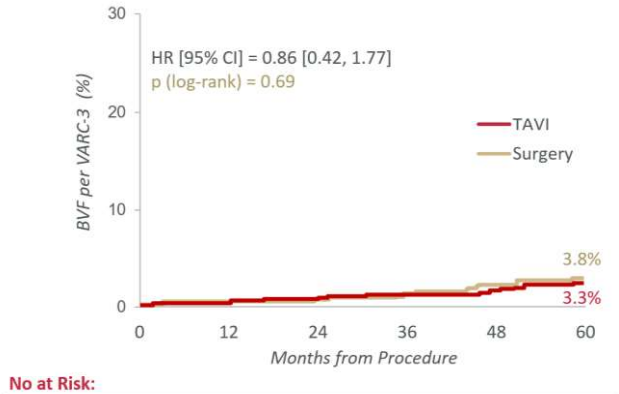
## Secondary Endpoints:

- No difference was reported for CV deaths, all and disabling strokes, rehospitalization, BVF, and aortic reintervention.
- **Valve thrombosis:** significantly higher in TAVI arm (2.5% vs 0.2% - HR 10.52 (1.37–80.93))
  - **No thrombosis-related death;** TAVI: only 1 thrombosis-related BVF
- **Hemodynamics: Sustained** mean gradient and aortic valve area in both cohorts and in **all SAPIEN 3 valve sizes.**

## Bioprosthesis-valve Failure:




| BVF Cause[&] (%) | TAVI (N=496) | SAVR (N=454) |
|---|---|---|
| SVD | 1.4% | 2.0% |
| Endocarditis | 0.2% | 0.9% |
| PVL | 0.8% | 0.2% |
| Thrombosis | 0.2% | 0.2% |
| PPM | 0.2% | 0% |
| Undetermined[♯] | 0.2% | 0% |

& according to VARC-3 criteria
♯The patient had a valve-in-valve reintervention for stenosis

## Conclusion

Among patients with ssAS at low surgical risk who underwent TAVI or SAVR, the incidence of the two primary composite endpoints appeared to be similar in the two groups at 5 years of follow-up.

### Abbreviations

**BVF** = Bioprosthesis-valve Failure; **CV** = cardiovascular; **NC**= number of patients on the Control arm (SAVR); **NT**= number of patients on the Test arm (SAPIEN 3); **PVL** = Paravalvular leak; **PPM** = Patient-prosthesis mismatch; **SAVR** = surgical aortic valve replacement; **ssAS** = severe symptomatic aortic stenosis; **SVD** = Structural valve deterioration; **TAVI** = Transcatheter aortic valve implantation; **TF** = transfemoral; **VARC-3** = Valve Academic Research Consortium-3.



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ORIGINAL ARTICLE

# Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years

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## ABSTRACT

### BACKGROUND

A previous analysis in this trial showed that among patients with severe, symptomatic aortic stenosis who were at low surgical risk, the rate of the composite end point of death, stroke, or rehospitalization at 1 year was significantly lower with transcatheter aortic-valve replacement (TAVR) than with surgical aortic-valve replacement. Longer-term outcomes are unknown.

### METHODS

We randomly assigned patients with severe, symptomatic aortic stenosis and low surgical risk to undergo either TAVR or surgery. The first primary end point was a composite of death, stroke, or rehospitalization related to the valve, the procedure, or heart failure. The second primary end point was a hierarchical composite that included death, disabling stroke, nondisabling stroke, and the number of rehospitalization days, analyzed with the use of a win ratio analysis. Clinical, echocardiographic, and health-status outcomes were assessed through 5 years.

### RESULTS

A total of 1000 patients underwent randomization: 503 patients were assigned to undergo TAVR, and 497 to undergo surgery. A component of the first primary end point occurred in 111 of 496 patients in the TAVR group and in 117 of 454 patients in the surgery group (Kaplan–Meier estimates, 22.8% in the TAVR group and 27.2% in the surgery group; difference, −4.3 percentage points; 95% confidence interval [CI], −9.9 to 1.3; P=0.07). The win ratio for the second primary end point was 1.17 (95% CI, 0.90 to 1.51; P=0.25). The Kaplan–Meier estimates for the components of the first primary end point were as follows: death, 10.0% in the TAVR group and 8.2% in the surgery group; stroke, 5.8% and 6.4%, respectively; and rehospitalization, 13.7% and 17.4%. The hemodynamic performance of the valve, assessed according to the mean (±SD) valve gradient, was 12.8±6.5 mm Hg in the TAVR group and 11.7±5.6 mm Hg in the surgery group. Bioprosthetic-valve failure occurred in 3.3% of the patients in the TAVR group and in 3.8% of those in the surgery group.

### CONCLUSIONS

Among low-risk patients with severe, symptomatic aortic stenosis who underwent TAVR or surgery, there was no significant between-group difference in the two primary composite outcomes. (Funded by Edwards Lifesciences; PARTNER 3 ClinicalTrials.gov number, NCT02675114.)

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*A complete list of the PARTNER 3 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Transcatheter aortic-valve replacement (TAVR) has been increasingly used as an alternative to surgery for treating patients with severe, symptomatic aortic stenosis.[1,2] Randomized trials of both balloon-expandable and self-expanding TAVR valves have shown that in patients at intermediate or high risk for death by 30 days after surgery, TAVR was either noninferior or superior to surgical aortic-valve replacement at 5 years of follow-up.[3-11] In two randomized trials involving younger patients who were at low surgical risk, TAVR was either noninferior or superior to surgery at 2 or 3 years.[12-15] The Placement of Aortic Transcatheter Valves (PARTNER) 3 trial showed that the rate of the composite end point of death, stroke, or rehospitalization at 1 and 2 years was significantly lower with TAVR than with surgery.[13-15] Here, we report the 5-year outcomes in this trial.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

This multicenter, randomized trial compared the use of the SAPIEN 3 transcatheter heart valve (Edwards Lifesciences) with surgical aortic-valve replacement in patients with severe, symptomatic aortic stenosis who were at low surgical risk. The trial design, details regarding oversight, and results at 1 and 2 years have been published previously.[13,15] The trial protocol (available with the full text of this article at NEJM.org) was designed by the sponsor (Edwards Lifesciences), with input from the trial steering committee and the Food and Drug Administration, and was approved by the institutional review board at each site. The sponsor funded all trial-related activities and participated in site selection, data collection, monitoring, and statistical analysis. The trial leadership had unrestricted access to all the data, prepared all the drafts of the manuscript, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### PATIENTS

Patients were eligible for inclusion if they had severe, symptomatic aortic stenosis and were considered to be at low surgical risk on the basis of clinical and anatomical assessment, including a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of less than 4% (with scores ranging from 0 to 100% and higher scores indicating a greater risk of death within 30 days after the procedure) and on the basis of assessment by the heart team. Patients also had to be eligible for TAVR through transfemoral access. The eligibility of all the patients was reviewed and approved by a case review board. Key anatomical and clinical exclusions have been reported previously and are provided in the Supplementary Appendix, available at NEJM.org.[13] Details about the representativeness of the patients in the trial are also provided in the Supplementary Appendix.

### RANDOMIZATION, PROCEDURES, AND FOLLOW-UP

Patients were assigned in a 1:1 ratio to undergo either TAVR with a SAPIEN 3 valve or surgical aortic-valve replacement with a commercially available bioprosthetic valve. The SAPIEN 3 system and the procedures for TAVR and surgery have been described previously.[13] Clinical outcomes and transthoracic echocardiography data were assessed at baseline, after the implantation procedure, at hospital discharge, 30 days, 6 months, 1 year, and then annually to 5 years.

### END POINTS

The original primary end point, assessed at 1 year, was a nonhierarchical composite of death from any cause, stroke, or rehospitalization related to the procedure, the valve, or heart failure (see the Supplementary Appendix). A time-to-first-event analysis was used to evaluate this end point. However, some patients had more than one end-point event or more than one rehospitalization over the 5-year period. To better reflect the patient outcomes through 5 years, two primary end points were prespecified in the 5-year extension statistical analysis plan: the original nonhierarchical composite end point and a hierarchical composite end point that included death from any cause, disabling stroke, nondisabling stroke, and the number of rehospitalization days (see the Supplementary Appendix). Secondary end points of interest at 5 years were death or disabling stroke, new-onset atrial fibrillation, aortic-valve reintervention, endocarditis, and clinically significant valve thrombosis; definitions are provided in the Supplementary Appendix. Valve thrombosis was defined according to Valve Academic Re-

search Consortium 3 (VARC-3) criteria as clinically significant bioprosthetic-valve dysfunction as assessed with echocardiography or contrast-enhanced computed tomography with either no (stage 1), moderate (stage 2), or severe (stage 3) hemodynamic valve deterioration.[16] A clinical events committee adjudicated key 5-year clinical outcomes, including all components of the primary end points, valve thrombosis, and valve reintervention. Other secondary end points included functional status and quality of life as assessed with the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS). KCCQ-OS scores range from 0 to 100, with higher scores indicating better health status. The secondary end point of alive with a KCCQ-OS score of 75 or higher indicated the status of being alive and well.

#### ECHOCARDIOGRAPHIC ASSESSMENTS

All echocardiograms were assessed by a core laboratory with the use of standard hemodynamic measures. Total aortic regurgitation and paravalvular aortic regurgitation were assessed with the use of a multiparametric integrative approach.[16] Valve durability was assessed with the use of the VARC-3 definition of bioprosthetic-valve failure, which includes the occurrence of valve reintervention, valve-related death, or deterioration in hemodynamic valve function between the day 30 and follow-up echocardiograms. All potential cases of bioprosthetic-valve failure were adjudicated by a group of three experts for confirmation of the presence, stage, and cause of valve failure.[16]

#### STATISTICAL ANALYSIS

For the first primary end point (a nonhierarchical composite of death from any cause, stroke, or rehospitalization), we used the Wald test[17] to determine the superiority of TAVR to surgery; the percentage of patients with an event in each group at 5 years was estimated with the Kaplan–Meier method, and Greenwood's formula was used to estimate standard errors. The odds ratio and 95% confidence interval from the time-adjusted logistic-regression model were also calculated. The second primary end point (a hierarchal composite that included death from any cause, disabling stroke, nondisabling stroke, and the number of rehospitalization days) was tested with the use of the win ratio method (see the Supplementary Appendix).[18] The type I error was controlled between the two primary end points with the use of the Hochberg method.[19]

Time-to-event analyses from baseline to 1 year, 1 to 5 years (landmark analysis), and baseline to 5 years were performed, and hazard ratios and 95% confidence intervals were calculated for the clinical end points (see the Supplementary Appendix). If there was clear evidence of nonproportionality of hazards, the odds ratio and 95% confidence interval from the time-adjusted logistic-regression model were also reported.[20] For continuous variables, the means and the difference between the means, along with the 95% confidence intervals, were reported. For categorical variables, the percentage of patients in each trial group, the difference in the percentages, and the 95% confidence intervals were reported. The widths of the confidence intervals for continuous and categorical variables have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Additional methods are described in the Supplementary Appendix.

All clinical end-point analyses were performed in the as-treated population, which included the patients who had undergone randomization and in whom the index procedure was initiated (see the Supplementary Appendix). Echocardiographic end-point analyses were performed in the valve-implant population, which included the patients in whom the intended valve was implanted. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

#### PATIENTS, PROCEDURES, AND FOLLOW-UP

A total of 1000 patients underwent randomization at 71 clinical sites: 503 patients were assigned to undergo transfemoral TAVR and 497 to undergo surgery. The as-treated population included 496 patients in the TAVR group and 454 in the surgery group. A total of 948 patients (495 in the TAVR group and 453 in the surgery group) received the intended valve. Details regarding the implanted valve sizes and surgical valve types were published previously[21] and are provided in Figure S1 and Table S1 in the Supplementary Appendix. The mean age of the patients was 73 years, 69.3% of

the patients were men, and the mean STS-PROM score was 1.9% (Table S2). Details regarding randomization and follow-up through 5 years are shown in Figure 1. Follow-up data through 5 years were available for 91.6% of the patients, with a disproportional loss to follow-up in the surgery group; follow-up data were available for 469 of 496 patients (94.6%) in the TAVR group and 401

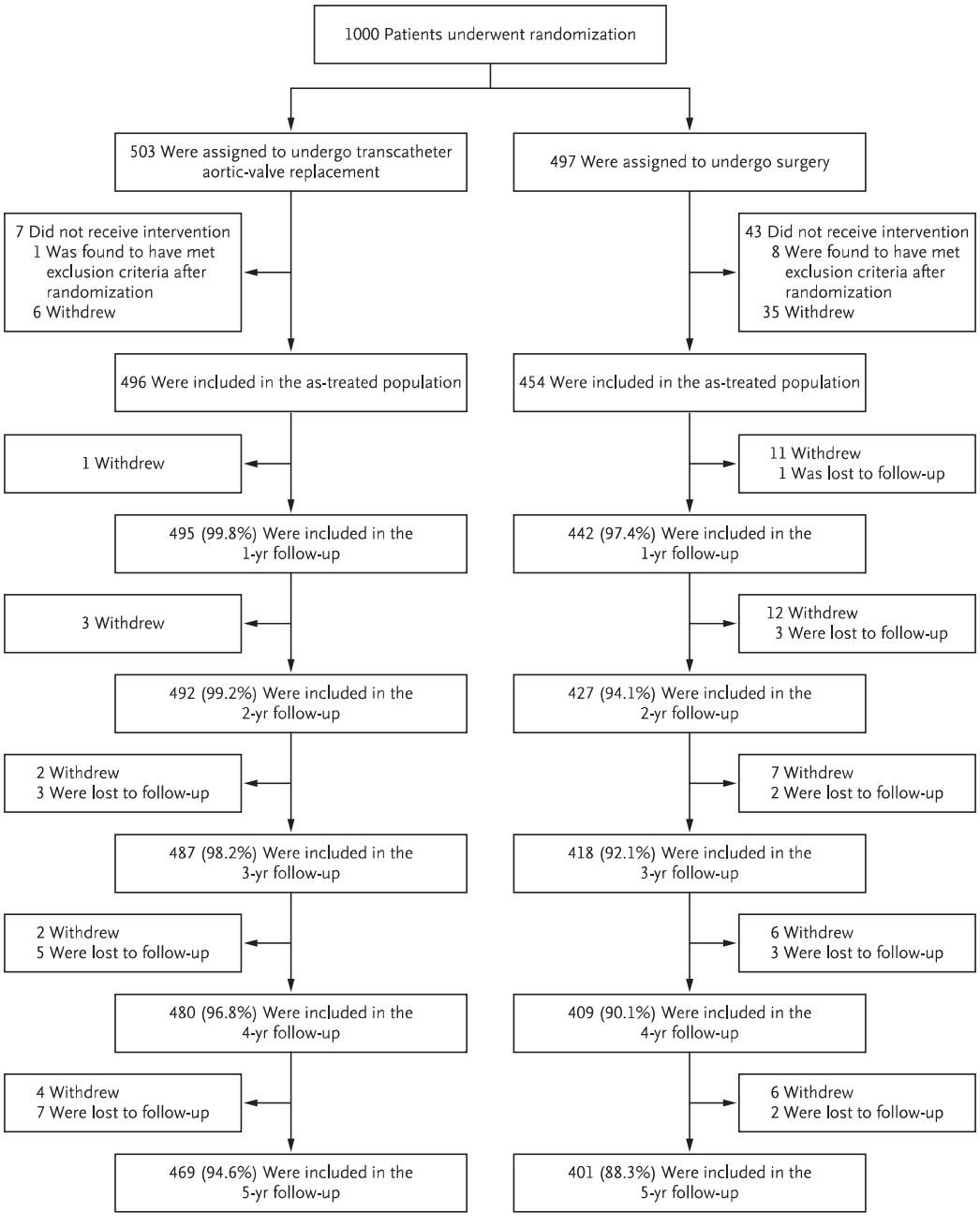


**Figure 1. Randomization and Follow-up.**

Patients who met the composite primary end point of death, stroke, or rehospitalization related to the valve, the procedure, or heart failure but who withdrew or were lost to follow-up are considered to have completed follow-up because they had already died, had a stroke, or had rehospitalization before trial exit. Data from the vital-status sweep are not shown.

of 454 (88.3%) in the surgery group. A vital-status sweep yielded data for 66 of 95 patients who had been lost to follow-up or had withdrawn from the trial (21 patients assigned to the TAVR group and 45 assigned to the surgery group) (Fig. S2). Therefore, vital status could be determined for 486 of 496 patients (98.0%) in the TAVR group and 441 of 454 patients (97.1%) in the surgery group.

