Three-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis

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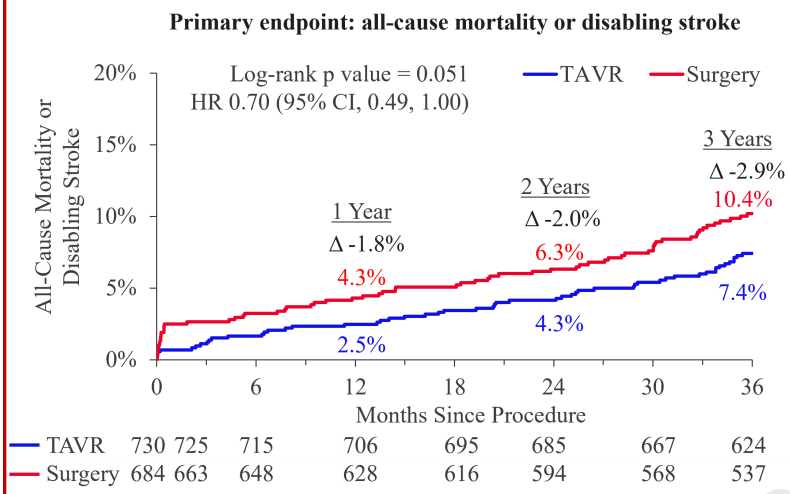
CENTRAL ILLUSTRATION: Three-Year Outcomes Following Transcatheter Aortic Valve Replacement or Surgery in Patients from the Evolut Low Risk Trial



All-cause mortality or disabling stroke was lower with self-expanding TAVR vs surgery at 3 years

Difference in KM rates for TAVR vs surgery remained broadly consistent over time

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ABSTRACT

Background: Randomized data comparing outcomes of transcatheter aortic valve replacement (TAVR) to surgery in low surgical risk patients at time points beyond 2 years is limited. This presents an unknown for physicians striving to educate patients as part of a shared decision-making process.

Objective: We evaluated 3-year clinical and echocardiographic outcomes from the Evolut Low Risk trial.

Methods: Low-risk patients were randomized to TAVR with a self-expanding, supra-annular valve or surgery. The primary endpoint of all-cause mortality or disabling stroke and several secondary endpoints were assessed at 3 years.

Results: There were 1414 attempted implants (730 TAVR; 684 surgery). Patients had a mean age of 74 years and 35% were women. At 3 years, the primary endpoint occurred in 7.4% of TAVR patients and 10.4% of surgery patients (HR, 0.70; 95% CI, 0.49–1.00; p=0.051). The difference between treatment arms for all-cause mortality or disabling stroke remained broadly consistent over time: -1.8% at year 1; -2.0% at year 2; -2.9% at year 3. The incidence of mild paravalvular regurgitation (20.3% TAVR vs. 2.5% surgery) and pacemaker placement (23.2% TAVR vs. 9.1% surgery; p<0.001) were lower in the surgery group. Rates of moderate or greater paravalvular regurgitation for both groups were <1% and not significantly different. Patients who underwent TAVR had significantly improved valve hemodynamics (mean gradient 9.1mmHg TAVR vs. 12.1mmHg surgery; p<0.001) at 3 years.

Conclusions: Within the Evolut Low Risk study, TAVR at 3 years showed durable benefits compared to surgery with respect to all-cause mortality or disabling stroke.

(ClinicalTrials.gov number, NCT02701283).

CONDENSED ABSTRACT

Three-year outcomes were assessed following TAVR with a self-expanding valve or surgery in patients from the Evolut Low Risk trial. There were 1414 attempted implants (730 TAVR; 684 surgery). At 3 years, the primary endpoint of all-cause mortality or disabling stroke was 7.4% with TAVR and 10.4% with surgery (HR, 0.70; 95% CI, 0.49–1.00; p=0.051); the difference between treatment arms remained broadly consistent over time: -1.8% year 1; -2.0% year 2; -2.9% year 3. Within the Evolut Low Risk study, TAVR at 3 years showed durable benefits compared to surgery with respect to all-cause mortality or disabling stroke.

KEY WORDS: TAVR, SAVR, aortic stenosis, low risk, self-expanding

ABBREVIATIONS

CEC = Clinical Events Committee

KCCQ = Kansas City Cardiomyopathy Questionnaire

TAVR = transcatheter aortic valve replacement

VARC-3 = Valve Academic Research Consortium 3

INTRODUCTION

For patients with severe symptomatic aortic stenosis undergoing valve replacement, transcatheter aortic valve replacement (TAVR) has become the dominant therapy, surpassing surgical aortic valve replacement in procedural volume across the US.(1) Much of the data supporting TAVR comes from patients at increased risk for surgery,(2-7) and while recent data in low-risk patient populations has shown promising short-term (≤2 year) outcomes,(8-11) there is a lack of intermediate and longer-term data for low-risk patients. Clear differences between TAVR and surgery have been demonstrated including recovery time,(4,9,10) paravalvular regurgitation,(2,4,5,7) hemodynamics,(10,12,13) ease of coronary access,(14) structural valve deterioration,(15) and need for new pacemaker.(10,12,13) The impact that these differences have on clinical outcomes for low-surgical risk individuals has not been evaluated beyond 2 years. This lack of data presents an unknown for physicians striving to fully educate patients as part of a shared decision-making process.(16,17)

The Evolut Low Risk trial randomized patients with severe aortic stenosis who had an indication for aortic valve replacement and were low risk for surgery to either TAVR or surgery. All patients in the Evolut Low Risk trial have now completed 3-year follow-up, and we herein provide an analysis of 3-year clinical outcomes.

METHODS

Study Design

The Evolut Low Risk trial (NCT02701283) is a multinational, prospective, randomized study comparing the safety and effectiveness of TAVR with a self-expanding and supra-annular bioprosthesis to surgery in patients with severe aortic valve stenosis. The study is being conducted at 86 sites in Australia, Canada, France, Japan, Netherlands, New Zealand, and the

United States. Full details of the study design, trial oversight, and randomization procedure have been described previously.(8) The study protocol was approved by the Institutional Review Board at each site. The study was conducted in accordance with Good Clinical Practice principles and the Declaration of Helsinki.

Patients

Complete inclusion and exclusion criteria have been reported previously.(8) In brief, eligible patients had severe aortic valve stenosis with trileaflet aortic valve morphology and a low predicted risk of death (< 3%) from surgery as assessed by a local multidisciplinary heart team. An independent Screening Committee confirmed patient eligibility and anatomic suitability for both TAVR and SAVR. All patients provided informed, written consent. Enrolled patients were randomized 1:1 to undergo TAVR with a self-expanding, supra-annular valve (CoreValve, Evolut R, or Evolut PRO; Medtronic) or surgery between March 2016 and May 2019. Surgical valve type was at investigator discretion but mechanical valves were not permitted. Patients are being followed for 10 years.

Study Endpoints

The primary study endpoint of the Evolut Low Risk trial was a nonhierarchical composite of all-cause mortality or disabling stroke at 2 years in the intention-to-treat population using Bayesian adaptive statistic methods.(8) The prespecified endpoints reported in this analysis include 3-year incidences of all-cause mortality and disabling stroke as well as valve performance as determined by Doppler echocardiographic assessment, quality of life as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) and New York Heart Association (NYHA) functional class, and 3-year safety events including new permanent pacemaker implantation, prosthetic valve endocarditis, prosthetic valve thrombosis, and aortic valve

rehospitalization. Post hoc analyses at 3 years included the composite of all-cause mortality, disabling stroke, and aortic valve hospitalization; the severity of prosthesis-patient mismatch, using Valve Academic Research Consortium 3 (VARC-3) criteria;(18) and the impact of paravalvular regurgitation or permanent pacemaker implantation at 30 days on mid-term clinical outcomes. Stroke was defined and adjudicated as described previously.(8)

A Clinical Events Committee (CEC) adjudicated all endpoints. An Echocardiography Core Laboratory (Mayo Clinic, Rochester, MN) evaluated all echocardiograms, and core laboratory assessments were used for echocardiographic trial endpoints.

Statistical analysis

Safety events and quality of life outcomes were assessed in patients who underwent an attempted implant ("as-treated" cohort). Annual echocardiographic measurements were assessed in the implanted cohort. Continuous variables were reported as mean ± SD or median (Q1, Q3), and categorical variables were reported as frequencies and percentages. Adverse events were reported as Kaplan Meier estimates and compared between treatment arms by log-rank test and using hazard ratios and 95% confidence intervals (CIs). For the primary endpoint, the difference in Kaplan Meier rates between TAVR and surgery groups was reported at yearly intervals. For the primary endpoint and components, the proportional hazards assumption was checked using the Grambsch-Therneau test and all $p>0.05$ supporting this assumption was not violated. Rates of moderate or greater paravalvular regurgitation and moderate or greater prosthesis-patient mismatch are reported with risk difference (TAVR-surgery) and 95% CIs. The impact of permanent pacemaker implantation and paravalvular regurgitation on 3-year clinical outcomes were landmarked at 30 days postprocedure. A post hoc subgroup analysis was performed using

Cox proportional hazards regression models. No statistical technique was used to impute missing data. No adjustments were made for multiplicity. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

An aortic valve replacement was attempted in 1414 patients, of whom 730 underwent TAVR and 684 underwent surgery **(Supplemental Figure 1**). Between years one and three, 20 patients in the TAVR group exited the study (18 withdrew and 2 were lost to follow-up) and 28 patients in the surgery group exited the study (21 withdrew and 7 were lost to follow-up). As a result, at 3 years data were available for 704 patients (96.4%) in the TAVR group and 624 patients (91.2%) in the surgery group.