### PRIMARY END POINTS

The composite of death, stroke, or rehospitalization related to the valve, the procedure, or heart failure (the first primary end point) occurred in 111 of 496 patients in the TAVR group and in 117 of 454 patients in the surgery group. The Kaplan–Meier estimates were 22.8% in the TAVR group and 27.2% in the surgery group (difference, −4.3 percentage points; 95% confidence interval

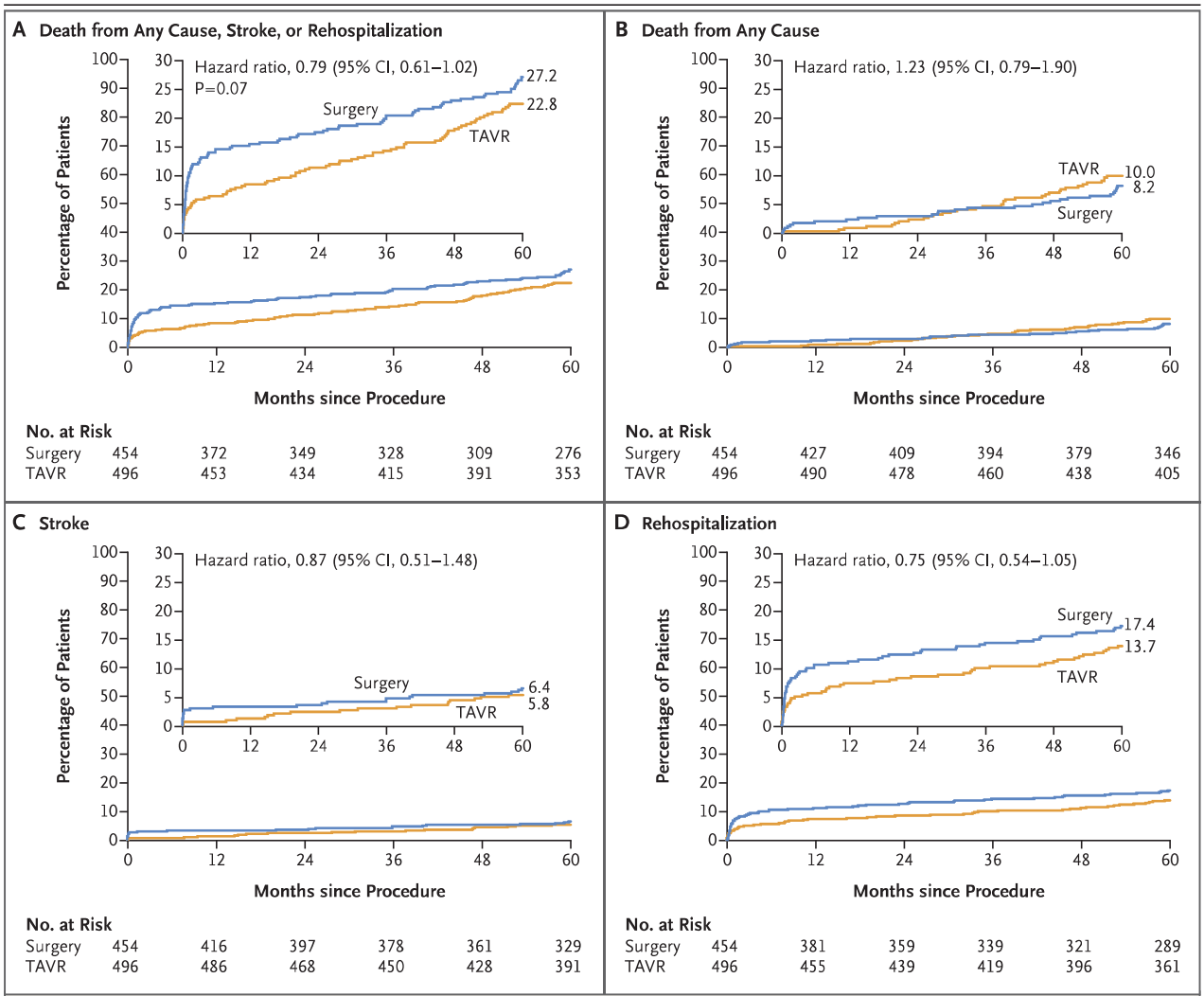


**Figure 2. Kaplan–Meier Curves for the First Primary End Point and Its Components.**

Panel A shows the Kaplan–Meier estimates of the first composite primary end point of death from any cause, stroke, or rehospitalization, and Panels B, C, and D show the estimates for the components. Rehospitalization was defined as rehospitalization related to the procedure, the valve, or heart failure. According to the statistical analysis plan, the analysis of the composite primary end point involved the difference in the Kaplan–Meier estimates between the transcatheter aortic-valve replacement (TAVR) group and the surgery group, calculated on the basis of the Wald test (difference, −4.3 percentage points; 95% CI, −9.9 to 1.3; P=0.07). The odds ratio and 95% confidence interval for death from any cause were calculated because there was evidence of nonproportionality of hazards from baseline to 5 years (odds ratio, 1.24; 95% CI, 0.79 to 1.97). The inset in each panel shows the same data on an enlarged y axis.

**Table 1. Key Clinical End Points.***

| End Point | Baseline to 5 Years | | | 1 Year to 5 Years | | |
|---|---|---|---|---|---|---|
| | TAVR (N=496) | Surgery (N=454) | Hazard Ratio (95% CI) | TAVR (N=490) | Surgery (N=427) | Hazard Ratio (95% CI) |
| | *no. of patients with event (Kaplan–Meier estimate, %)* | | | *no. of patients with event (Kaplan–Meier estimate, %)* | | |
| Death, stroke, or rehospitalization† | 111 (22.8) | 117 (27.2) | 0.79 (0.61–1.02)‡ | 69 (15.7) | 47 (13.7) | 1.17 (0.81–1.70) |
| Death from any cause | 48 (10.0) | 34 (8.2) | 1.23 (0.79–1.90)§ | 43 (9.1) | 23 (5.9) | 1.61 (0.97–2.67) |
| Death from cardiovascular causes | 26 (5.5) | 21 (5.1) | 1.08 (0.61–1.92)§ | 22 (4.7) | 12 (3.1) | 1.58 (0.78–3.19) |
| Death from noncardiovascular causes | 22 (4.8) | 13 (3.3) | 1.46 (0.74–2.90)§ | 21 (4.6) | 11 (2.8) | 1.64 (0.79–3.41) |
| Stroke | 27 (5.8) | 27 (6.4) | 0.87 (0.51–1.48) | 21 (4.6) | 12 (3.2) | 1.49 (0.73–3.02) |
| Disabling stroke | 13 (2.9) | 11 (2.7) | 1.03 (0.46–2.30) | 12 (2.7) | 6 (1.6) | 1.73 (0.65–4.61) |
| Nondisabling stroke | 15 (3.2) | 16 (3.7) | 0.82 (0.40–1.65) | 10 (2.2) | 6 (1.5) | 1.41 (0.51–3.89) |
| Death or disabling stroke | 55 (11.5) | 41 (9.8) | 1.17 (0.78–1.75)§ | 50 (10.6) | 27 (6.9) | 1.60 (1.00–2.55) |
| Rehospitalization† | 65 (13.7) | 74 (17.4) | 0.75 (0.54–1.05) | 29 (6.9) | 24 (6.9) | 0.98 (0.57–1.69) |
| Aortic-valve reintervention | 12 (2.6) | 12 (3.0) | 0.86 (0.39–1.92) | 9 (2.0) | 10 (2.6) | 0.77 (0.31–1.90) |
| Endocarditis | 6 (1.3) | 8 (2.0) | 0.65 (0.23–1.87) | 5 (1.1) | 6 (1.5) | 0.72 (0.22–2.35) |
| Valve thrombosis¶ | 12 (2.5) | 1 (0.2) | 10.52 (1.37–80.93) | 10 (2.1) | 1 (0.2) | 8.72 (1.12–68.12) |
| New-onset atrial fibrillation‖** | 55 (13.7) | 155 (42.4) | 0.25 (0.19–0.34) | 21 (6.0) | 5 (2.6) | 2.30 (0.87–6.10) |
| New pacemaker‖** | 63 (13.5) | 43 (10.4) | 1.33 (0.90–1.96) | 25 (6.1) | 18 (4.9) | 1.22 (0.67–2.24) |
| Serious bleeding‖ | 49 (10.2) | 64 (14.8) | 0.65 (0.45–0.95) | 25 (5.6) | 18 (5.1) | 1.15 (0.63–2.11) |
| Myocardial infarction‖ | 10 (2.1) | 18 (4.4) | 0.48 (0.22–1.05) | 6 (1.3) | 10 (2.6) | 0.51 (0.19–1.41) |
| Revascularization‖ | 17 (3.7) | 25 (6.0) | 0.59 (0.32–1.09) | 12 (2.7) | 12 (3.2) | 0.85 (0.38–1.88) |
| Percutaneous coronary intervention | 16 (3.5) | 20 (4.9) | 0.69 (0.36–1.34) | 11 (2.5) | 12 (3.2) | 0.78 (0.35–1.78) |
| Coronary-artery bypass grafting | 2 (0.5) | 5 (1.1) | 0.36 (0.07–1.85) | 1 (0.2) | 0 | — |

* The total number of patients in each column header represents the number of patients at risk for death at the beginning of the interval. TAVR denotes transcatheter aortic-valve replacement.

† Rehospitalization was defined as rehospitalization related to the valve, the procedure, or heart failure.

‡ According to the statistical analysis plan, the analysis of the two composite primary end points involved the difference in the Kaplan–Meier estimates between the TAVR group and the surgery group, calculated on the basis of the Wald test (difference, –4.3 percentage points; 95% CI, –9.9 to 1.3; P=0.07).

§ The following odds ratios with 95% confidence intervals were calculated for end points that showed evidence of nonproportionality of hazards from baseline to year 5: odds ratio for death from any cause, 1.24 (95% CI, 0.79 to 1.97); odds ratio for death from cardiovascular causes, 1.08 (95% CI, 0.60 to 1.95); odds ratio for death from noncardiovascular causes, 1.48 (95% CI, 0.74 to 2.97); and odds ratio for death or disabling stroke, 1.18 (95% CI, 0.77 to 1.81).

¶ Valve thrombosis was adjudicated according to Valve Academic Research Consortium 3 criteria.

‖ The outcome was reported by the trial site. Serious bleeding included events that led to death or another serious event; resulted in life-threatening illness, injury, or permanent impairment; resulted in medical or surgical intervention; or resulted in hospitalization or prolongation of existing hospitalization.

** These categories exclude atrial fibrillation and pacemakers that were present at baseline.





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[CI], −9.9 to 1.3; P=0.07; hazard ratio, 0.79; 95% CI, 0.61 to 1.02) (Fig. 2A and Table 1). These findings appeared to be consistent in all major subgroups (Fig. S3). The win ratio for the second primary end point (a hierarchical composite that included death, disabling stroke, nondisabling stroke, and the number of rehospitalization days) was 1.17 (95% CI, 0.90 to 1.51; P=0.25) (Fig. 3). The results of a sensitivity analysis that used multiple imputation for missing data and was adjusted for nonproportional hazards seemed to be consistent with those of the primary analysis (Table S3). In a landmark analysis of years 1 to 5, a total of 69 of 453 patients in the TAVR group and 47 of 372 patients in the surgery group had died or had had a stroke or rehospitalization. The Kaplan–Meier estimates were 15.7% in the TAVR group and 13.7% in the surgery group (hazard ratio, 1.17; 95% CI, 0.81 to 1.70) (Table 1 and Fig. S4). The restricted mean event-free survival in the