Baseline characteristics were broadly similar between treatment groups (**Table 1)**. At the time of treatment, mean age for all patients was 74 years, 35.3% were women, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score was 2.0% in the TAVR group and 1.9% in the surgery group. The median (Q1, Q3) duration of follow-up is 48.4 (38.9, 52.3) months in the TAVR group and 48.1 (36.8, 50.6) months in the surgery group.

Clinical Outcomes

The primary endpoint of all-cause mortality or disabling stroke at 3 years was 7.4% in the TAVR group and 10.4% in the surgery group (hazard ratio, 0.70; 95% CI, 0.49 to 1.00; log-rank p=0.051) **(Table 2**). The difference in Kaplan Meier (KM) rates for the primary endpoint of all-cause mortality or disabling stroke for TAVR and surgery remained broadly consistent over time: -1.8% at year 1; -2.0% at year 2; -2.9% at year 3 **(Central Illustration**). At 3 years, all-

cause mortality was 6.3% in the TAVR group and 8.3% in the surgery group (hazard ratio, 0.75; 95% CI, 0.51 to 1.17; p=0.16), and disabling stroke was 2.3% in the TAVR group and 3.4% in the surgery group (hazard ratio, 0.65; 95% CI, 0.34 to 1.24; p=0.19; **Table 2 and Figure 1**). Landmark analyses for the primary endpoint and its components are shown in **Supplemental Figure 2**. The composite endpoint of all-cause mortality, disabling stroke, or aortic valve rehospitalization was 13.2% in the TAVR group and 16.8% the surgery group (hazard ratio, 0.76; 95% CI, 0.58 to 1.00; p=0.050; **Figure 2**). No significant interactions in the treatment effect were observed for all-cause mortality or disabling stroke among various demographic groups **(Figure 3)**.

Rates of myocardial infarction at 3 years were low (3.4% TAVR vs 2.3% surgery, hazard ratio, 1.46; 95% CI, 0.76 to 2.78; p=0.25) **(Table 2**). Patients who underwent TAVR had a lower incidence of atrial fibrillation (13.1% vs. 40.0%, hazard ratio, 0.27; 95% CI, 0.22 to 0.35; p<0.001), while new permanent pacemaker implantation was higher in the TAVR group (23.2% vs 9.1%, hazard ratio, 2.81; 95% CI, 2.08 to 3.79; p<0.001). In an analysis of all-cause mortality landmarked at 30 days, 3-year data demonstrated that patients who had prior pacemaker had the highest mortality (17.5%), followed by patients who received a new pacemaker within 30 days of TAVR (9.8%), followed by patients without a new pacemaker at 30 days (4.6%). **(Supplemental Results and Supplemental Table 2**).

Rates of aortic valve reintervention were similar between the two groups (1.0% TAVR vs. 0.9% surgery, hazard ratio, 1.06; 95% CI, 0.36 to 3.15; p=0.92) **(Table 2).** Clinical (0.3% TAVR vs. 0.2% surgery; p=0.61) and subclinical (0.4% TAVR vs. 0.5% surgery; p=0.91) valve thrombosis rates were very low in both groups **(Table 2).** Between 30 days and 3 years, a total of 9 patients had a CEC-adjudicated repeat aortic valve replacement (4 in patients who received a

TAVR index procedure and 5 in surgical patients). Among the TAVR patients, all 4 reinterventions consisted of surgical aortic valve replacement – 3 due to leaflet tears in patients who had a 34mm Evolut R valve and 1 due to endocarditis. Among the 5 surgical patients, 4 underwent redo surgical aortic valve replacement (3 due to endocarditis and 1 due to valve thrombosis), and 1 patient underwent valve-in-valve TAVR (TAV-in-SAV) due to stenosis of the surgical valve (**Supplemental Table S3).**

Echocardiographic Findings

At 3 years, patients in the TAVR group had consistently significantly lower aortic valve mean gradients (9.1mmHg TAVR vs. 12.1mmHg surgery; difference, -3.0; 95% CI, -3.6 to -2.4; p<0.001) and larger effective orifice areas (2.2 cm^2 TAVR vs. 2.0 cm^2 surgery; difference, 0.2; 95% CI, 0.2 to 0.3; p<0.001) (**Figure 4A and Supplemental Figure 3**). Moderate or greater prosthesis-patient mismatch was 10.6% in TAVR patients and 25.1% in surgery patients (difference, -14.%; 95% CI, -19.6% to -9.4%) **(Table 2**). Mild paravalvular regurgitation was more frequent in the TAVR group (20.3% vs. 2.5%) **(Table 2)**. At 3 years, there was no significant difference in the presence of moderate or greater paravalvular regurgitation (0.9% TAVR vs. 0.2% surgery; difference, 0.7%; 95% CI, -0.2% to 1.6%) **(Table 2)**. Between years 1 and 3, there was no increase in paravalvular regurgitation observed for either TAVR or surgical groups (**Figure 4B).** The degree of paravalvular regurgitation on 30-day echocardiography was not associated with the rate of all-cause mortality or disabling stroke at 3 years in a landmarked analysis **(Supplemental Figure 4**).

Quality of Life

Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score demonstrated that patients who underwent TAVR had a more rapid improvement in quality of

life (at 30 days) and that both groups had maintained improvements between years 1 and 3. At 3 years there was an approximately 20-point increase from baseline KCCQ for both groups (**Figure 5**) consistent with a very large improvement in quality of life.(18,19) Improvement in New York Heart Association score by at least 1 functional class from baseline to 3 years occurred in 72.7% of TAVR and 68.1% of surgery patients.

DISCUSSION

The major finding from this study of low-risk patients undergoing aortic valve replacement is that at three years, patients who received TAVR with a self-expanding, supra-annular valve had a lower rate of death or disabling stroke compared to patients undergoing surgery (7.4% vs 10.4%, hazard ratio, 0.70; 95% CI, 0.49 to 1.00; p=0.051). Furthermore, during the first three years after aortic valve replacement, the absolute difference in the primary outcome of death or disabling stroke between patients who underwent TAVR compared with surgery remained broadly consistent: year 1 delta -1.8%, year 2 delta -2.0%, and year 3 delta -2.9%.

Since the first randomized studies comparing TAVR to surgery were conducted in high-risk patients,(2,3) there has been a steady expansion of populations for whom a transcatheter approach is a viable and potentially advantageous alternative to surgery.(4,5,8,9) As TAVR has moved into younger populations, the importance of understanding intermediate and long-term data has become paramount. Unfortunately, such data are limited due in part to the fact that while all commercial TAVR procedures in the US are tracked through a national registry (STS/American College of Cardiology Transcatheter Valve Therapy [STS/ACC TVT] Registry), patients within this database are followed for only 1 year.(1) For low-risk patients in whom

short-term benefits must be balanced with long-term durability, this lack of intermediate and longer-term data is particularly important. Given many variables that go into choosing a therapy for low-risk patients, the current ACC/AHA guidelines recommend that for patients between the age of 65-80 years, a shared decision-making process should be utilized by heart teams when discussing options for aortic valve replacement.(17) These 3-year results demonstrating sustained valve performance and a low rate of mortality or disabling stroke with TAVR provide patients and their physicians significant information that will further guide this shared decision-making process.

All patients within this study underwent TAVR with a self-expanding, supra-annular valve (CoreValve/Evolut platform) with tall commissures designed to optimize hemodynamics and decrease bioprosthetic leaflet stress.(6) There is evidence that this design results in improved hemodynamics when compared to valves that function at the annular level.(2,8,20) In our analysis at 3 years, there was a significant difference in moderate or greater prosthesis-patient mismatch (10.6% TAVR vs. 25.1% surgery). Prosthesis-patient mismatch after surgical aortic valve replacement has been associated with the development of structural valve deterioration in multiple studies,(21-23) and recent data from O'Hair and colleagues using pooled data from the CoreValve US High Risk and SURTAVI clinical trials demonstrated that at 5-years there was a two-fold increase in structural valve deterioration for patients who had surgery compared with TAVR, and that this was associated with increased mortality.(15) Longer-term follow-up within our study will help to further our understandings of the impact that hemodynamics have on both surgical and transcatheter valve durability.

One of the early challenges of TAVR was the significant amount of moderate or severe paravalvular regurgitation seen with first generation transcatheter valves(12,24) and associated

with an increased risk of mortality at 5 years.(25) Within this study, the majority of patients underwent TAVR with the Evolut R platform, which unlike the first generation CoreValve can be repositioned to achieve a desired implant depth prior to final release. At 3 years there was no difference in moderate or greater paravalvular regurgitation for patients who had TAVR compared with surgery (0.9% vs. 0.2%), and while differences in mild paravalvular regurgitation remained significant (20.1% vs. 2.4%), this finding at 30 days was not associated with an increased incidence of mortality or disabling stroke at 3 years. In addition, since this study was completed, the Evolut R valve has been replaced with the Evolut PRO and PRO+ valves which have an external pericardial wrap on the lower valve frame that has been shown to further reduce paravalvular regurgitation.(26) The incidence of new pacemakers has long been an Achilles heel of TAVR with self-expanding supra-annular valves, and in this study the rate remained significantly higher for TAVR than surgery at 3 years (23.2% vs. 9.1%). While recent procedural adaptations, including the use of the "cusp-overlap" implant technique, have been shown to decrease need for permanent pacemaker placement after TAVR,(27) the increased rate of pacemakers in this study stands in contrast to balloon-expandable transcatheter valves where the rate of new pacemakers in low-risk patients after TAVR was comparable to surgery.(11)

This study has several important limitations. First, while these three-year data are reassuring, longer term data for low-risk patients are needed and patients enrolled in this study will be followed for 10 years. This is particularly true for valve reintervention rates, which are too low at 3 years to allow for appropriate statistical analysis. Second, this study did not evaluate the ability to engage the coronary arteries after TAVR and recent studies have suggested that the supra-annular nature of the Evolut valve may make coronary reaccess more difficult.(28) While some of these challenges may be mitigated by proper commissural alignment,(29) a recent

analysis by Faroux and colleages demonstrated that STEMI after TAVR is associated with increased mortality, longer door-to-balloon times, and higher percutaneous coronary intervention failure rates.(30) In addition, a subset of low-risk patients may outlive the durability of their bioprosthetic valve, and although transcatheter valve in valve (TAV-in-TAV) may be feasible in selected patients,(31) for those in whom TAV-in-TAV is not possible, surgical explant of a transcatheter valve may have increased risks.(32) Given these limitations, while these data demonstrate that low-risk patients with severe aortic stenosis who undergo TAVR with a self-expanding supra-annular bioprosthesis have consistent outcomes compared to surgery with respect to all-cause mortality or disabling stroke at three years, further follow-up is needed due to the infrequent number of primary outcome events, and as such providers and patients should continue to engage in a shared decision-making process when faced with decisions regarding aortic valve replacement.

CONCLUSIONS

At three years, low surgical risk patients who underwent TAVR with a self-expanding supra-annular bioprosthesis had durable benefits with regards to all-cause mortality and disabling stroke compared to surgical aortic valve replacement.

CLINICAL PERSPECTIVES

- **Competency in Patient Care and Procedural Skills:** Compared to patients undergoing surgical aortic valve replacement at 3 years, those at low surgical risk who undergo TAVR have favorable outcomes in terms of avoidance of all-cause mortality and disabling stroke.

  Translational Outlook: Longer term studies involving low-risk patients are in progress to assess prosthetic valve durability after TAVR.

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FIGURE LEGENDS

Figure 1. Time-to-Event All-Cause Mortality and Disabling Stroke. Kaplan-Meier estimates and log-rank p values for the primary endpoint components of all-cause mortality (A) and disabling stroke (B). TAVR = transcatheter aortic valve replacement

Figure 2. Time-to-Event All Cause Mortality, Disabling Stroke, or Aortic Valve Hospitalization. Kaplan-Meier estimates and log-rank p values are shown for the composite endpoint of all-cause mortality, disabling stroke, or aortic valve hospitalization through 3 years. Patients in the TAVR group had lower rates of the composite endpoint at 3 years. AV = aortic valve; HR = hazard ratio; TAVR = transcatheter aortic valve replacement

Figure 3. Three-Year Death or Disabling Stroke by Baseline Demographics. A consistency of treatment effect was observed across eight demographic subgroups. Black squares indicate the hazard ratio for TAVR vs surgery, and horizontal lines indicate the 95% confidence intervals. No adjustment was made for multiplicity. COPD = chronic obstructive pulmonary disease; KCCQ = Kansas City Cardiomyopathy Questionnaire; KM = Kaplan Meier; STS = Society of Thoracic Surgeons**.** P values are based on the Cox proportional hazards model. CI = confidence interval; HR = hazard ratio

Figure 4. Hemodynamic Valve Performance. Aortic valve mean gradient and effective orifice area and parvalvular regurgitation through 3 years for the TAVR and surgery groups as reported by the echocardiography core laboratory. Panel A. Patients in the TAVR group had significantly lower mean gradient ($p<0.001$) and significantly larger effective orifice area ($p<0.001$) at all follow-up timepoints. Mean (SD) values are reported for each timepoint. Panel B. Between years 1 and 3, there was no increase in paravalvular regurgitation observed for either TAVR or surgical

groups. EOA = effective orifice area; MG = mean gradient; TAVR = transcatheter aortic valve replacement

Figure 5. Kansas City Cardiomyopathy Questionnaire. Mean KCCQ overall summary scores by study visit are shown in the graph. Mean ± SD change in KCCQ score from baseline and difference with 95% confidence intervals for each time point are shown in the table. KCCQ = Kansas City Cardiomyopathy Questionnaire; surgery = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

Central Illustration. Three-year outcomes from the Evolut Low Risk Trial. Patients in the Evolut Low Risk trial were randomized to TAVR with a self-expanding, supra-annular valve or surgery and followed for 3 years. Kaplan Meier time-to-event curves for the primary endpoint of all-cause mortality or disabling stroke were compared in the TAVR and surgery groups at Years 1, 2, and 3 of the study. HR = hazard ratio; KM = Kaplan Meier; TAVR = transcatheter aortic valve replacement

Table 1. Baseline Patient Characteristics

Characteristic	TAVR (N = 730)	Surgery (N = 684)
Age, yr	74.1 ± 5.8	73.7 ± 5.9
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2
Female sex	266 (36.4)	233 (34.1)
STS-PROM score, %	2.0 ± 0.7	1.9 ± 0.7
NYHA functional class		
I	76 (10.4)	63 (9.2)
II	472 (64.7)	428 (62.6)
III	181 (24.8)	190 (27.8)
IV	1 (0.1)	3 (0.4)
Diabetes	229 (31.4)	210 (30.7)
Hypertension	618/729 (84.8)	564/683 (82.6)
Chronic lung disease, COPD	106/700 (15.1)	118/655 (18.0)
Peripheral arterial disease	54/723 (7.5)	56/683 (8.2)
Cerebrovascular disease	74 (10.1)	82 (12.0)
Previous coronary artery bypass graft	18 (2.5)	14 (2.0)
Previous valve	0 (0.0)	0 (0.0)
Previous percutaneous coronary intervention	103 (14.1)	88 (12.9)
Previous myocardial infarction	49 (6.7)	33 (4.8)
Atrial fibrillation/atrial flutter	112/727 (15.4)	98/682 (14.4)
Pre-existing permanent pacemaker or defibrillator	24 (3.3)	26/683 (3.8)
SYNTAX Score I	1.9 ± 3.7	2.1 ± 3.9
Left ventricular ejection fraction, %	61.7 ± 7.9	61.9 ± 7.7

Data are presented as n (%) or mean ± standard deviation. There were no significant differences ($P<0.05$) in baseline characteristics between study groups. COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR = transcatheter aortic valve replacement

Table 2. Three Year Clinical Outcomes and Valve Performance

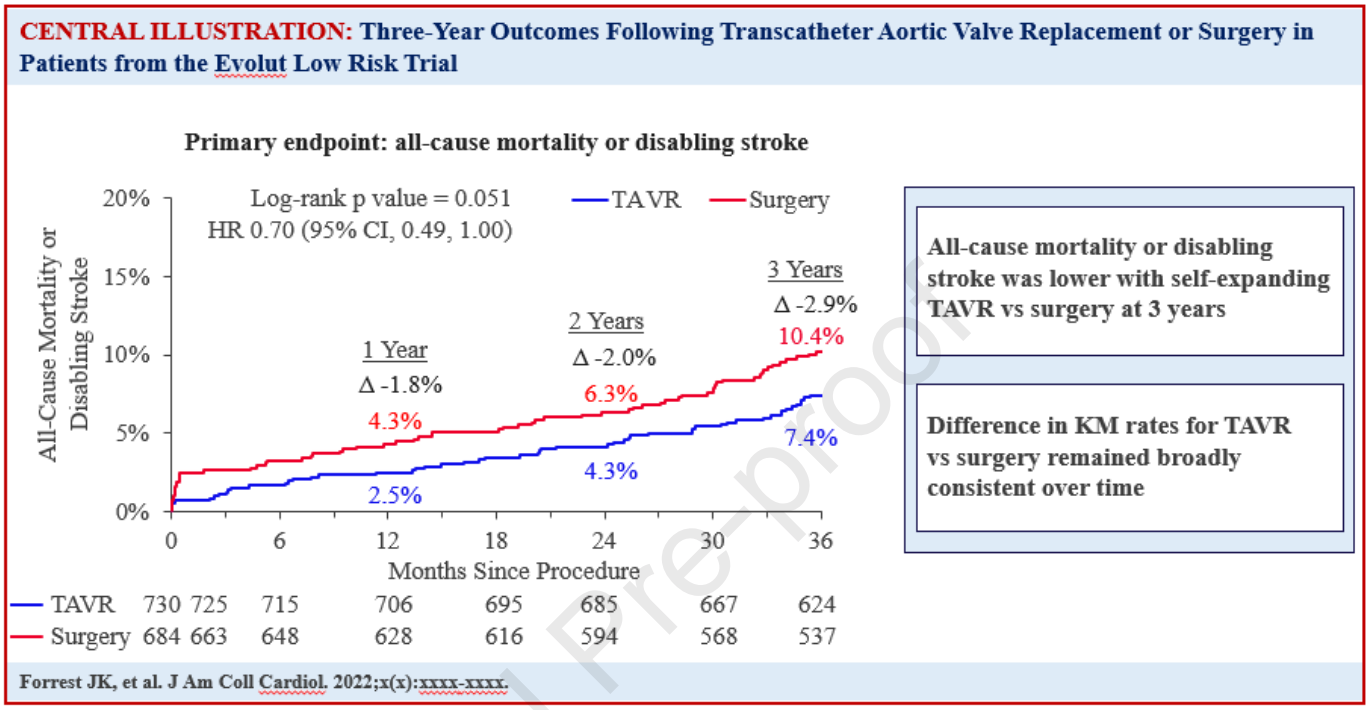
Outcome	TAVR	Surgery	Hazard Ratio or Risk Difference[a] (95% CI)	P Value[b]
Clinical Outcomes				
All-cause mortality or disabling stroke	53 (7.4)	67 (10.4)	0.70 (0.49, 1.00)	0.051
All-cause mortality	45 (6.3)	53 (8.3)	0.75 (0.51, 1.12)	0.16
Cardiovascular death	29 (4.1)	36 (5.6)	0.72 (0.44, 1.17)	0.18
All stroke	53 (7.4)	43 (6.6)	1.13 (0.76, 1.69)	0.55
Disabling stroke	16 (2.3)	22 (3.4)	0.65 (0.34, 1.24)	0.19
Aortic valve hospitalization[c]	52 (7.4)	59 (9.2)	0.78 (0.54, 1.14)	0.20
All-cause mortality, disabling stroke, or aortic valve hospitalization	95 (13.2)	110 (16.8)	0.76 (0.58, 1.00)	0.050
Major vascular complication	30 (4.1)	25 (3.7)	1.12 (0.66, 1.90)	0.67
Myocardial infarction	24 (3.4)	15 (2.3)	1.46 (0.76, 2.78)	0.25
Permanent pacemaker implant[d]	162 (23.2)	58 (9.1)	2.81 (2.08, 3.79)	<0.001
Atrial fibrillation	94 (13.1)	271 (40.0)	0.27 (0.22, 0.35)	<0.001
Valve endocarditis	5 (0.7)	8 (1.3)	0.56 (0.18, 1.70)	0.30
Valve Performance				
Reintervention	7 (1.0)	6 (0.9)	1.06 (0.36, 3.15)	0.92
Paravalvular regurgitation[e]				<0.001
None/trace	426 (78.7)	435 (97.3)	-	
Mild	110 (20.3)	11 (2.5)	-	
Moderate	4 (0.7)	1 (0.2)	-	
Severe	1 (0.2)	0 (0)	-	
≥ Mild	115/541 (21.3)	12/447 (2.7)	18.6% (14.8, 22.3)	<0.001
≥ Moderate	5/541 (0.9)	1/447 (0.2)	0.7% (-0.2, 1.6)	0.16
Prosthesis-patient mismatch[e]				<0.001
None	437/489 (89.4)	295/394 (74.9)		
Moderate	45/489 (9.2)	80/394 (20.3)	-	
Severe	7/489 (1.4)	19/394 (4.8)	-	
≥ Moderate	52/489 (10.6)	99/394 (25.1)	-14.5% (-19.6, -9.4)	
Valve thrombosis				
Clinical[f]	2 (0.3)	1 (0.2)	1.84 (0.17, 20.25)	0.61
Subclinical[g]	3 (0.4)	3 (0.5)	0.91 (0.18, 4.50)	0.91