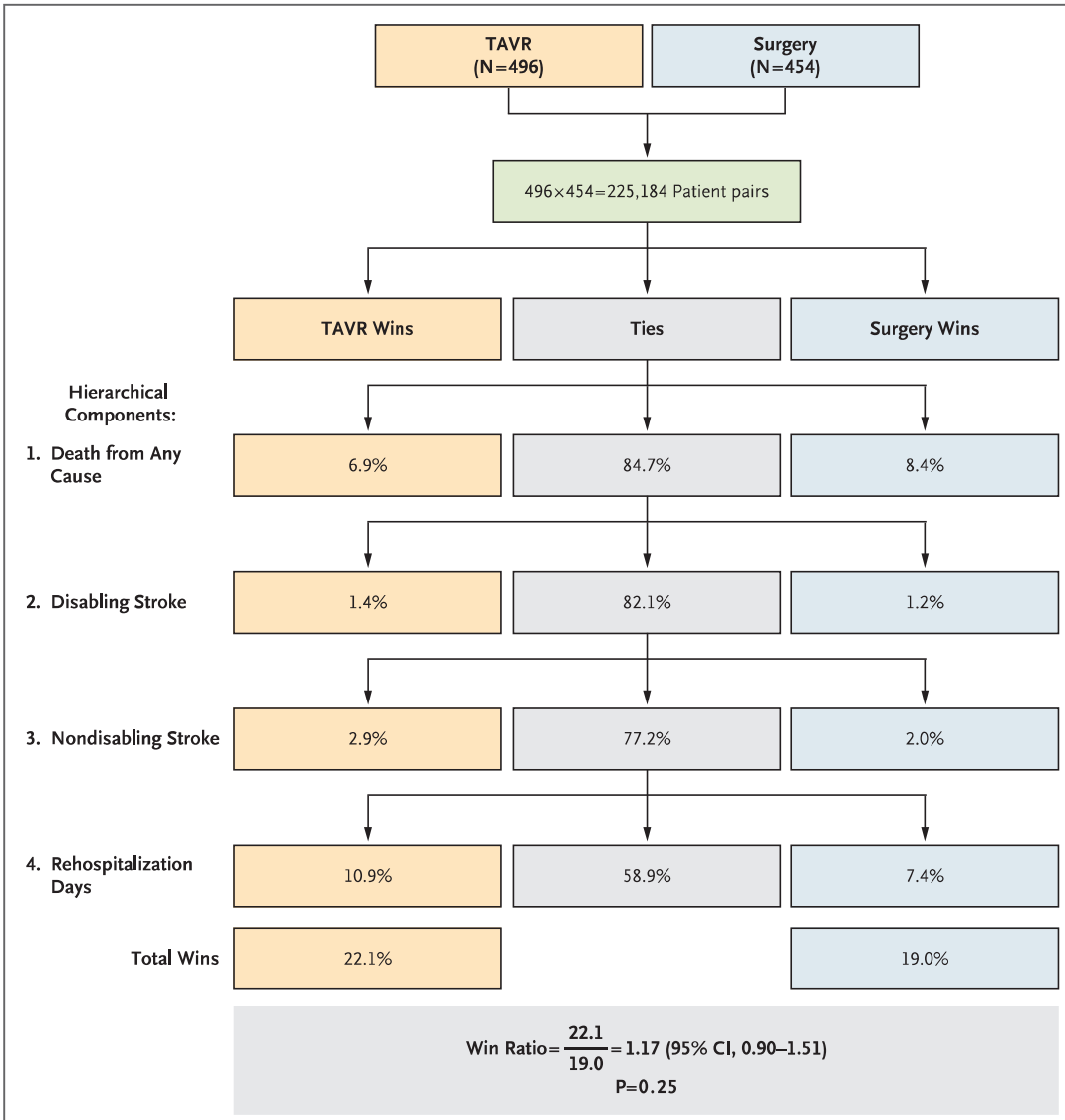


**Figure 3. Win Ratio Diagram for the Second Primary End Point.**

Shown are the results of the win ratio analysis of the second primary end point (a hierarchical composite that included death, disabling stroke, nondisabling stroke, and the number of rehospitalization days related to the valve, the procedure, or heart failure).

analysis of the first primary end point at 5 years was longer by 103 days (95% CI, 26 to 180) with TAVR than with surgery (Table S4).

With respect to the individual components of the first primary end point at 5 years, the Kaplan–Meier estimates were as follows: death from any cause, 10.0% in the TAVR group and 8.2% in the surgery group (odds ratio, 1.24; 95% CI, 0.79 to 1.97); stroke, 5.8% and 6.4%, respectively (hazard ratio, 0.87; 95% CI, 0.51 to 1.48); and rehospitalization, 13.7% and 17.4% (hazard ratio, 0.75; 95% CI, 0.54 to 1.05) (Fig. 2B, 2C, and 2D and Table 1). The Kaplan–Meier estimates at 1 year are provided in Table S5. There were 82 deaths through 5 years of follow-up: 48 in the TAVR group (26 from cardiovascular causes and 22 from noncardiovascular causes) and 34 in the surgery group (21 from cardiovascular causes and 13 from noncardiovascular causes) (Fig. S5 and Tables S6 and S7). Three patients in the TAVR group and 1 patient in the surgery group died from coronavirus disease 2019 (Covid-19). The 5-year mortality was 10.2% in the TAVR group and 9.0% in the surgery group when additional patient information obtained from the vital-status sweep was included. Figure S6 shows the Kaplan–Meier curves for the landmark analysis at 1 year for death from any cause, death from any cause with the inclusion of data from the vital-status sweep, death from cardiovascular causes, and death from noncardiovascular causes. Additional 5-year data — including data for stroke, disabling stroke, death, and rehospitalization — are provided in Table 1, Tables S5 through S8, and Figures S6, S7, and S8.

#### SECONDARY END POINTS

Data regarding aortic-valve reintervention and endocarditis are provided in Table 1 and Table S10. New-onset atrial fibrillation occurred in 55 patients in the TAVR group and in 155 patients in the surgery group (Kaplan–Meier estimates, 13.7% and 42.4%, respectively). Serious bleeding occurred in 49 patients in the TAVR group and in 64 patients in the surgery group. A new permanent pacemaker was implanted in 13.5% of the patients in the TAVR group and in 10.4% of those in the surgery group (Table 1). Clinically significant valve thrombosis, according to VARC-3 criteria, occurred in 12 patients (2.5%) in the TAVR group and in 1 patient (0.2%) in the surgery group (Table 1). None of the patients with valve thrombosis died. Of the 12 patients in the TAVR group with thrombosis, hemodynamic valve deterioration was absent (stage 1) in 4 patients, was moderate (stage 2) in 5 patients, and was severe (stage 3) in 3 patients (Table S11). Of the 13 patients with thrombosis, 7 had shortness of breath or dyspnea on exertion, 3 had a stroke (1 disabling and 2 nondisabling), and 3 had no symptoms. The patient with thrombosis in the surgery group had no hemodynamic valve deterioration (stage 1) and had dyspnea on exertion. The percentages of patients who received anticoagulation therapy are provided in Table S12.

#### ECHOCARDIOGRAPHIC FINDINGS

At 5 years, the mean (±SD) aortic-valve gradient according to echocardiography was 12.8±6.5 mm Hg in the TAVR group and 11.7±5.6 mm Hg in the surgery group; the mean aortic-valve area was 1.9±0.5 $cm^2$ and 1.8±0.5 $cm^2$ in the two groups, respectively (Fig. 4A and 4B). At 5 years, aortic regurgitation of mild or greater severity was present in 81 of 331 patients (24.5%) in the TAVR group and in 18 of 284 patients (6.3%) in the surgery group; paravalvular aortic regurgitation of mild or greater severity was present in 69 of 331 patients (20.8%) in the TAVR group and in 9 of 283 patients (3.2%) in the surgery group (Fig. S9). In the TAVR group, 5-year mortality was 9.1% among patients with no or trace paravalvular aortic regurgitation at 30 days after the procedure and 11.1% among those who had mild paravalvular aortic regurgitation at 30 days after the procedure (hazard ratio, 0.78; 95% CI, 0.42 to 1.45) (Fig. S10). The Kaplan–Meier estimates of bioprosthetic-valve failure of any cause were 3.3% in the TAVR group and 3.8% in the surgery group. The estimates of irreversible stage 3 (severe) structural or hemodynamic valve deterioration were 1.1% in the TAVR group and 1.0% in the surgery group. The estimates of aortic-valve reintervention were 2.2% and 2.6%, respectively. The estimates of valve-related death were 0.0% in the TAVR group and 0.2% in the surgery group (Fig. 4C and 4D). The incidence of bioprosthetic-valve failure related to structural valve deterioration was 1.4% in the TAVR group and 2.0% in the surgery group (Table S13). At 5 years, 392 of 454 patients (86.3%) in the TAVR group and 334 of 382 patients (87.4%) in the surgery group were alive and had a normally functioning valve.

### FUNCTIONAL AND HEALTH STATUS

Functional outcomes appeared to be similar in the two groups. A total of 84.4% of the patients in the TAVR group and 86.0% of those in the surgery group were alive and had New York Heart Association (NYHA) class I or II heart failure at 5 years (Fig. S11). Disease-specific health status appeared to be similar in the two groups, with a mean KCCQ-OS score of 86.2 in the TAVR group and 85.9 in the surgery group (Fig. 4E). At 5 years, 284 of 400 patients (71.0%) in the TAVR group and 238 of 331 patients (71.9%) in the surgery group were alive with a KCCQ-OS score of 75 or higher (Fig. 4F).

## DISCUSSION

In this 5-year follow-up of the PARTNER 3 trial, the incidence of the composite end point of death, stroke, or rehospitalization was similar in the TAVR group and the surgery group; the incidence of the individual components of the primary end points (including death from any cause, disabling stroke, nondisabling stroke, and rehospitalization) was also similar in the two groups. The restricted mean event-free survival time over 5 years was longer in the TAVR group than in the surgery group, a result driven mainly by the between-group difference in rehospitalization. Aortic-valve durability according to VARC-3 definitions of bioprosthetic-valve failure appeared to be similar in the two groups at 5 years. Among the secondary end points, atrial fibrillation and bleeding appeared to be less frequent in the TAVR group than in the surgery group, whereas paravalvular aortic regurgitation, valve thrombosis, and pacemaker implantation appeared to be less frequent in the surgery group. Functional and health-status outcomes assessed according to NYHA class, KCCQ-OS score, and the percentage of patients who were alive and well at 5 years appeared to be similar in the two groups.

TAVR has been widely adopted over the past decade largely owing to an abundance of clinical evidence from randomized trials, resulting in twice as many patients with severe aortic stenosis being treated as compared with a decade ago.[1,2,22,23] Comparative outcomes between TAVR and surgery among patients who were followed for 5 years and beyond have shown similar findings in high-risk and intermediate-risk patients.[3-11] With respect to low-risk patients, outcomes from the PARTNER 3 trial were reported at 1 year and 2 years, and outcomes from a trial of TAVR with a self-expanding valve as compared with surgery were reported at 1 and 3 years.[12-15] Those reports showed that TAVR resulted in similar or better early outcomes as compared with surgery. Because low-risk patients are typically younger than high-risk patients, longer-term results are critical to inform clinical decision making. We report the longer-term follow-up of low-risk patients undergoing TAVR or surgery, with adjudicated clinical and echocardiographic outcomes.

After the first year, there was an attenuation of the differences between the TAVR group and the surgery group with respect to the nonhierarchical composite primary end point, which had previously favored TAVR. There was a greater number of deaths among patients assigned to TAVR than among those assigned to surgery from year 1 to year 5; these deaths were due to both cardiovascular and noncardiovascular causes (Tables S6 and S7). Whether follow-up during the Covid-19 pandemic disproportionately affected adverse outcomes could not be definitively determined. The incidence of stroke at 5 years appeared to be similar in the two groups, as was the incidence of disabling and nondisabling strokes, with most strokes being ischemic in origin. Although the incidence of stroke at 5 years was low, stroke remains one of the most serious complications of aortic-valve replacement.[24,25]

Valve durability is of critical importance, especially in younger patients. Hemodynamic valve performance of both TAVR and surgical valves seemed to be similar to that reported previously at 2 years.[26] The incidence of bioprosthetic-valve failure and of the need for reintervention was similar in the two groups at 5 years; these results are consistent with reported findings in intermediate-risk patients.[27,28] A higher percentage of patients in the TAVR group than in the surgery group had paravalvular aortic regurgitation of mild or greater severity; however, mild aortic regurgitation was not associated with higher mortality at 5 years in the TAVR group.[29,30]

Observed improvements in functional status and quality of life in the first year were greater in the TAVR group than in the surgery group, a finding most likely attributable to the more invasive nature of surgery and the longer recovery time. By 1 year, both groups had similar im-

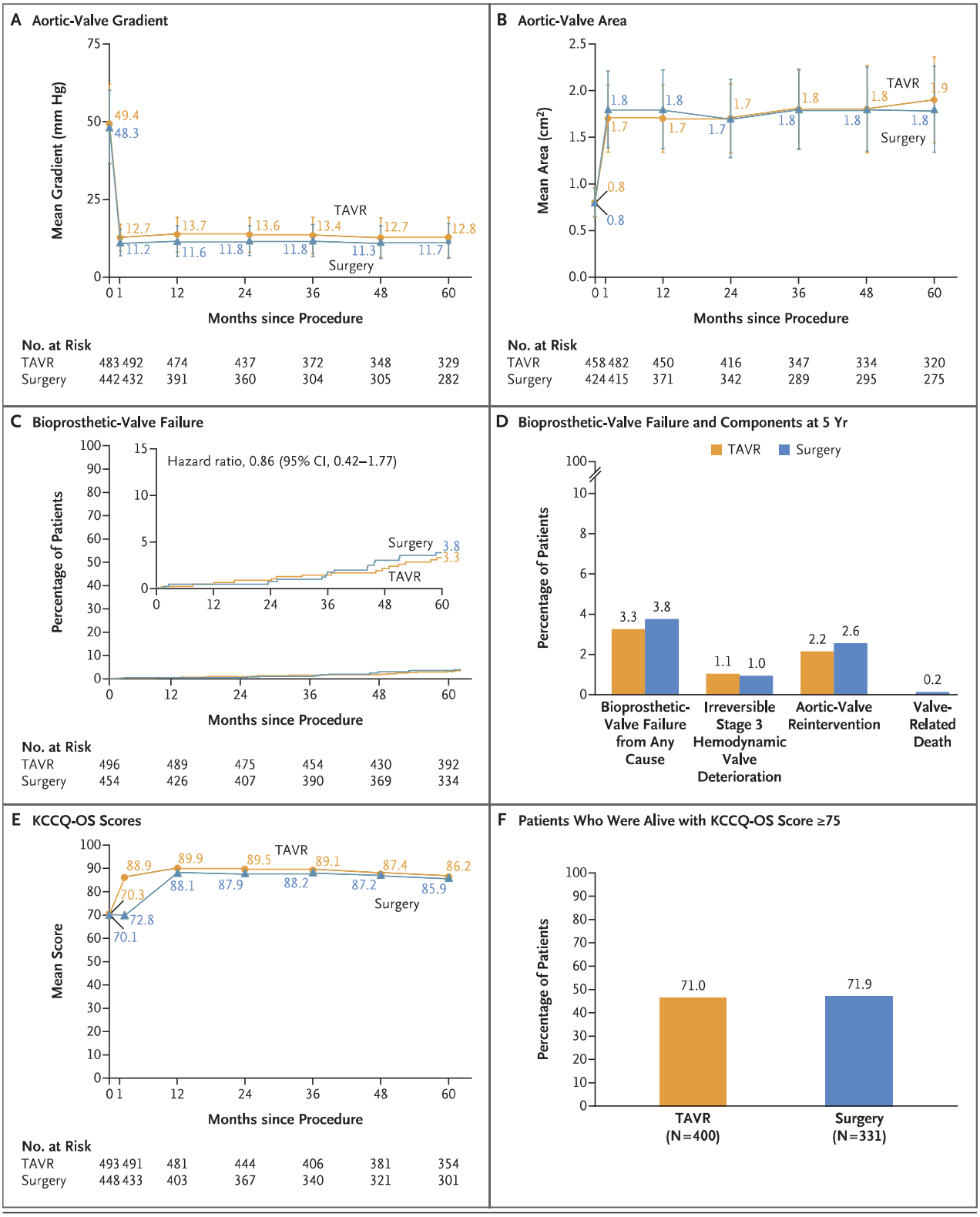

**Figure 4 (facing page). Echocardiographic Outcomes, Bioprosthetic-Valve Failure, and Quality-of-Life Outcomes.**

The mean aortic-valve gradients, shown in Panel A, and the mean aortic-valve areas, shown in Panel B, were assessed by an echocardiography core laboratory. I bars indicate standard deviations. Kaplan–Meier estimates for bioprosthetic-valve failure, adjudicated according to Valve Academic Research Consortium 3 criteria, are shown in Panel C. The inset in Panel C shows the same data on an enlarged y axis. The components of bioprosthetic-valve failure at 5 years are shown in Panel D. The mean Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) scores are shown in Panel E, and the percentage of patients who were alive with a KCCQ-OS score of 75 or higher are shown in Panel F. KCCQ-OS scores range from 0 to 100, with higher scores indicating better health status.

provements in NYHA functional class and mean KCCQ-OS scores that were sustained to 5 years. Furthermore, the percentage of patients who were alive with a KCCQ-OS score of 75 or higher (indicative of being well) appeared to be similar in the two groups.