[a]Clinical outcomes are presented as n (Kaplan-Meier estimate %) with hazard ratio (95% CI); paravalvular regurgitation (PVR) and prosthesis-patient mismatch (PPM) are presented as n/N (%) with risk difference (95% CI). [b]P values were based on the chi-square test for PVR and PPM; p values for all other clinical outcomes were based on the log-rank test. [c]Not adjudicated by the Clinical Events Committee (CEC). [d]Patients with pacemaker or implantable cardioverter defibrillator at baseline are not included. Not adjudicated by the CEC. [e]PVR and PPM through 3 years was reported by the echocardiography core laboratory. PPM was defined per Valve

Academic Research Consortium 3 (VARC-3) criteria. [f]Clinical valve thrombosis rates were CEC adjudicated and defined as any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment and is associated with any of the following clinical sequelae: any ischemic stroke, any peripheral embolic event, ST segment elevation or non-ST elevation myocardial infarction, or hemodynamic impairment associated with a worsening heart failure. [g]Subclinical valve thromboses were defined as those without evident clinical sequelae causing a hemodynamic impediment meeting the following criteria: increase in aortic regurgitation resulting in moderate or severe, a post-discharge mean gradient of ≥ 20 mmHg that increased by > 50%, or a decrease in the Doppler Velocity Index (DVI) by > 50%. CI = confidence intervals; TAVR = transcatheter aortic valve replacement

FIGURES

Central Illustration. Three-year outcomes from the Evolut Low Risk Trial.



Central Illustration Legend: Three-year outcomes from the Evolut Low Risk Trial. Patients in the Evolut Low Risk trial were randomized to TAVR with a self-expanding, supra-annular valve or surgery and followed for 3 years. Kaplan Meier time-to-event curves for the primary endpoint of all-cause mortality or disabling stroke were compared in the TAVR and surgery groups at Years 1, 2, and 3 of the study. HR = hazard ratio; KM = Kaplan Meier; TAVR = transcatheter aortic valve replacement

Figure 1. All-Cause Mortality and Disabling Stroke Through 3 Years

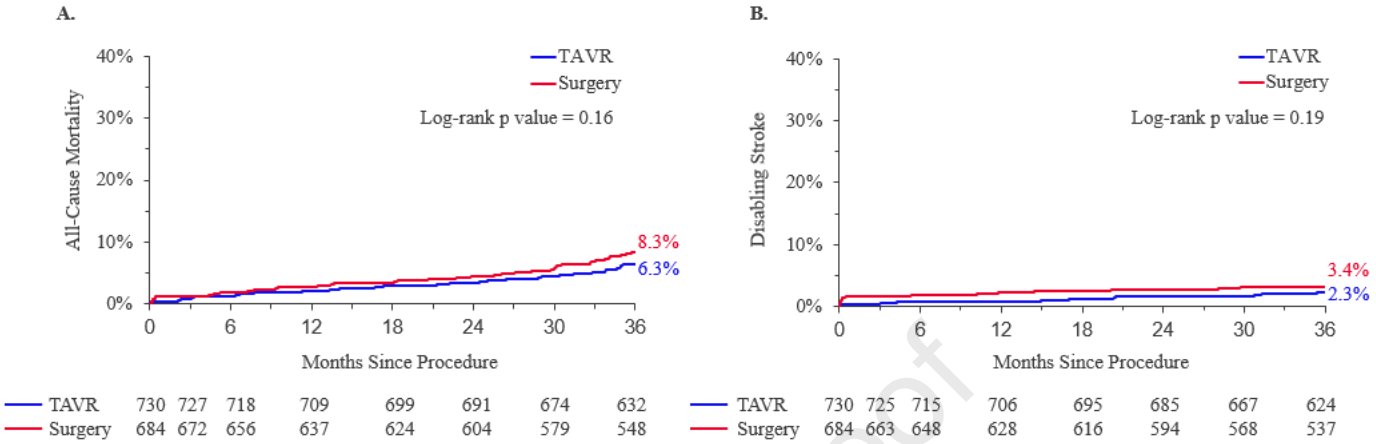


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Figure 2. Time-to-Event All Cause Mortality, Disabling Stroke, or Aortic Valve Hospitalization

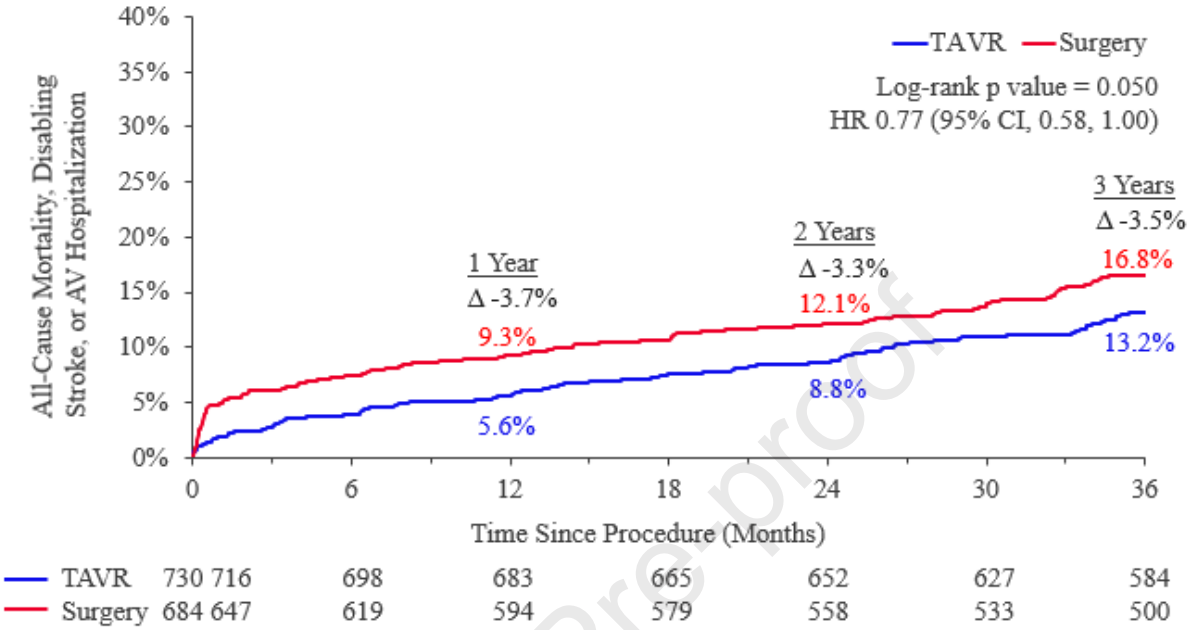


Figure 2 Legend: Kaplan-Meier estimates and log-rank p values for the composite endpoint of all-cause mortality, disabling stroke, or aortic valve hospitalization through 3 years. Patients in the TAVR group had lower rates of the composite endpoint at 3 years. AV = aortic valve; HR = hazard ratio; TAVR = transcatheter aortic valve replacement

Figure 3. Three-Year Death or Disabling Stroke by Baseline Demographics

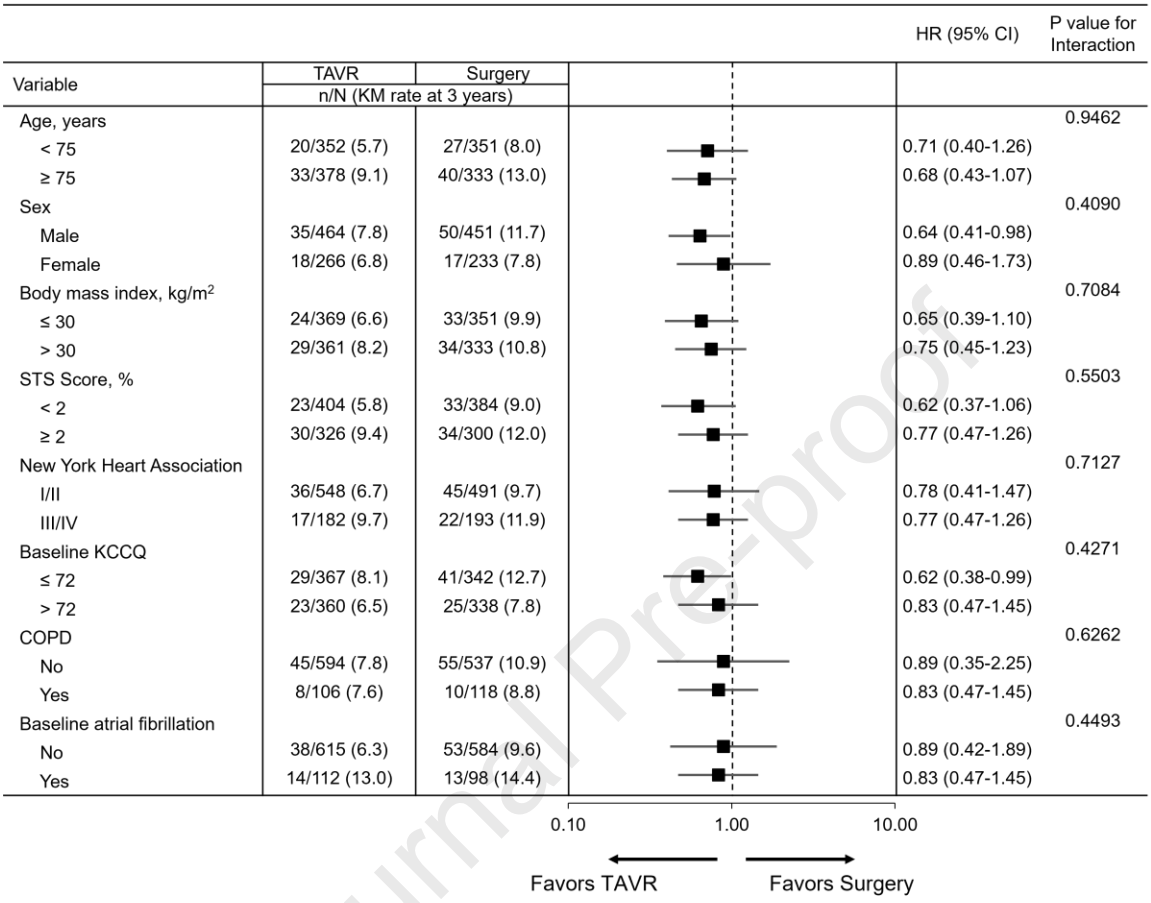
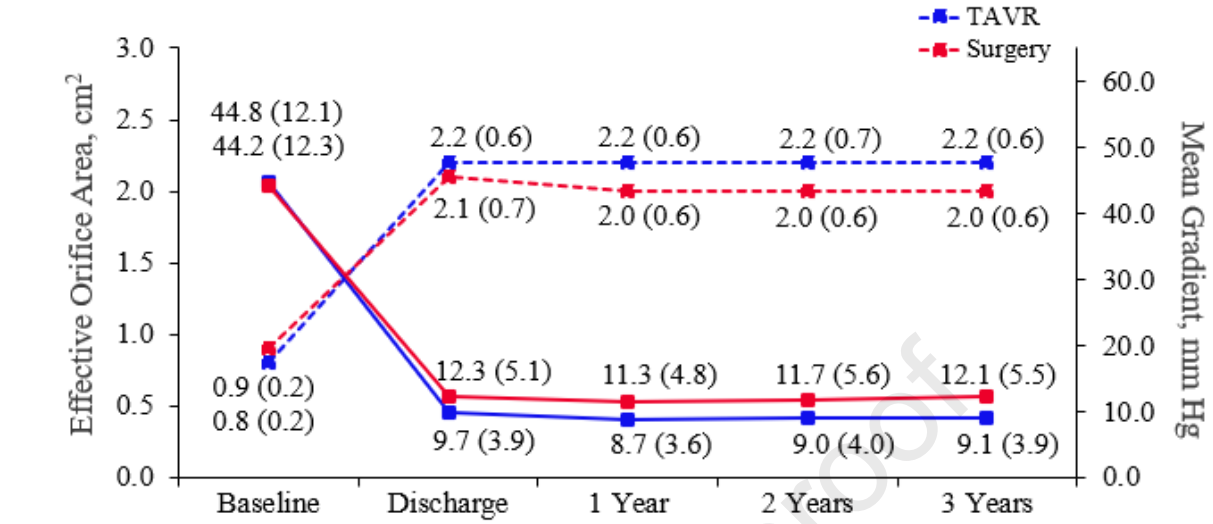


Figure 3 Legend: A consistency of treatment effect was observed across eight demographic subgroups. Black squares indicate the hazard ratio for TAVR vs surgery, and horizontal lines indicate the 95% confidence intervals. No adjustment was made for multiplicity. COPD = chronic obstructive pulmonary disease; KCCQ = Kansas City Cardiomyopathy Questionnaire; KM = Kaplan Meier; STS = Society of Thoracic Surgeons**.** P values are based on the Cox proportional hazards model. CI = confidence interval; HR = hazard ratio

Figure 4A. Aortic Valve Mean Gradient and Effective Orifice Area



No. of patients					
TAVR EOA	637	576	565	535	493
Surgery EOA	596	406	525	434	396
TAVR MG	717	703	662	607	547
Surgery MG	679	632	597	514	456