Clinically significant valve thrombosis was rare but occurred in more patients in the TAVR group than in the surgery group over the course of 5 years. The reasons for the greater incidence of valve thrombosis among TAVR patients remain speculative, but this event did not appear to affect valve durability at 5 years. It is possible that the differences between the groups in the use of anticoagulation therapies during the first years after the procedure may have contributed to the higher incidence of thrombosis in the TAVR group, but this is also unknown. Patients in this trial will continue to be followed for 10 years to shed further light on the durability of both the transcatheter and surgical bioprosthetic valves.

The main limitations of this trial have been discussed previously.[13,15] This report addresses some of those limitations by focusing on longer-term clinical outcomes and valve durability. However, other limitations remain, including the constraints of a carefully defined trial population, which excluded patients with poor transfemoral access, bicuspid aortic valves, or other anatomical or clinical factors that increased the risk of complications associated with either TAVR or surgery. It is important to note, as reported previously, that more patients who underwent surgery than who underwent TAVR withdrew from the trial, which potentially biased the findings. To help address missing vital-status data, a vital-status sweep was conducted to obtain information about the patients who withdrew or were lost to follow-up; the data from this sweep reduced the mortality difference between the two groups. However, these data cannot correct for possible bias in underreporting of nonfatal events. Last, missing data regarding NYHA class, KCCQ-OS score, and follow-up echocardiography could not be fully accounted for with multiple imputation.

Among patients with severe, symptomatic aortic stenosis at low surgical risk who underwent TAVR or surgery, the incidence of the two primary composite end points appeared to be similar in the two groups at 5 years of follow-up.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

## APPENDIX

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# Five-year Clinical Outcomes from The PARTNER 3 Trial

Edwards

# The PARTNER 3 Trial 5-year data

5-year data from The PARTNER 3 Trial continues to prove the Edwards SAPIEN 3 platform is the strategy for lifetime management—from the index procedure and beyond.

The 1st valve choice matters, and Edwards SAPIEN 3 platform delivers:

- **Life:** Consistent outcomes that matter, starting with the index procedure
- **Time:** Proven long-term outcomes and design that supports comprehensive durability
- **Management:** Making future options possible

Life | Time | Management

# The Edwards SAPIEN 3 platform

Built for now and what's next.

THE PARTNER 3 TRIAL

## Life

The only THV valve with

**1%**

death and disabling stroke at 1 year[1]

## Time

The only THV valve with

**90%**

survival at 5 years[2]

## Management

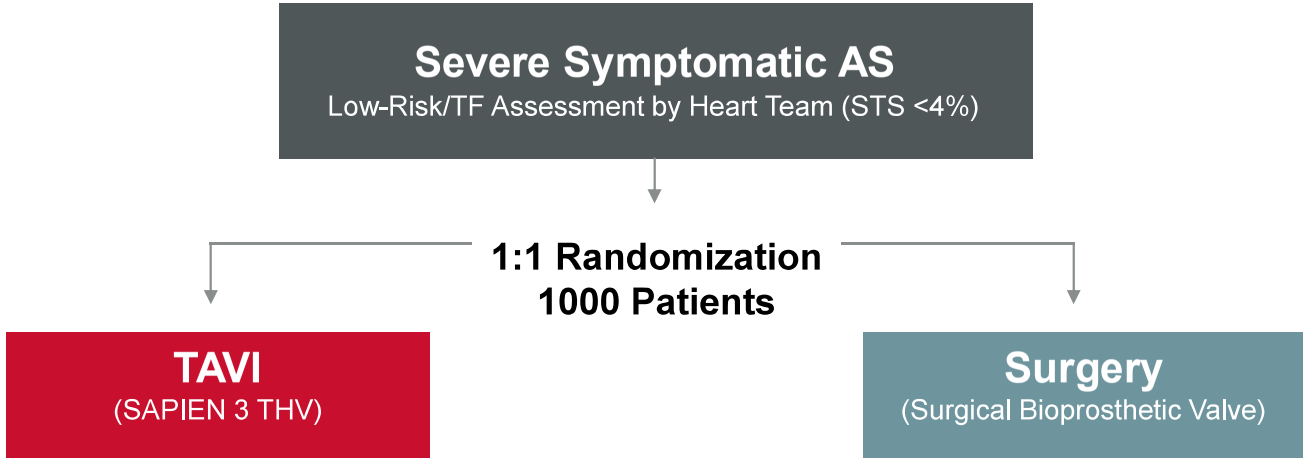
The only THV valve with a

**THV-in-THV**

indication[6]

THV = transcatheter heart valve

# The PARTNER 3 Trial design[1]: 1,000 low-risk patients across 71 sites with a comprehensive primary endpoint




## Primary Endpoint

Composite of all-cause mortality, stroke, or rehospitalization* at 1-year post-procedure

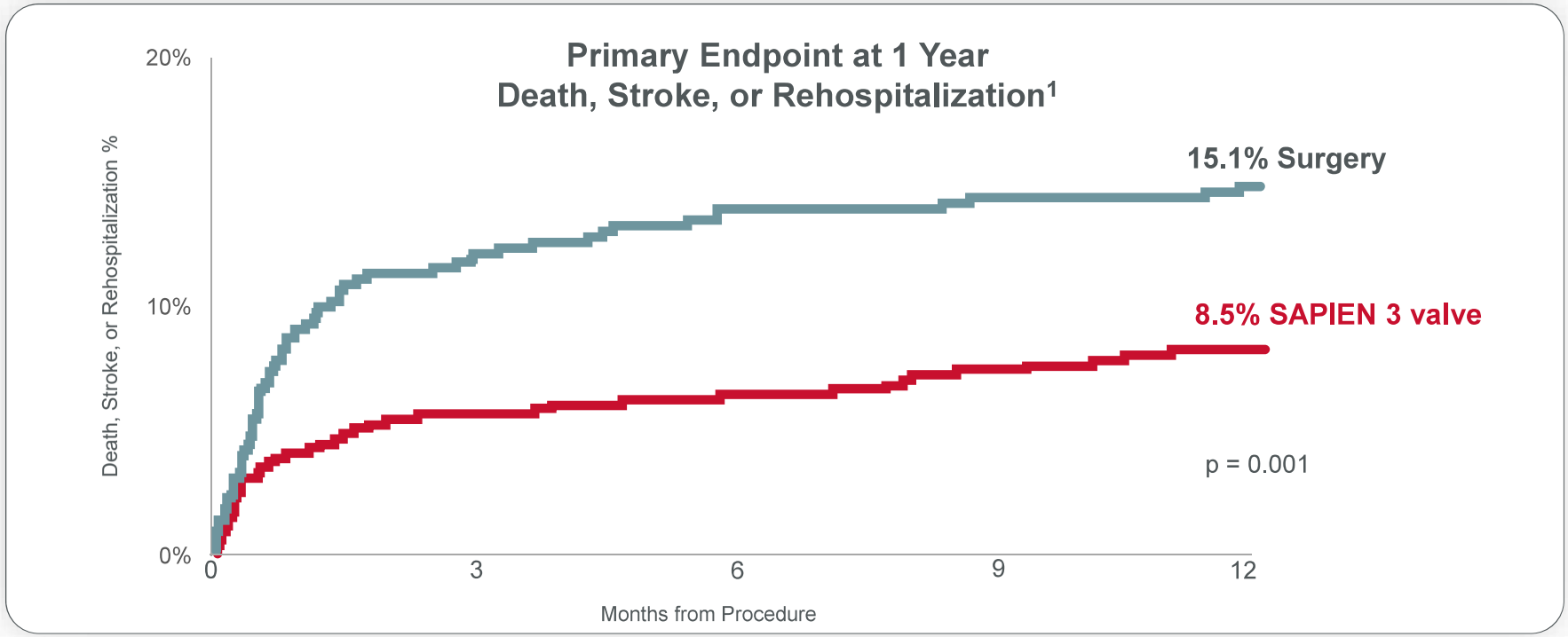
Follow-up: 30 days, 6 months, and annually through 10 years

AS = Aortic Stenosis
TAVI = Transcatheter aortic valve implantation

*rehospitalization defined as valve-related, procedure related, or heart-failure related rehospitalization.

# SAPIEN 3 valve: Superior to surgery in low-risk patients

THE PARTNER 3 TRIAL

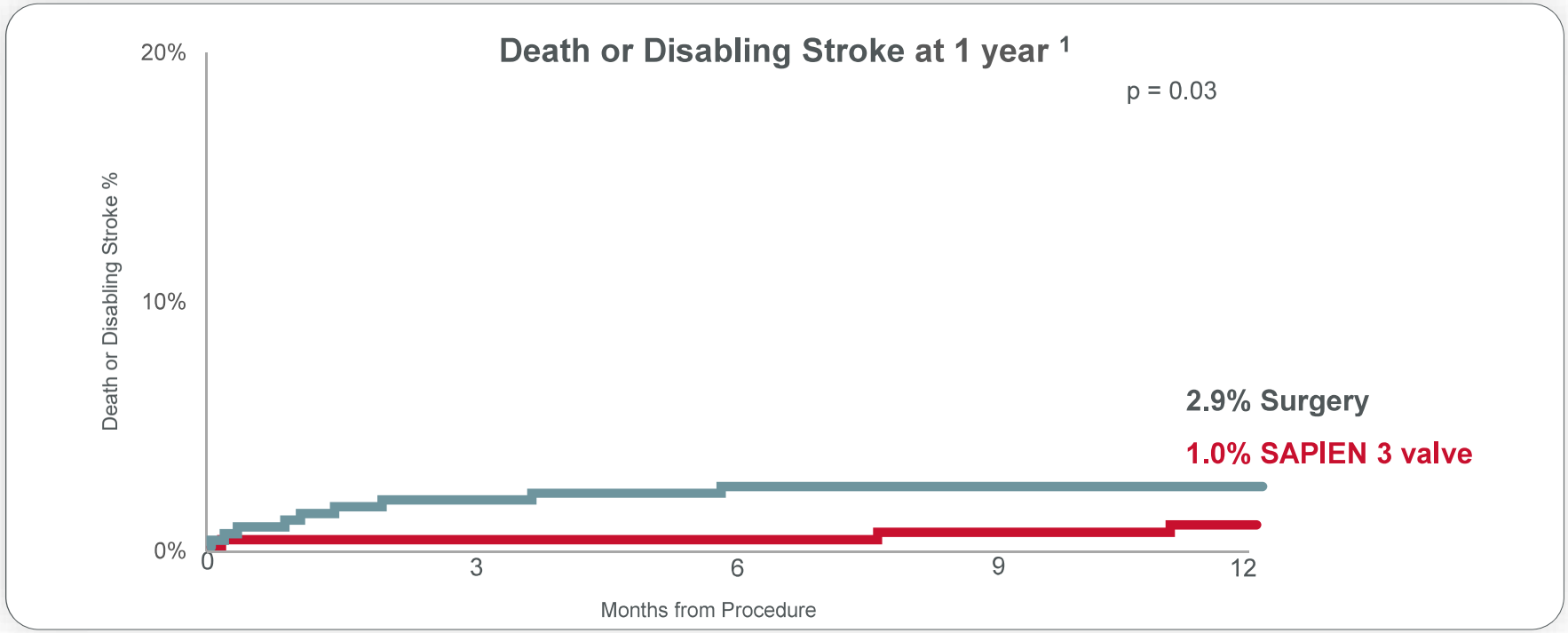



| Number at Risk | | | | | |
|---|---|---|---|---|---|
| **Surgery** | 454 | 390 | 381 | 377 | 374 |
| **SAPIEN 3 valve** | 496 | 467 | 462 | 456 | 451 |

rehospitalization defined as valve-related, procedure related, or heart-failure related rehospitalization.

# The only transcatheter heart valve (THV) with 1% death or disabling stroke at 1 year

THE PARTNER 3 TRIAL




| Number at Risk | | | | | |
|---|---|---|---|---|---|
| **Surgery** | 454 | 436 | 432 | 430 | 426 |
| **SAPIEN 3 valve** | 496 | 494 | 493 | 491 | 488 |

# SAPIEN 3 valve: Faster recovery, more likely to return home, and less rehospitalization than surgery

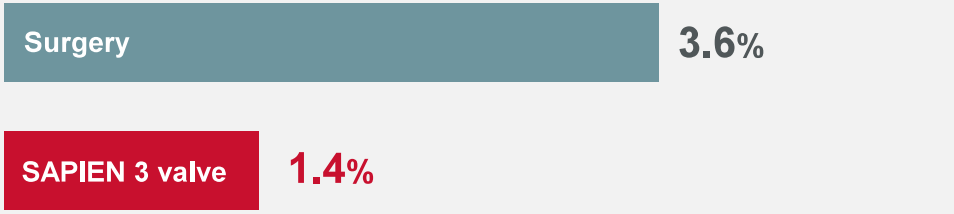
THE PARTNER 3 TRIAL

## Length of Stay (Days)[1]

p < 0.001


## Rehospitalization for Heart Failure at 1 year[7]

p = 0.029




## Discharge Home[1]

p < 0.001


## KCCQ Overall Summary Score[1]

(Percent Change from Baseline at 30days)

p < 0.01

# The SAPIEN 3 platform provides excellent index outcomes

THE PARTNER 3 TRIAL

*At year 1, patients that underwent TAVI with the SAPIEN 3 platform experienced [1]:*

**1.0%**
**All-cause mortality**
(n = 496)

**0.2%**
**Disabling stroke**
(n = 496)

**0.6%**
**Moderate or severe paravalvular regurgitation**
(n = 496)

**7.3%**
**Permanent pacemaker implantation***
(n = 496)

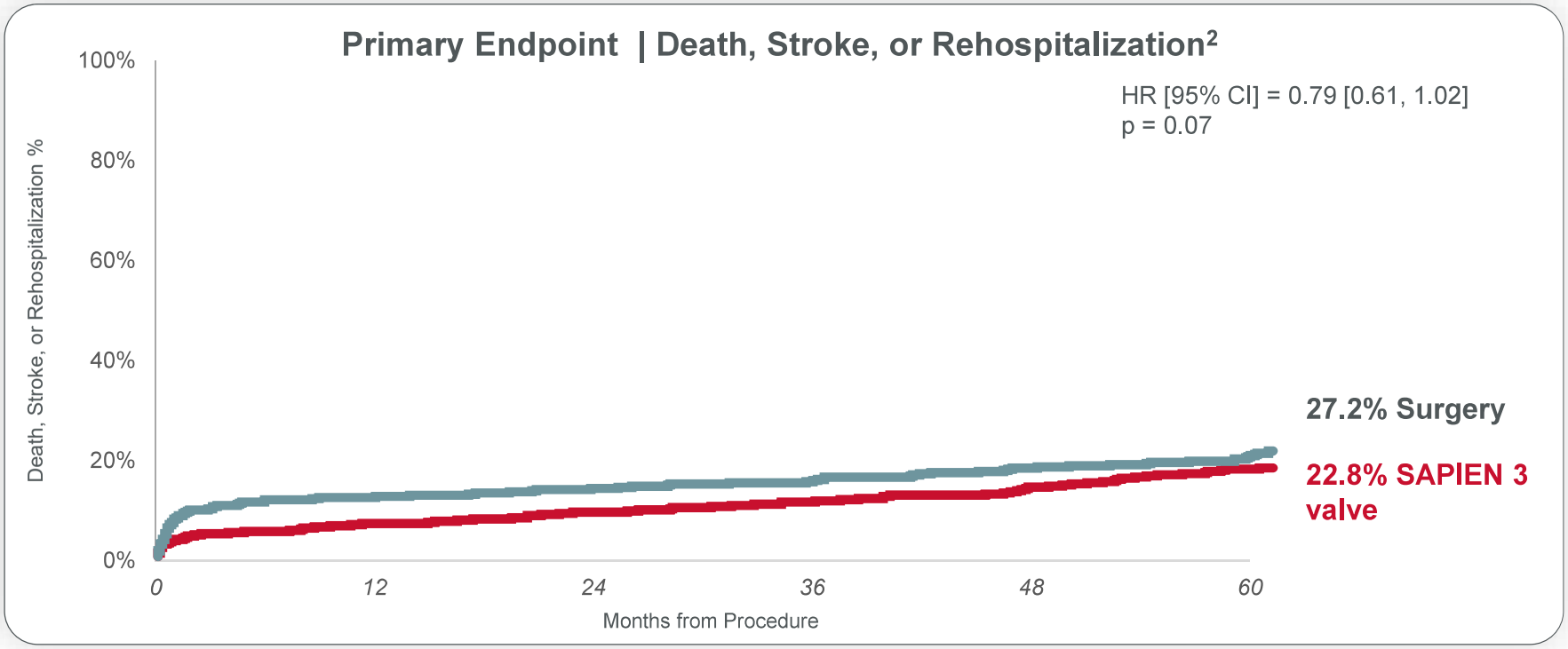
**Strong outcomes allow patients to stay out of the hospital**

**92.7%**
of patients did not require rehospitalization within 1 year.[1]

*Includes patients who had pacemaker at baseline.

# Early, immediate benefits of SAPIEN 3 valve sustained out to five years

THE PARTNER 3 TRIAL

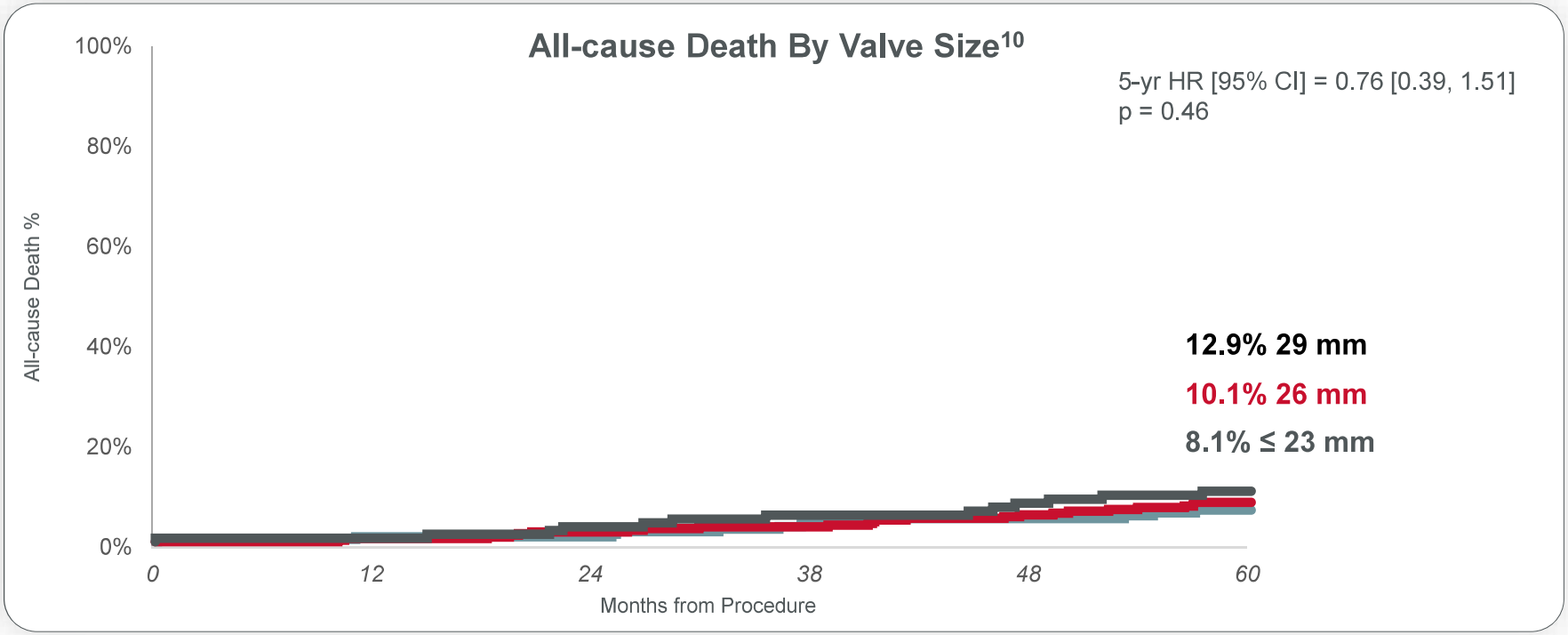



| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| **Surgery** | 454 | 372 | 349 | 328 | 309 | 276 |
| **SAPIEN 3 valve** | 496 | 453 | 434 | 415 | 391 | 353 |

rehospitalization defined as valve-related, procedure related, or heart-failure related rehospitalization.

# Excellent performance across all valve sizes

THE PARTNER 3 TRIAL

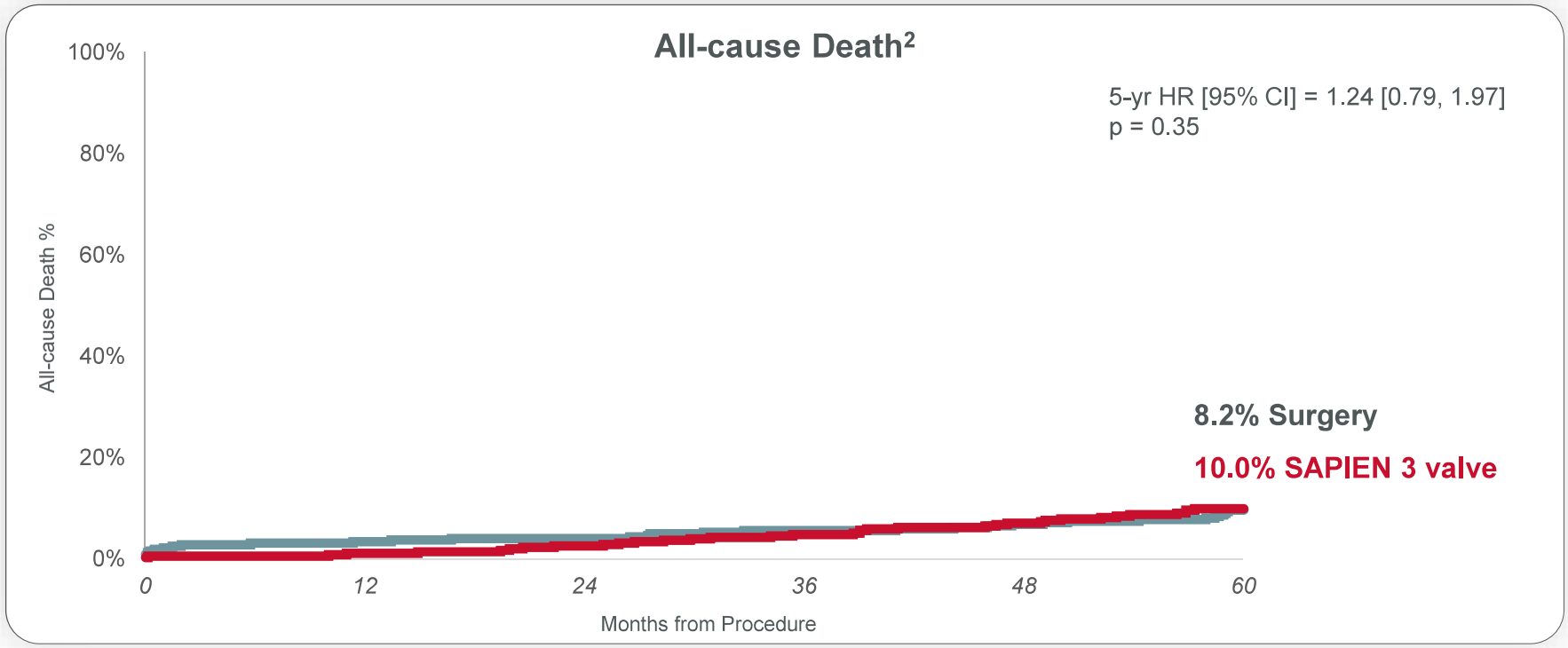



| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| ≤ 23 mm | 156 | 153 | 150 | 143 | 139 | 125 |
| 26 mm | 236 | 234 | 228 | 223 | 210 | 196 |
| 29 mm | 104 | 103 | 100 | 94 | 89 | 84 |

*There were 11 patients with a 20 mm valve*

# The only THV valve with 90% survival at 5 years

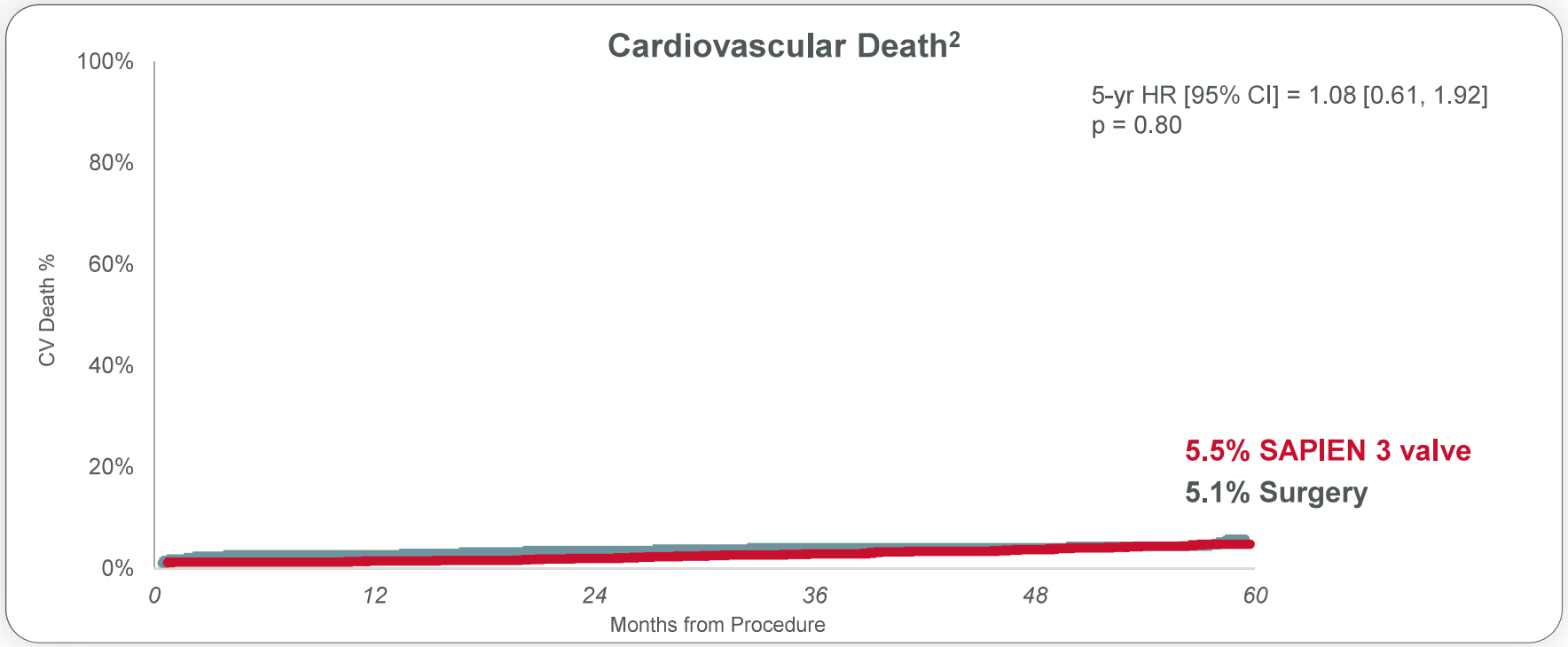
THE PARTNER 3 TRIAL




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 427 | 409 | 394 | 379 | 346 |
| SAPIEN 3 valve | 496 | 490 | 478 | 460 | 438 | 405 |