Figure 4B. Paravalvular Regurgitation

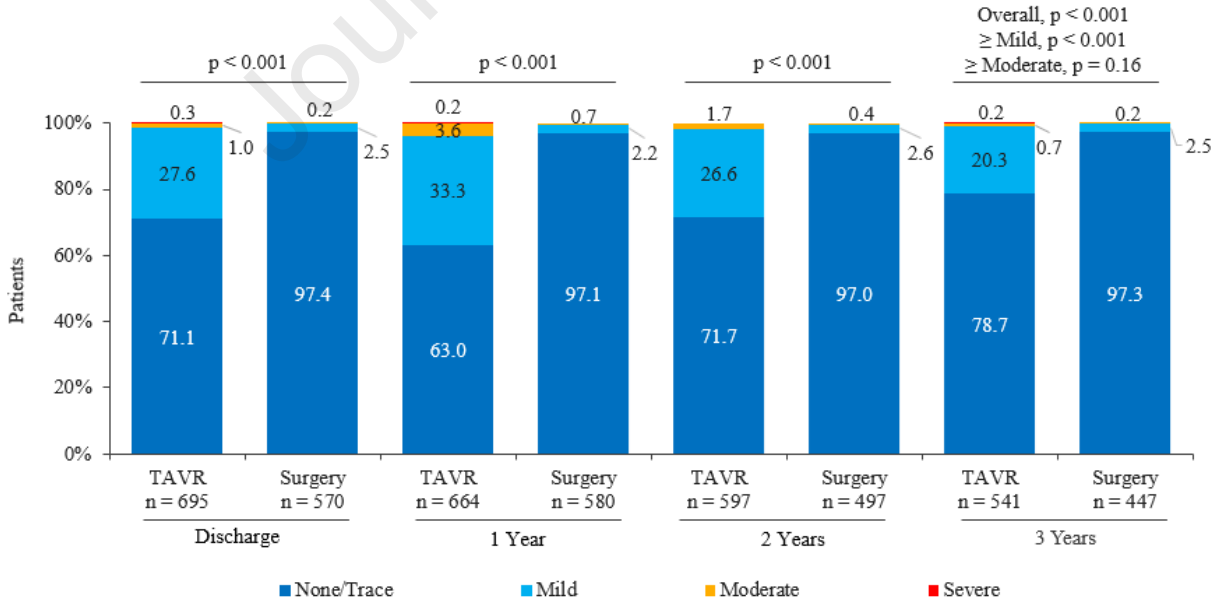


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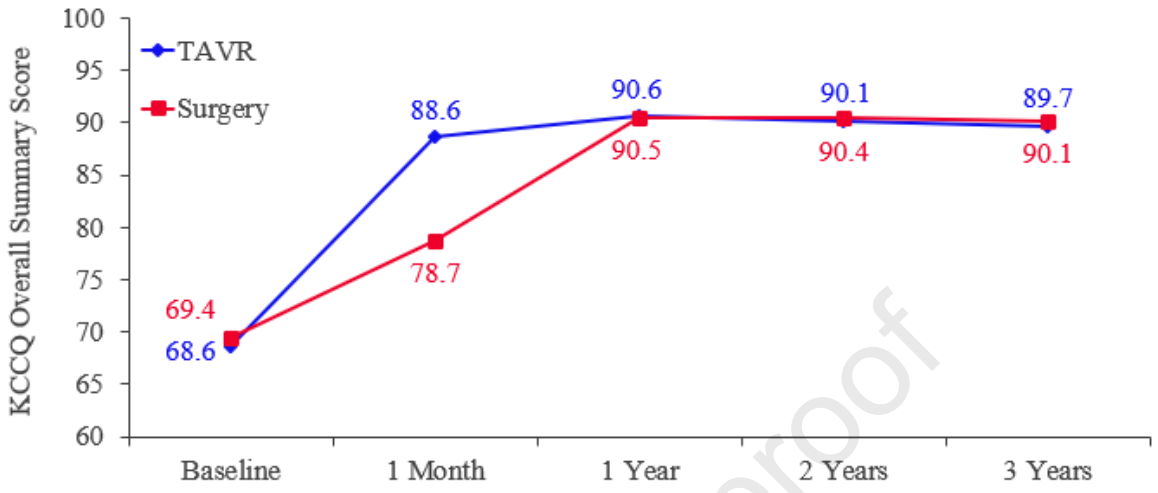
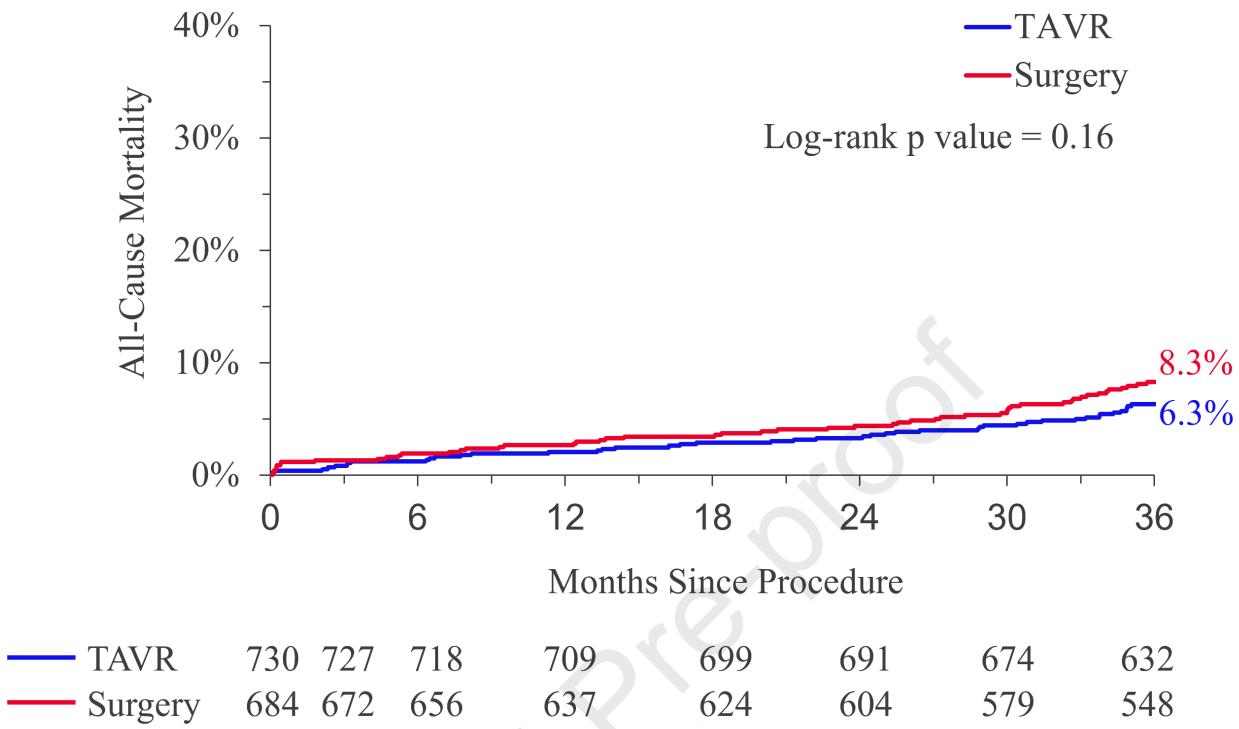
Figure 5. Kansas City Cardiomyopathy Questionnaire Overall Summary Score



Change from Baseline				
TAVR	20.0 ± 21.1	21.6 ± 20.6	20.9 ± 20.8	20.1 ± 20.6
Surgery	9.2 ± 22.3	20.7 ± 20.3	20.0 ± 20.0	19.3 ± 21.1
Difference (95% CI)	10.7 (8.4, 13.0)	0.9 (-1.3, 3.1)	0.9 (-1.4, 3.2)	0.8 (-1.7, 3.2)

Figure 5 Legend. Mean KCCQ overall summary scores by study visit are shown in the graph. Mean ± SD change in KCCQ score from baseline and difference with 95% confidence intervals for each time point are shown in the table. KCCQ = Kansas City Cardiomyopathy Questionnaire; surgery = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement

A.



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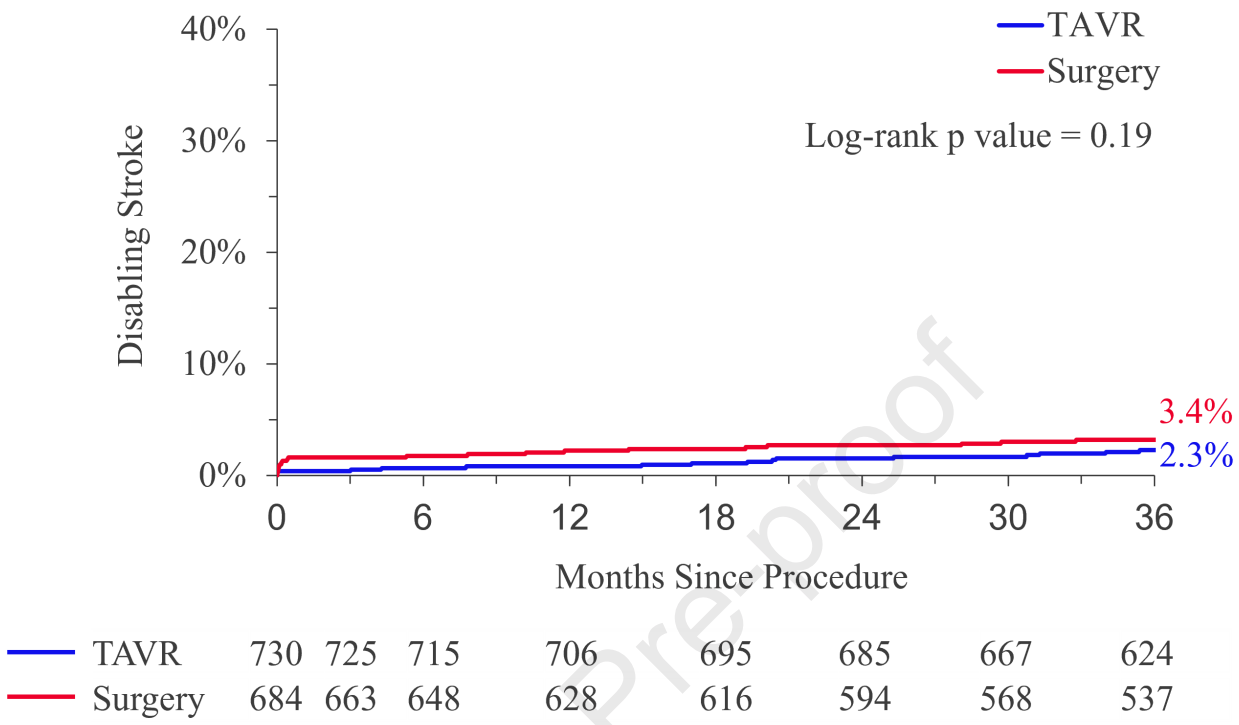
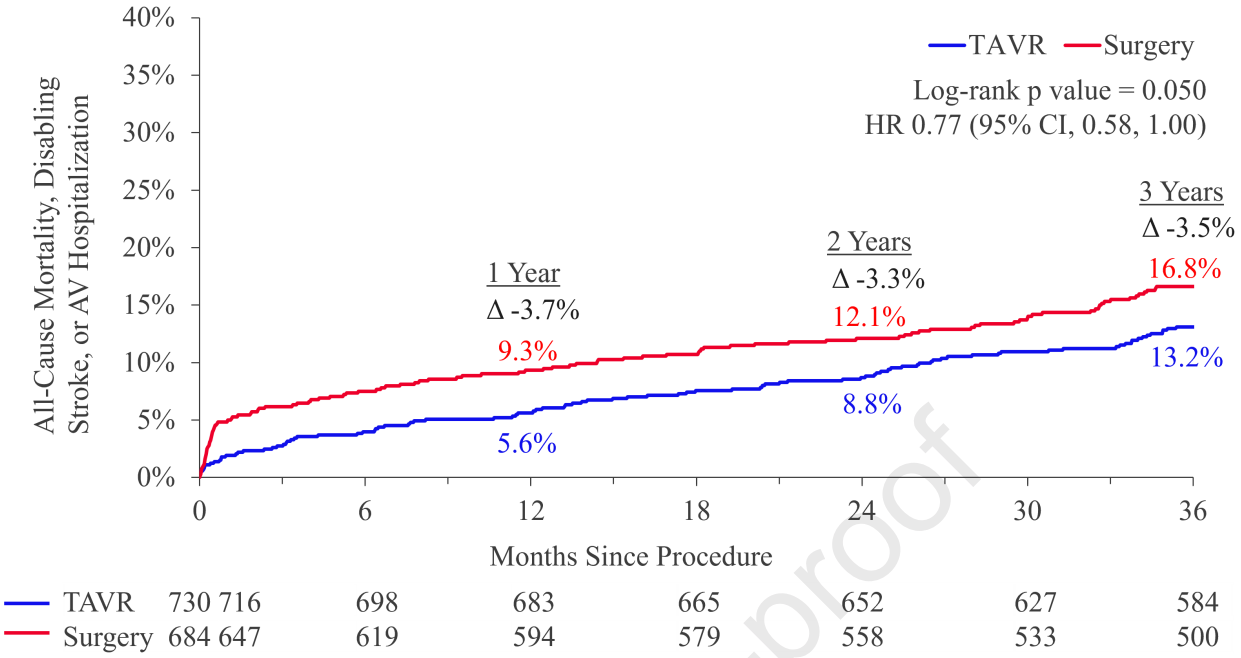
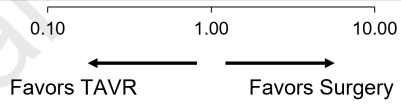
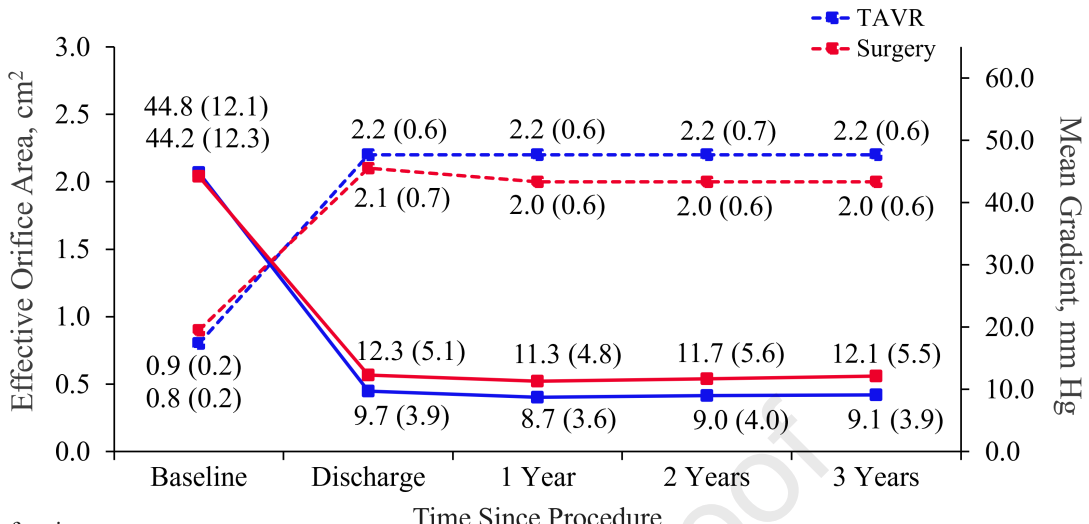