# Low and similar rates of cardiovascular mortality through 5 years

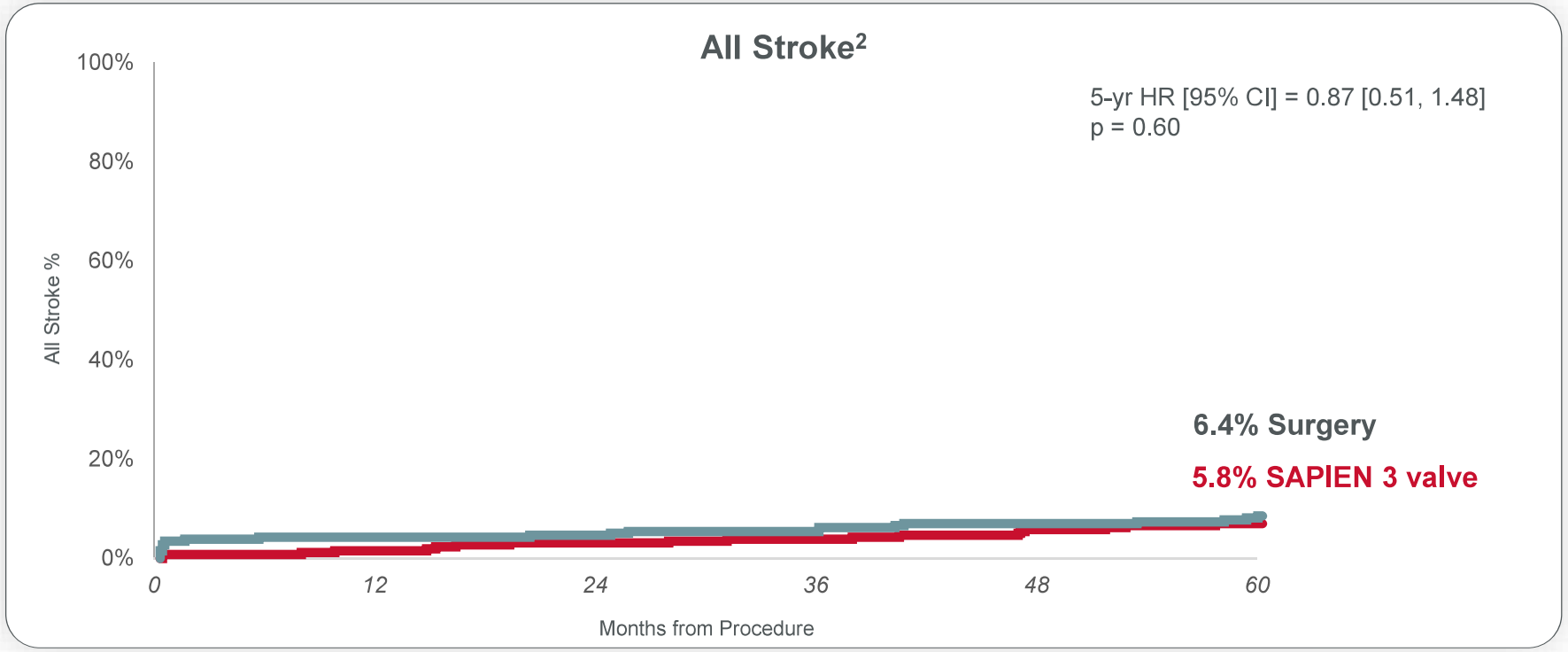
THE PARTNER 3 TRIAL




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 427 | 409 | 394 | 379 | 346 |
| SAPIEN 3 valve | 496 | 490 | 478 | 460 | 438 | 404 |

# Low and similar rates of stroke through 5 years

THE PARTNER 3 TRIAL




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 416 | 397 | 378 | 361 | 329 |
| SAPIEN 3 valve | 496 | 486 | 468 | 450 | 428 | 391 |

# Low and similar rates of disabling stroke through 5 years

THE PARTNER 3 TRIAL

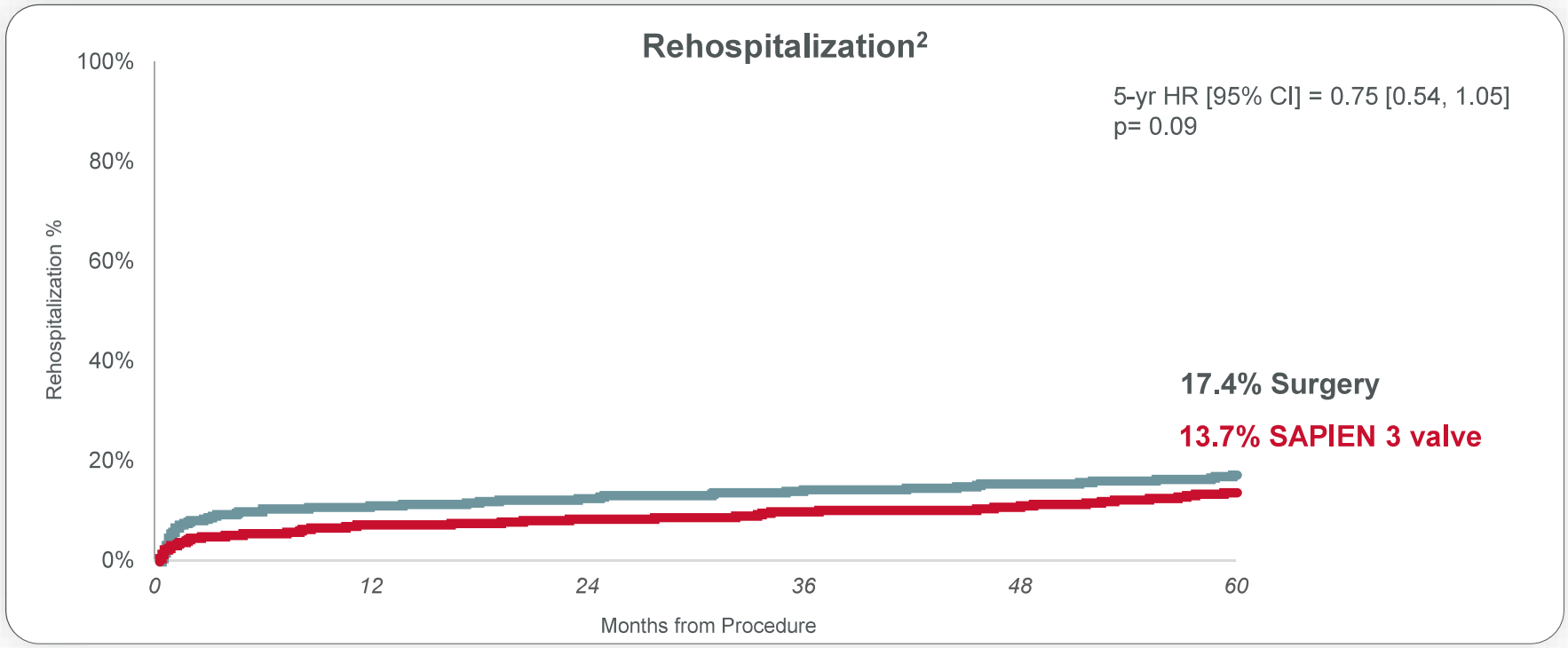
| Endpoint (0-5 years) | TAVI | Surgery |
|---|---|---|
| **All Stroke[2]** | **5.8% (27)*** | **6.4% (27)** |
| **Disabling** | **2.9% (13)*** | **2.7% (11)** |
| Ischemic | 10 | 8 |
| Hemorrhagic | 3 | 3 |
| **Non-disabling** | **3.2% (15)*** | **3.7% (16)** |
| Ischemic | 14 | 13 |
| Hemorrhagic | 1 | 1 |
| Undetermined | 0 | 2 |

KM Rate (No. of pts)

*3 patients in the TAVI arm had multiple strokes

# Low rates of rehospitalization through 5 years

THE PARTNER 3 TRIAL




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 381 | 359 | 339 | 321 | 289 |
| SAPIEN 3 valve | 496 | 455 | 439 | 419 | 396 | 361 |

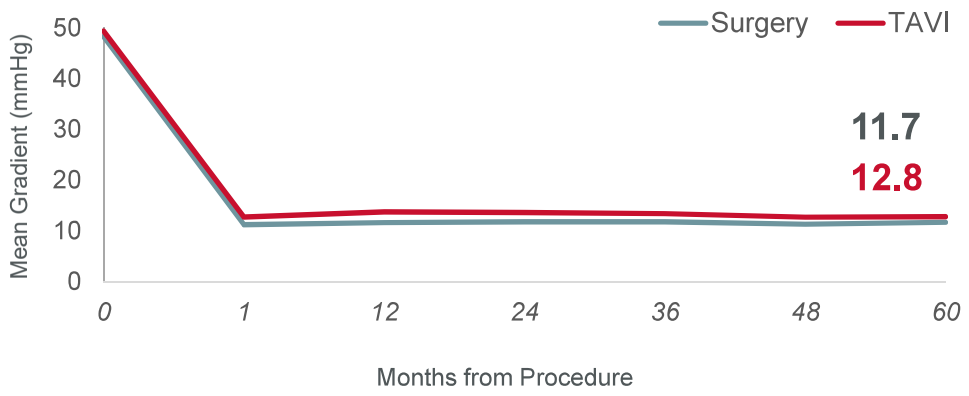
rehospitalization defined as valve-related, procedure related, or heart-failure related rehospitalization.

# Stable valve hemodynamics out to 5 years[2]

THE PARTNER 3 TRIAL

## Mean Gradient

p < 0.001

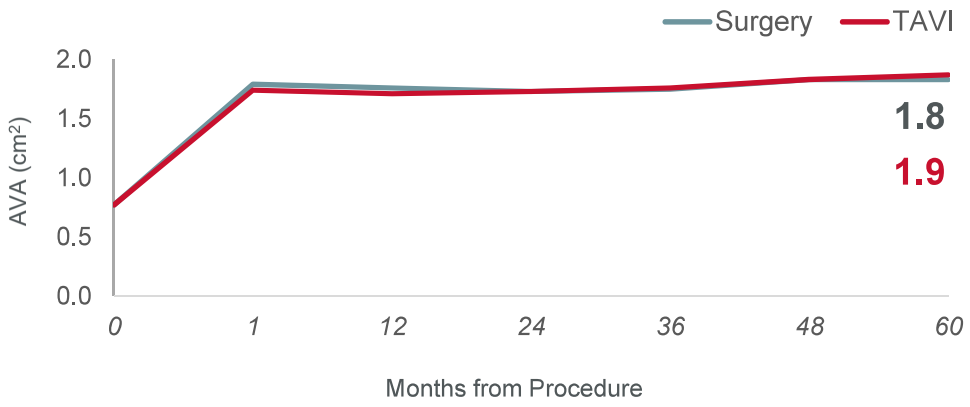



Number of Echos

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Surgery** | 442 | 432 | 391 | 360 | 304 | 305 | 282 |
| **TAVI** | 483 | 492 | 474 | 437 | 372 | 348 | 329 |

## Aortic Valve Area

p = 0.90




Number of Echos

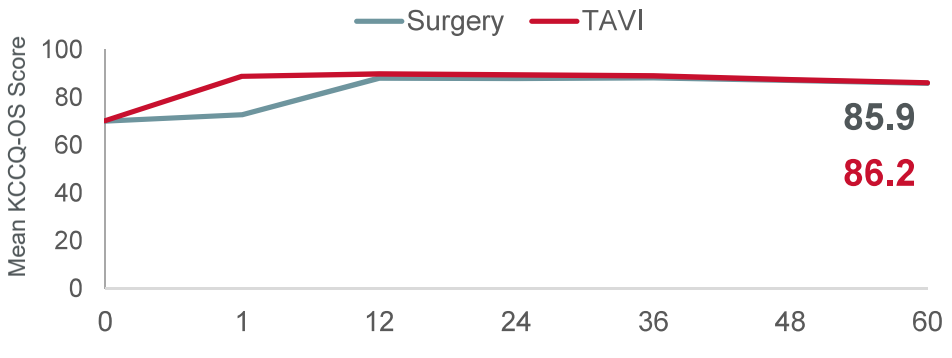
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Surgery** | 424 | 415 | 371 | 342 | 289 | 295 | 275 |
| **TAVI** | 458 | 482 | 450 | 416 | 347 | 334 | 320 |

# Early quality of life benefits – maintained and similar for both therapies out to 5 years[2]

THE PARTNER 3 TRIAL

## Mean KCCQ-OS Score

p = 0.99

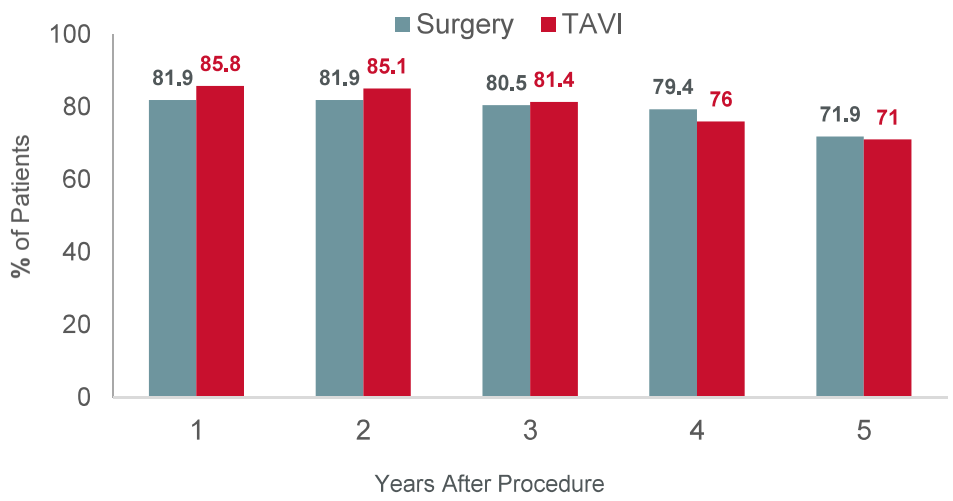



Number of Patients

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Surgery** | 448 | 433 | 403 | 367 | 340 | 321 | 301 |
| **TAVI** | 493 | 491 | 481 | 444 | 406 | 381 | 354 |

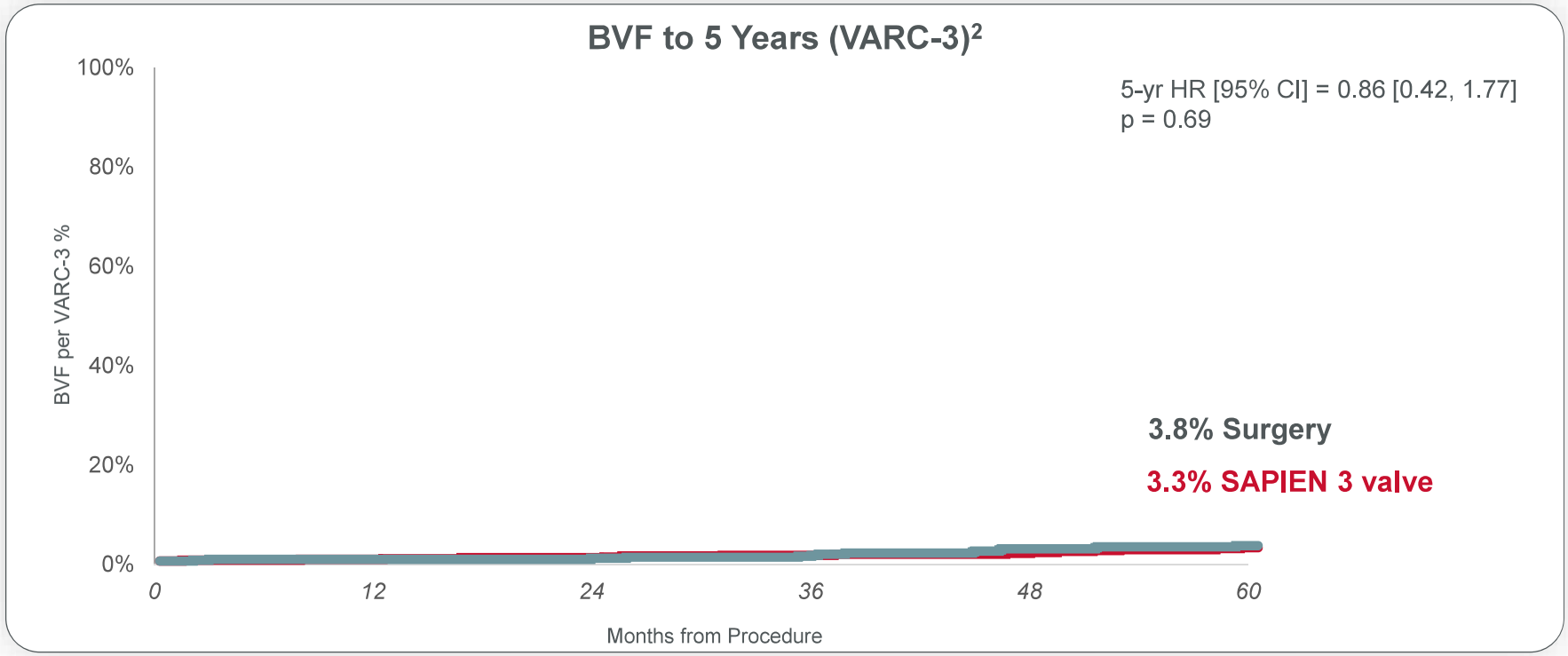
## Alive with a KCCQ-OS Score > 75 [8]

p = NS at all time points



# Ultra-low rates of valve failure at 5 years

THE PARTNER 3 TRIAL

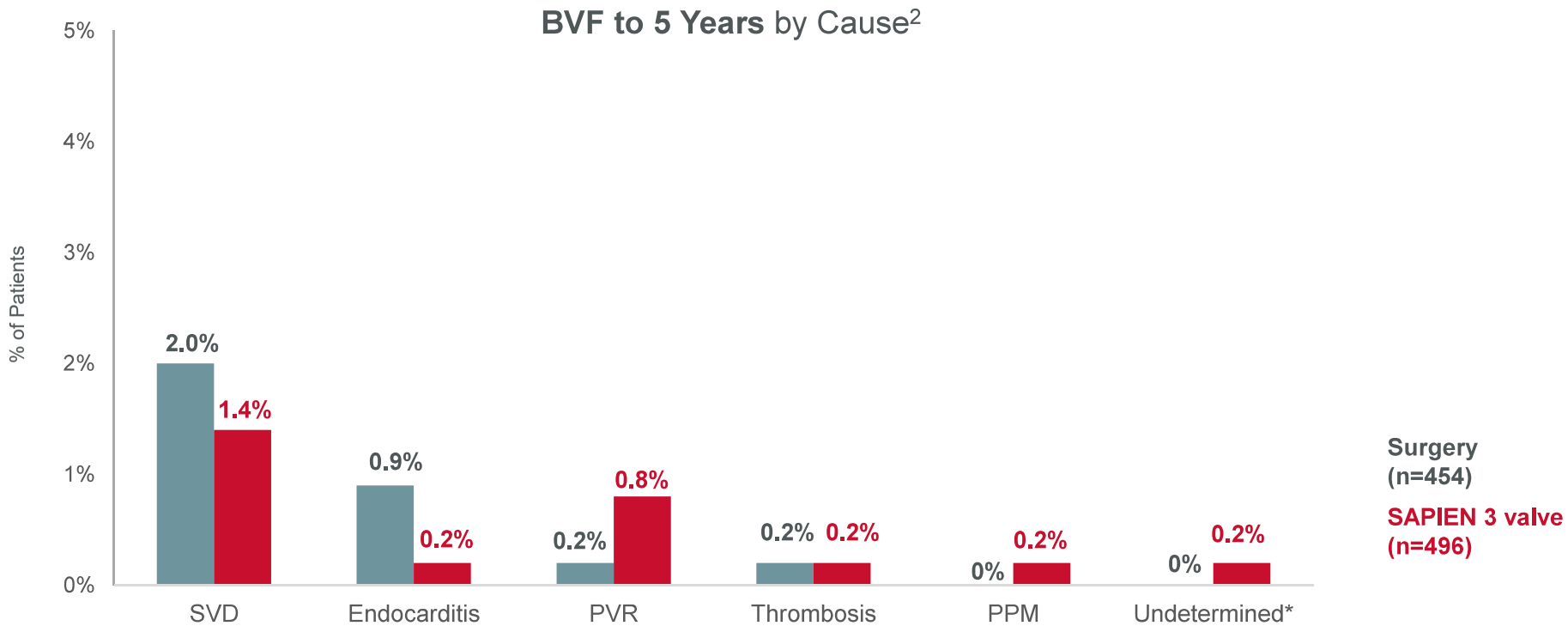



| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 426 | 407 | 390 | 369 | 334 |
| SAPIEN 3 valve | 496 | 489 | 475 | 454 | 430 | 392 |

BVF = Bioprosthetic valve failure

# Stable, low and similar rates of structural valve deterioration and nonstructural valve dysfunction

THE PARTNER 3 TRIAL

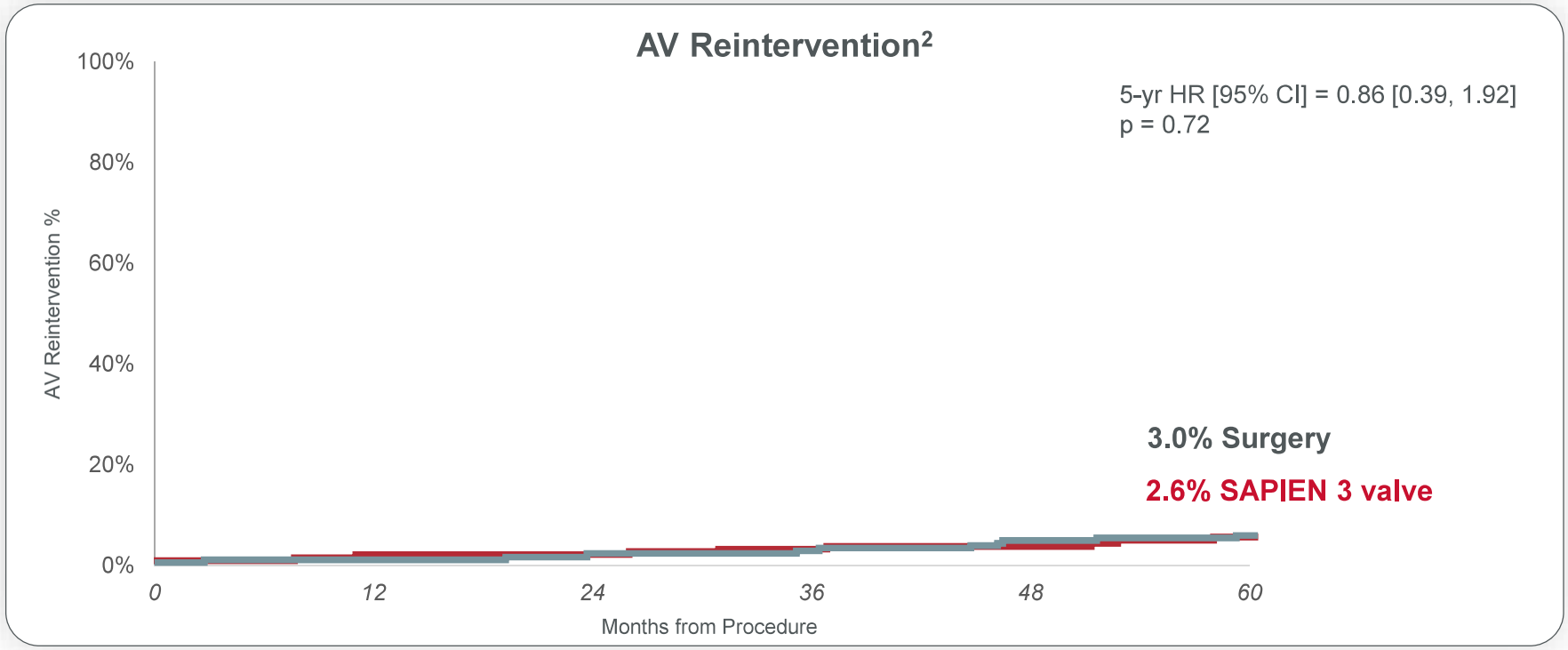



BVF = Bioprosthetic valve failure
SVD = Structural valve deterioration
PPM = Patient prosthesis mismatch
PVR = Paravalvular Regurgitation

*1 patient had a ViV for stenosis with undetermined cause of BVF

# Low rates of aortic valve reintervention

THE PARTNER 3 TRIAL




| Number at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Surgery | 454 | 426 | 406 | 390 | 371 | 337 |
| SAPIEN 3 valve | 496 | 488 | 475 | 456 | 433 | 396 |

Aortic Valve (AV) reintervention includes any of balloon aortic valvuloplasty, surgical aortic valve replacement, valve in valve, percutaneous paravalvular regurgitation closure

# SAPIEN 3 valve makes future options possible

A valve system ready for intervention **and** reintervention

**The only valve**
approved for THV-in-THV[6]

A valve platform with excellent real-world results for continued coronary access[9]

A valve platform designed to host future valve interventions with a low-risk plane

# Consistently delivering innovation for patient needs

**SAPIEN valve**
Introduced TAVI

*A life-saving treatment option for inoperable–or high-surgical risk–patients.*[3]

**SAPIEN XT valve**
Streamlined profile

*Streamlined to reduce French size and minimize vascular complications.*[4]

**SAPIEN 3 valve**
Proven superior to surgery in low-risk patients

*Addition of outer [PET] skirt to reduce paravalvular leak (PVL), optimized cell size for future coronary access, and introduced a new delivery system for predictable deployment.* [1†]

**SAPIEN 3 Ultra valve**
Extended PVL skirt height

*Extended PVL skirt height to reduce occurrences of moderate and mild PVL.*[5]

**2007**

THE PARTNER 3 TRIAL

† The PARTNER 3 Trial, SAPIEN 3 TAVI proven superior to surgery on the primary endpoint of all-cause death, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at one year, and multiple pre-specified secondary endpoints.

# Clinical implications from The PARTNER 3 Trial investigators

The 5-year follow-up findings from
The PARTNER 3 Trial reaffirm the clinical and echocardiographic benefits of SAPIEN 3 valve as a meaningful alternative to surgical therapy for low-risk, severe symptomatic AS patients

# The Edwards SAPIEN 3 platform

Built for now and what's next.

THE PARTNER 3 TRIAL

## Life

The only THV valve with

**1%**

death and disabling stroke at 1 year[1]

## Time

The only THV valve with

**90%**

survival at 5 years[2]

## Management

The only THV valve with a

**THV-in-THV**

indication[6]

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3. Leon MB, Smith CR, Mack MJ, *et al.* Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med. 2010.
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**Medical device for professional use. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (consult eifu.edwards.com where applicable).**



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# The strategy for lifetime management

Edwards SAPIEN 3 platform

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# Life

## Consistently demonstrating the results you need for the outcomes that matter

Only SAPIEN 3 transcatheter aortic valve replacement (TAVR) is proven superior to surgery in low-risk patients*[1]

**PARTNER 3 trial clinical events at 30 days and 1 year**

| | 30 days | | 1 year | | |
|---|---|---|---|---|---|
| | **SAPIEN 3 TAVR (n = 496)** | Surgery (n = 454) | **SAPIEN 3 TAVR (n = 496)** | Surgery (n = 454) | *P*-value |
| **Primary endpoint** | | | | | |
| All-cause death, all stroke, and rehospitalization at 1 year 8.5% TAVR vs 15.1% for surgery $P_{superiority}$ = 0.001 | | | | | |
| All-cause death | **0.4%** | 1.1% | **1.0%** | 2.5% | *P* = 0.09 |
| All stroke | **0.6%** | 2.4% | **1.2%** | 3.1% | *P* = 0.04 |
| Rehospitalization* | **3.4%** | 6.5% | **7.3%** | 11.0% | *P* = 0.046 |

### Consistently strong procedural outcomes for a variety of patient morphologies

Excellent clinical outcomes in **low-risk bicuspid patients**.[2]

Consistently strong outcomes across indicated annular sizes.[3]

*In the PARTNER 3 trial, SAPIEN 3 TAVR was proven superior to surgery on the primary endpoint of all-cause death, all stroke, and rehospitalization (valve-related or procedure-related, and including due to heart failure) at 1 year and multiple prespecified secondary endpoints in low-risk patients.

## What's your strategy for lifetime management?

With patients of all ages living longer and having high expectations for their quality of life, lifetime management is increasingly important.

**The first valve choice matters.** From outstanding outcomes and excellent durability* today to facilitating future interventions tomorrow, the SAPIEN platform is designed to deliver a TAVR experience an implanter can count on.

**Life** — **Consistently demonstrating the results you need, for the outcomes that matter**

**Time** — **A comprehensive approach to durability that addresses the key drivers of reintervention**

**Management** — **Making future options possible**[1,4-6]

*Propensity-matched analysis of intermediate-risk patients using VARC-3 definitions of structural valve deterioration (SVD) and SVD-related bioprosthetic valve failure (BVF) at 5 years.

# Life

## Consistently demonstrating the results you need for the outcomes that matter

Only SAPIEN 3 transcatheter aortic valve replacement (TAVR) is proven superior to surgery in low-risk patients*[1]

**PARTNER 3 trial clinical events at 30 days and 1 year**

| | 30 days | | 1 year | | |
|---|---|---|---|---|---|
| | **SAPIEN 3 TAVR (n = 496)** | Surgery (n = 454) | **SAPIEN 3 TAVR (n = 496)** | Surgery (n = 454) | *P*-value |
| **Primary endpoint** | | | | | |
| All-cause death, all stroke, and rehospitalization at 1 year 8.5% TAVR vs 15.1% for surgery $P_{superiority} = 0.001$ | | | | | |
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# Time

## SAPIEN valve technology is designed specifically to support valve durability

A unique design built for differentiated outcomes

**Structural valve deterioration**[7]

Bovine pericardium collagen structure that **reduces the potential for tissue tear**

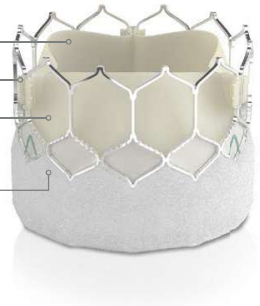
Circularity for **high radial strength** and **optimal hemodynamics**

Three independently matched leaflets for **thickness** and **elasticity**

**Nonstructural valve dysfunction**

SAPIEN 3 Ultra transcatheter aortic valve replacement (TAVR) technology features a 40% taller, textured outer skirt for paravalvular leak (PVL) protection*

- Delivered real-world low rates of PVL in a propensity-matched analysis[4]



## SAPIEN 3 transcatheter aortic valve replacement has demonstrated excellent durability

**5 years**

The PARTNER II S3i trial demonstrated:

- SAPIEN 3 transcatheter aortic valve replacement **durability similar to surgery**[18]
- **Low rates of structural valve deterioration (SVD)** and **SVD-related bioprosthetic valve failure,** similar to surgery at 5 years[8]

Real-world data has demonstrated:

- Excellent 5-year SAPIEN valve **durability performance for small-annuli patients**[9]

*Compared to SAPIEN 3 valve.
†Propensity-matched analysis of intermediate-risk patients using VARC-3 definitions of structural valve deterioration (SVD) and SVD-related bioprosthetic valve failure at 5 years.