TAVR	730	716	698	683	665	652	627	584
Surgery	684	647	619	594	579	558	533	500

Variable	TAVR n/N (KM rate at 3 years)	Surgery n/N (KM rate at 3 years)	HR (95% CI)	P value for Interaction
Age, years				0.9462
< 75	20/352 (5.7)	27/351 (8.0)	0.71 (0.40-1.26)	
≥ 75	33/378 (9.1)	40/333 (13.0)	0.68 (0.43-1.07)	
Sex				0.4090
Male	35/464 (7.8)	50/451 (11.7)	0.64 (0.41-0.98)	
Female	18/266 (6.8)	17/233 (7.8)	0.89 (0.46-1.73)	
Body mass index, kg/m^2				0.7084
≤ 30	24/369 (6.6)	33/351 (9.9)	0.65 (0.39-1.10)	
> 30	29/361 (8.2)	34/333 (10.8)	0.75 (0.45-1.23)	
STS Score, %				0.5503
< 2	23/404 (5.8)	33/384 (9.0)	0.62 (0.37-1.06)	
≥ 2	30/326 (9.4)	34/300 (12.0)	0.77 (0.47-1.26)	
New York Heart Association				0.7127
I/II	36/548 (6.7)	45/491 (9.7)	0.78 (0.41-1.47)	
III/IV	17/182 (9.7)	22/193 (11.9)	0.77 (0.47-1.26)	
Baseline KCCQ				0.4271
≤ 72	29/367 (8.1)	41/342 (12.7)	0.62 (0.38-0.99)	
> 72	23/360 (6.5)	25/338 (7.8)	0.83 (0.47-1.45)	
COPD				0.6262
No	45/594 (7.8)	55/537 (10.9)	0.89 (0.35-2.25)	
Yes	8/106 (7.6)	10/118 (8.8)	0.83 (0.47-1.45)	
Baseline atrial fibrillation				0.4493
No	38/615 (6.3)	53/584 (9.6)	0.89 (0.42-1.89)	
Yes	14/112 (13.0)	13/98 (14.4)	0.83 (0.47-1.45)	





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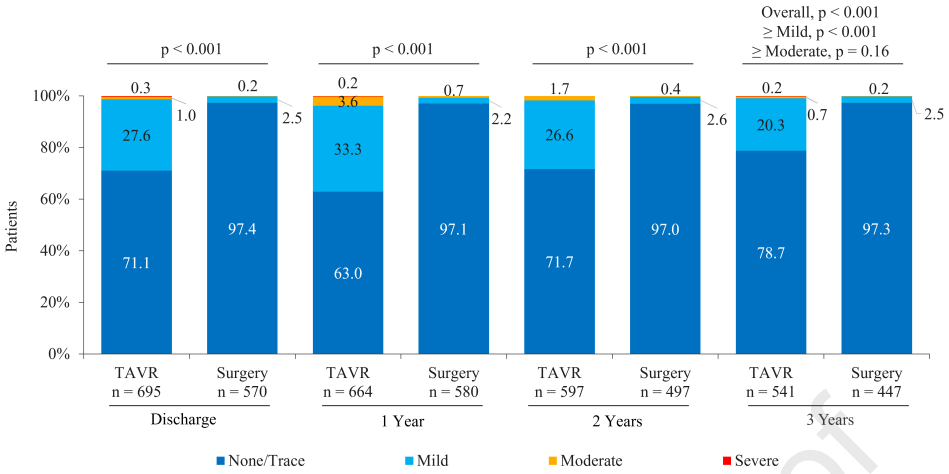

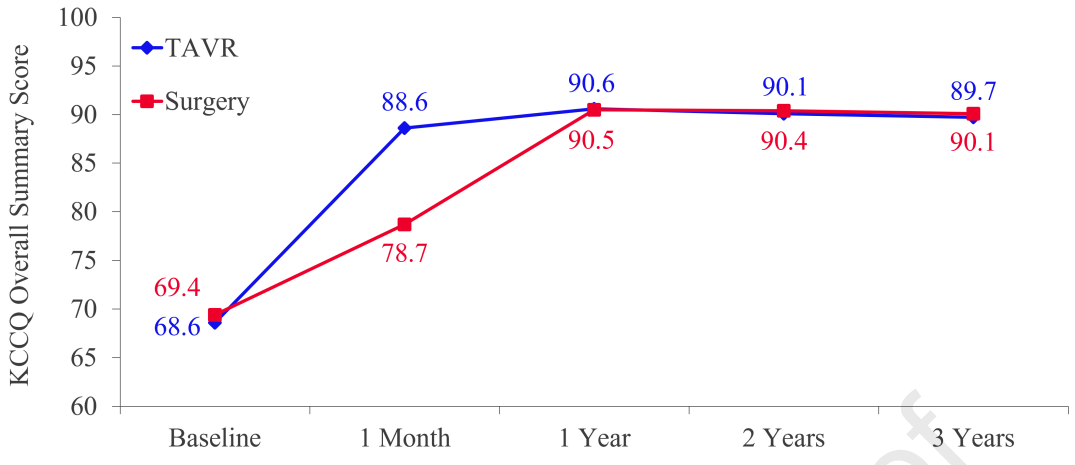

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TAVR	20.0 ± 21.1	21.6 ± 20.6	20.9 ± 20.8	20.1 ± 20.6
Surgery	9.2 ± 22.3	20.7 ± 20.3	20.0 ± 20.0	19.3 ± 21.1
Difference (95% CI)	10.7 (8.4, 13.0)	0.9 (-1.3, 3.1)	0.9 (-1.4, 3.2)	0.8 (-1.7, 3.2)

SUPPLEMENTAL APPENDIX

Three-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis

John K. Forrest MD, G. Michael Deeb MD, Steven J. Yakubov MD, Hemal Gada MD, Mubashir A. Mumtaz MD, Basel Ramlawi MD, Tanvir Bajwa MD, Paul S. Teirstein MD, Michael DeFrain MD, Murali Muppala MD, Bruce J. Rutkin MD, Atul Chawla MD, Bart Jenson MD, Stanley J. Chetcuti MD, Robert C. Stoler MD, Marie-France Poulin MD, Kamal Khabbaz MD, Melissa Levack MD, Kashish Goel MD, Didier Tchétché MD, Ka Yan Lam MD, Pim A. L. Tonino MD, Saki Ito MD, Jae K. Oh MD, Jian Huang MD, MSc, Jeffrey J. Popma MD, Neal Kleiman MD, Michael J. Reardon MD, for the Low Risk Trial Investigators

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SUPPLEMENTAL TABLE 1. STUDY SITES AND PRINCIPAL INVESTIGATORS

Abbott Northwestern Hospital – Minneapolis Heart Institute Minneapolis, Minnesota	Principal investigator: Paul Sorajja
Abrazo Arizona Heart Hospital Phoenix, Arizona	Principal investigators: Timothy Byrne, Merick Kirshner
Aurora/St Luke's Hospital Milwaukee, Wisconsin	Principal investigators: Tanvir Bajwa, John Crouch
Baylor Saint Luke's Medical Center Houston, Texas	Principal investigators: Joseph Coselli, Guilherme Silva
Baylor Jack and Jane Hamilton Heart and Vascular Hospital Dallas, Texas	Principal investigators: Robert Hebeler, Robert Stoler
Baystate Medical Center Springfield, Massachusetts	Principal investigators: Ashequl Islam, Anthony Rousou
Beth Israel Deaconess Medical Center Boston, Massachusetts	Principal investigators: Marie-France Poulin, Kamal Khabbaz
Bon Secours Heart & Vascular Institute Richmond, Virginia	Principal investigators: Mark Bladergroen
Cardiovascular Institute of the South / Terrebonne General Medical Center Houma, Louisiana	Principal investigators: Peter Fail, Donald Netherland
Catharina Hospital Eindhoven Eindhoven, The Netherlands	Principal investigators: Ka Yan Lam, W.A.L. Tonino