# Management

## Facilitates coronary access, reducing obstacles to future therapy options[4,5]

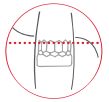
SAPIEN 3 transcatheter valve system technology is designed to minimize obstacles to future therapy

- Excellent real-world results for continued coronary access*

**100%** successful coronary access post transcatheter aortic valve replacement (68/68)[5]

- The **only platform** indicated for both TAV-in-TAV and TAV-in-SAV procedures*
  - A valve platform with excellent safety and procedural outcomes for surgical valve-in-valve procedures*[10]
  - Outcomes for TAV-in-TAV with the SAPIEN 3 valve platform are similar to native transcatheter aortic valve replacement†[11]

### Designed to host future valve interventions



**Low risk plane**

**2.0%** risk of future sinus sequestration‡[12]

*For patients assessed at high risk for surgical replacement.
†There are limited data evaluating safety and efficacy of redo-TAVR.
‡Risk of sinus sequestration if (1) prior TAV commissure level above sinotubular junction (STJ), and (2) the distance between TAV and STJ was <2.0 mm in each coronary sinus.

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a propensity-matched analysis from the United States. *Circ Cardiovasc Interv*. 2021;14(9):e010543. **5.** Tarantini G, Nai Fovino L, Le Prince P, et al. Coronary access and percutaneous coronary intervention up to 3 years after transcatheter aortic valve implantation with a balloon-expandable valve. *Circ Cardiovasc Interv*. 2020;13(7):e008972. **6.** Leon MB, Mack MJ, Hahn RT, et al. Outcomes 2 years

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**Please see enclosed Important Safety Information.**

**CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a physician. See Instructions for Use for full prescribing information.**

**For professional use. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (consult eifu.edwards.com where applicable).**



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# Important Safety Information

**Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, and Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve System**

**Indications:** The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve, a surgical bioprosthetic mitral valve, or a native mitral valve with an annuloplasty ring who are judged by a Heart Team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

**Contraindications:** The valves and delivery systems are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections, or who have significant annuloplasty ring dehiscence.

**Warnings:** Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation. There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients. The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing. Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch), and/or annular rupture. Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, or young adults and in patients with an altered calcium metabolism. Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve. Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease. Patients with pre-existing prostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment. Do not use the valve if the tamper-evident seal is broken or the storage solution does not completely cover the valve (SAPIEN 3 and SAPIEN 3 Ultra only), the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed. Do not mishandle the delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g., kinked or stretched), or if the expiration date has elapsed. Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored. Patient injury could occur if the delivery system is not un-flexed prior to removal. Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials. The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting. Valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without anticoagulation. Do not add or apply antibiotics to the storage solution (SAPIEN 3 and SAPIEN 3 Ultra only), rinse solution, or to the valve. Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets. Do not perform stand-alone balloon aortic valvuloplasty procedures in the INSPIRIS RESILIA aortic valve for the sizes 19-25 mm. This may expand the valve causing aortic incompetence, coronary embolism or annular rupture. Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of partial annuloplasty ring dehiscence due to high risk of PVL. Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of partial (incomplete) annuloplasty rings in the absence of annular calcium due to increased risk of valve embolization. Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of rigid annuloplasty rings due to increased risk of PVL or THV deformation.

**Precautions:** Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established. Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Safety Data Sheet available from Edwards Lifesciences. If a significant increase in resistance occurs when advancing the catheter through the vasculature, stop advancement and investigate the cause of resistance before proceeding. Do not force passage, as this could increase the risk of vascular complications. As compared to SAPIEN 3, system advancement force may be higher with the use of SAPIEN 3 Ultra/SAPIEN 3 Ultra RESILIA THV in tortuous/challenging vessel anatomies. To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon. Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis. Additional precautions for transseptal replacement of a failed mitral valve bioprosthesis include, the presence of devices or thrombus or other abnormalities in the caval vein precluding safe transvenous femoral access for transseptal approach; and the presence of an Atrial Septal Occluder Device or calcium preventing safe transseptal access. Special care must be exercised in mitral valve replacement to avoid entrapment of the subvalvular apparatus. Safety and effectiveness have not been established for patients with the following characteristics/comorbidities: non-calcified aortic annulus; severe ventricular dysfunction with ejection fraction < 20%; congenital unicuspid aortic valve; pre-existing prosthetic ring in the tricuspid position; severe mitral annular calcification (MAC); severe (> 3+) mitral insufficiency, or Gorlin syndrome; blood dyscrasias defined as leukopenia (WBC < 3000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy; hypertrophic cardiomyopathy with or without obstruction (HOCM); echocardiographic evidence of intracardiac mass, thrombus, or vegetation; a known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately premedicated; significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater, marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta; access characteristics that would preclude safe placement of the Edwards sheath, such as severe obstructive calcification or severe tortuosity; bulky calcified aortic valve leaflets in close proximity to coronary ostia; a concomitant paravalvular leak where the failing prosthesis is not securely fixed in the native annulus or is not structurally intact (e.g., wireform frame fracture, annuloplasty ring dehiscence); or a partially detached leaflet of the failing

Edwards

bioprosthesis that in the aortic position may obstruct a coronary ostium. For Left axillary approach, a left subclavian takeoff angle ~ ≥ 90° from the aortic arch causes sharp angles, which may be responsible for potential sheath kinking, subclavian/axillary dissection and aortic arch damage. For left/right axillary approach, ensure there is flow in Left Internal Mammary Artery (LIMA)/Right Internal Mammary Artery (RIMA) during procedure and monitor pressure in homolateral radial artery. Residual mean gradient may be higher in a "THV-in-failing prosthesis" configuration than that observed following implantation of the valve inside a native aortic annulus using the same size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting prosthesis be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

**Potential Adverse Events:** Potential risks associated with the overall procedure, including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography: death; stroke/transient ischemic attack, clusters, or neurological deficit; paralysis; permanent disability; respiratory insufficiency or respiratory failure; hemorrhage requiring transfusion or intervention; cardiovascular injury including perforation or dissection of vessels, ventricle, atrium, septum, myocardium, or valvular structures that may require intervention; pericardial effusion or cardiac tamponade; thoracic bleeding; embolization including air, calcific valve material, or thrombus; infection including septicemia and endocarditis; heart failure; myocardial infarction; renal insufficiency or renal failure; conduction system defect which may require a permanent pacemaker; arrhythmia; retroperitoneal bleed; arteriovenous (AV) fistula or pseudoaneurysm; reoperation; ischemia or nerve injury or brachial plexus injury; restenosis; pulmonary edema; pleural effusion; bleeding; anemia; abnormal lab values (including electrolyte imbalance); hypertension or hypotension; allergic reaction to anesthesia, contrast media, or device materials; hematoma; syncope; pain or changes (e.g., wound infection, hematoma, and other wound care complications) at the access site; exercise intolerance or weakness; inflammation; angina; heart murmur; and fever. Additional potential risks associated with the use of the valve, delivery system, and/or accessories include: cardiac arrest; cardiogenic shock; emergency cardiac surgery; cardiac failure or low cardiac output; coronary flow obstruction/transvalvular flow disturbance; device thrombosis requiring intervention; valve thrombosis; device embolization; device migration or malposition requiring intervention; left ventricular outflow tract obstruction; valve deployment in unintended location; valve stenosis; structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis); device degeneration; paravalvular or transvalvular leak; valve regurgitation; hemolysis; device explants; nonstructural dysfunction; mechanical failure of delivery system and/or accessories; and non-emergent reoperation.

## Edwards Crimper

**Indications:** The Edwards crimper is indicated for use in preparing the Edwards SAPIEN 3 transcatheter heart valve, Edwards SAPIEN 3 Ultra transcatheter heart valve, and the Edwards SAPIEN 3 Ultra RESILIA transcatheter heart valve for implantation.

**Contraindications:** There are no known contraindications.

**Warnings:** The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing. Do not mishandle the device. Do not use the device if the packaging or any components are not sterile, have been opened or are damaged, or the expiration date has elapsed.

**Precautions:** For special considerations associated with the use of the Edwards crimper prior to THV implantation, refer to the THV Instructions for Use.

**Potential Adverse Events:** There are no known potential adverse events associated with the Edwards crimper.



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# Your first move defines the next

## The PARTNER 3 Trial 5-year data

5-year data from the PARTNER 3 Trial continues to prove the Edwards SAPIEN 3 platform is the strategy for lifetime management – from the index procedure and beyond

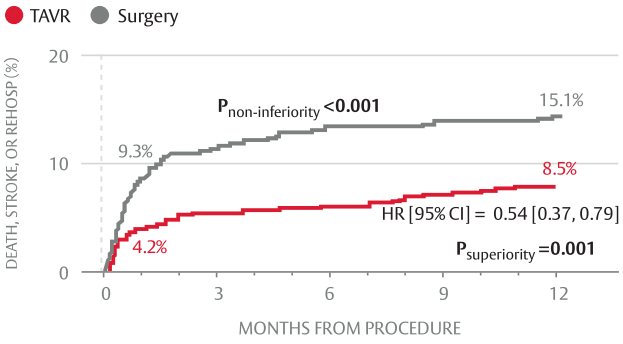
**Life** | **Time** | **Management**

**The only transcatheter valve** with 1% death or disabling stroke at 1 year

# 1%

death or disabling stroke at 1 year

## Primary Endpoint Superior* to Surgery




| Number at risk: | | | | | | |
|---|---|---|---|---|---|---|
| TAVR | 496 | 475 | 467 | 462 | 456 | 451 |
| Surgery | 454 | 408 | 390 | 381 | 377 | 374 |

* In the PARTNER 3 trial, SAPIEN 3 TAVR was proven superior to surgery on the primary endpoint of all-cause death, all stroke, and rehospitalization (valve-related or procedure-related, and including due to heart failure) at one year and multiple pre-specified secondary endpoints in low-risk patients.

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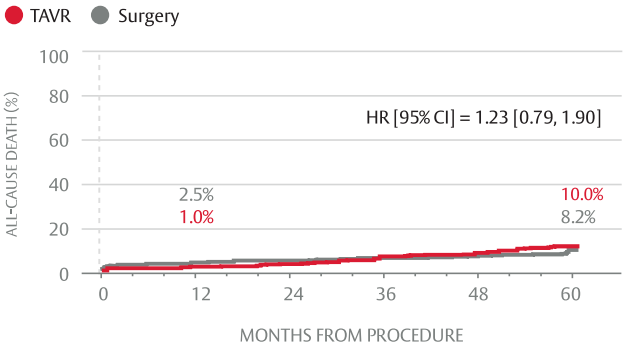
Life Time Management

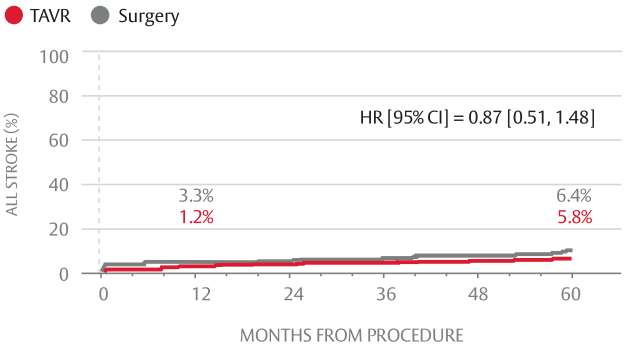
## **The only transcatheter valve** that demonstrates 90% survival at 5 years

### All-cause Death



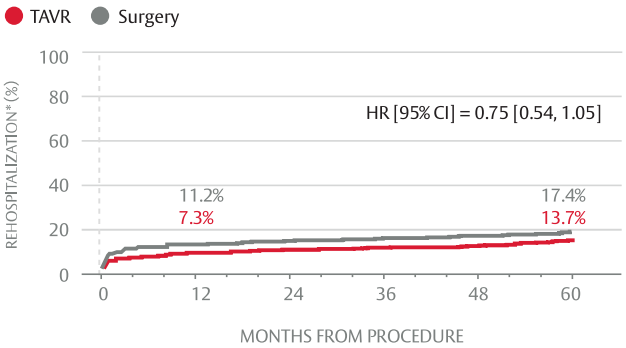

| Number at risk: | | | | | | |
|---|---|---|---|---|---|---|
| TAVR | 496 | 490 | 478 | 460 | 438 | 405 |
| Surgery | 454 | 427 | 409 | 394 | 379 | 346 |

### All Stroke




| Number at risk: | | | | | | |
|---|---|---|---|---|---|---|
| TAVR | 496 | 486 | 468 | 450 | 428 | 391 |
| Surgery | 454 | 416 | 397 | 378 | 361 | 329 |

### Rehospitalization*




| Number at risk: | | | | | | |
|---|---|---|---|---|---|---|
| TAVR | 496 | 455 | 439 | 419 | 396 | 361 |
| Surgery | 454 | 381 | 359 | 339 | 321 | 289 |

*Rehospitalization defined as valve-, procedure-, or heart failure-related

| Cardiovascular mortality (5 years) | | |
|---|---|---|
| SAPIEN 3 TAVR | SAVR | HR (95% CI) |
| 5.5% | 5.1% | 1.08 (0.61, 1.92) |

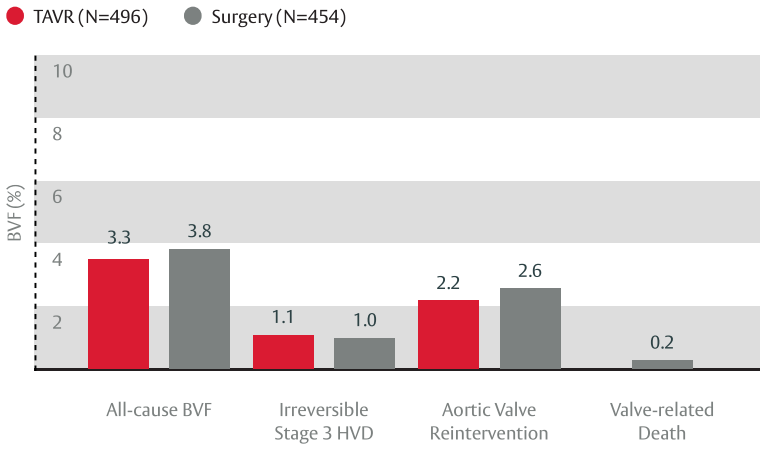
| Disabling stroke (5 years) | | |
|---|---|---|
| SAPIEN 3 TAVR | SAVR | HR (95% CI) |
| 2.9% | 2.7% | 1.03 (0.46, 2.30) |

| Death or disabling stroke (5 years) | | |
|---|---|---|
| SAPIEN 3 TAVR | SAVR | HR (95% CI) |
| 11.5% | 9.8% | 1.17 (0.78, 1.75) |

Life > Time > Management

**The only valve** approved with a THV-in-THV indication*

# Ultra-Low Rates of Valve Failure or Reintervention at 5 Years




*For patients assessed at high-risk for surgical replacement

**Your first move defines the next.**

Choose the Edwards SAPIEN 3 platform as your proven strategy for success.

**References:** 1. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients at Five Years. *NEJM* 2023.

**Medical device for professional use. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (consult eifu.edwards.com where applicable).**



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