Centre Hospitalier Régional Universitaire (CHRU) de Lille Lille, France	Principal investigators: Arnaud Sudre
Clinique Pasteur Toulouse Toulouse, France	Principal investigators: Pierre Berthoumieu, Didier Tchétché
Delray Medical Center Delray Beach, Florida	Principal investigators: Houman Khalili
Duke University Medical Raleigh, North Carolina	Principal investigators: G. Chad Hughes, J Kevin Harrison
El Camino Hospital Mountain View, California	Principal investigators: Ajanta De, Pei Tsau
Erasmus Medical Center Rotterdam Rotterdam, The Netherlands	Principal investigators: Nicolas M. van Mieghem
Fiona Stanley Hospital Murdoch, Western Australia	Principal investigators: Robert Larbalestier, Gerald Yong
Geisinger Medical Center Danville, Pennsylvania	Principal investigators: Shikhar Agarwal, William Martin
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RESULTS

Impact of 30-day permanent pacemaker implantation at 30 days on mid-term clinical outcomes. Patients in the TAVR group were stratified by the need for permanent pacemaker implantation (PPI) (baseline PPI vs new PPI within 30 days of the implant procedure vs no PPI within 30 days of the implant procedure) and followed through 3 years to assess impact on all-cause mortality. The analysis of clinical outcomes was landmarked at 30 days post-procedure. Baseline characteristics of the three groups are shown in **Supplemental Table 2.** The number of patients available for evaluation at 30 days was 24 in the baseline PPI group, 124 in the new PPI within 30 days group, and 576 in the no PPI within 30 days group; the number of patients at risk at 3 years was 18, 102, and 509, respectively. TAVR patients who entered the study with a permanent pacemaker had higher rates of all-cause mortality at 3 years than patients who received a new permanent pacemaker within 30 days of implant or those without a permanent pacemaker within 30 days (17.5% vs 9.8% vs 4.6%, respectively).

TABLES

Supplemental Table 2. Baseline Characteristics in TAVR Patients by Permanent Pacemaker Implantation

Characteristics	Baseline PPI[a] (N=24)	New PPI within 30 days[a] (N=124)	No PPI within 30 days[a] (N=576)
Age, yrs	74.3 ± 6.3	74.7 ± 5.3	74.0 ± 5.9
Body surface area, m^2	2.1 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
Female sex	7 (29.2)	40 (32.3)	217 (37.7)
STS score, %	2.2 ± 0.8	1.9 ± 0.6	1.9 ± 0.7
NYHA functional class			
I	1 (4.2)	18 (14.5)	57 (9.9)
II	13 (54.2)	72 (58.1)	381 (66.1)
III	10 (41.7)	34 (27.4)	137 (23.8)
IV	0 (0.0)	0 (0.0)	1 (0.2)
Diabetes	5 (20.8)	40 (32.3)	181 (31.4)
Hypertension	20 (83.3)	106 (85.5)	486/575 (84.5)
COPD	5 (20.8)	16/119 (13.4)	84/551 (15.2)
Peripheral arterial disease	2 (8.3)	6/122 (4.9)	46/571 (8.1)
Cerebrovascular disease	3 (12.5)	12 (9.7)	59 (10.2)
Previous coronary artery bypass graft	2 (8.3)	4 (3.2)	12 (2.1)
Previous valve	0 (0.0)	0 (0.0)	0 (0.0)
Previous PCI	4 (16.7)	12 (9.7)	84 (14.6)
Previous myocardial infarction	3 (12.5)	6 (4.8)	38 (6.6)
Atrial fibrillation/atrial flutter	13 (54.2)	16 (12.9)	84/573 (14.7)
SYNTAX score I	2.3 ± 4.4	2.5 ± 4.5	1.8 ± 3.5
Left ventricular ejection fraction, %	59.2 ± 9.1	62.3 ± 6.3	61.7 ± 8.1

Data are presented as n (%) or mean ± SD. [a]Patients who exited or died at ≤30 days were excluded. COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPI = permanent pacemaker implantation; SYNTAX = SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery coronary scoring system

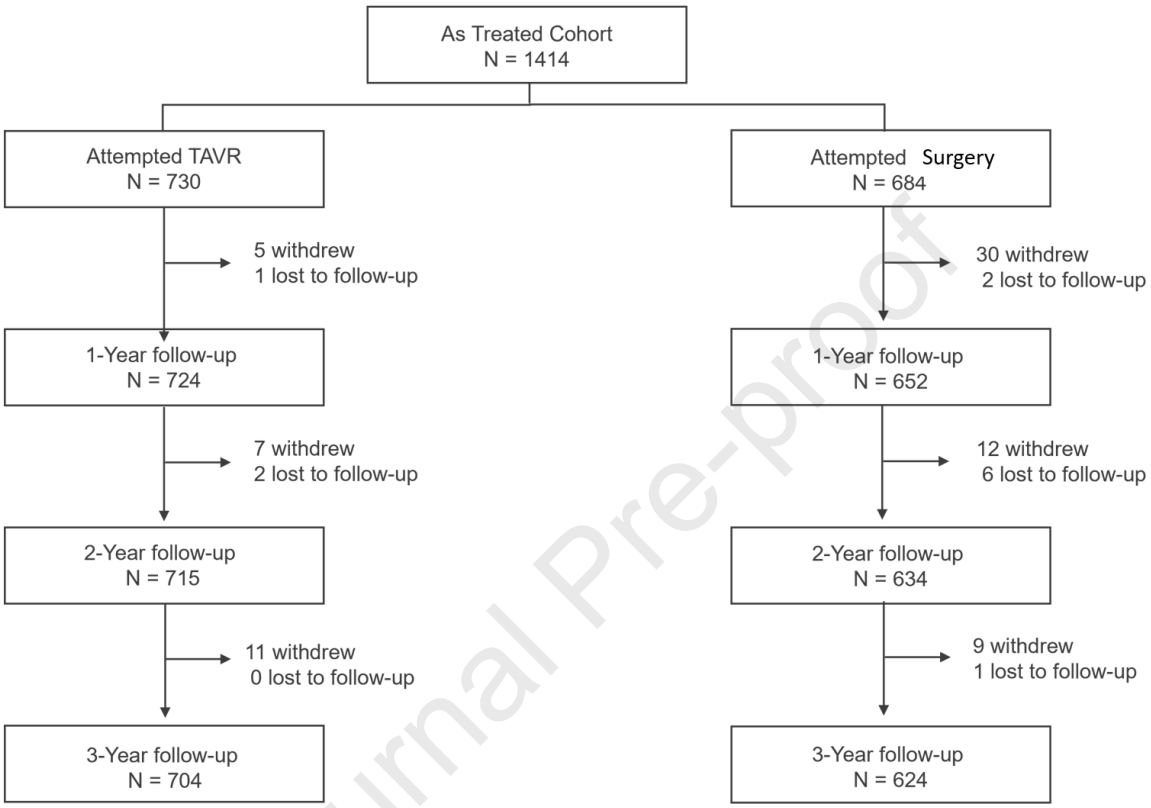
Supplemental Table 3. Reintervention Between 30 Days and 3 Years

Days	Assignment	Valve Type	Etiology	Event
91	TAVR	34 mm Evolut R	Leaflet tear and aortic insufficiency	Surgical aortic valve replacement
173	Surgery	29 mm Trifecta	Endocarditis	Surgical aortic valve replacement
241	Surgery	23 mm Perimount	Thrombosis	Surgical aortic valve replacement
386	TAVR	34 mm Evolut R	Leaflet tear and aortic insufficiency	Surgical aortic valve replacement
437	Surgery	25 mm Trifecta	Endocarditis	Surgical aortic valve replacement
556	TAVR	34 mm Evolut R	Endocarditis	Surgical aortic valve replacement
644	Surgery	25 mm Trifecta	Endocarditis	Surgical aortic valve replacement
735	TAVR	34 mm Evolut R	Leaflet tear and aortic insufficiency	Surgical aortic valve replacement
751	Surgery	27 mm Mosaic	Stenosis	Transcatheter aortic valve replacement

TAVR = transcatheter aortic valve replacement

FIGURES

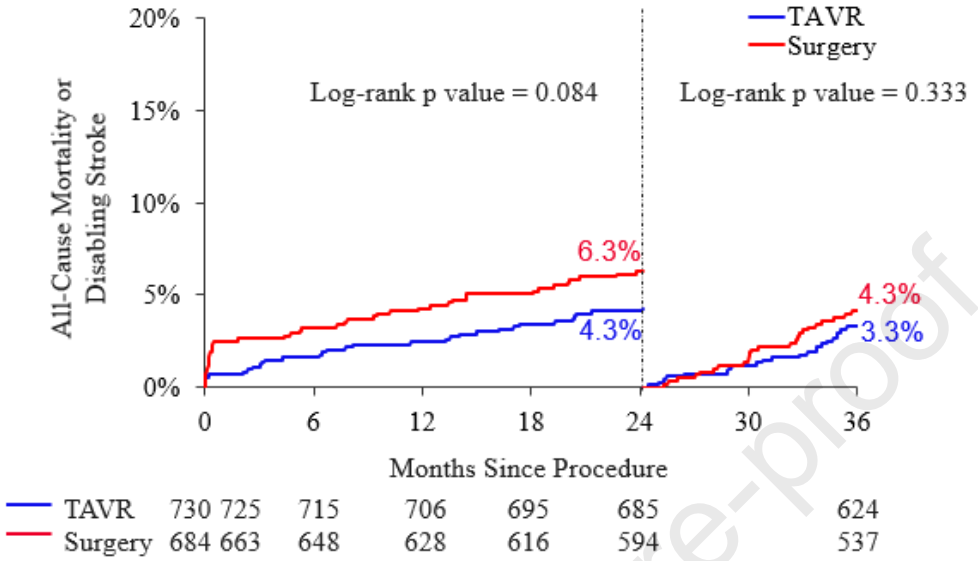
Supplemental Figure 1: Patient Flow Through 3 Years



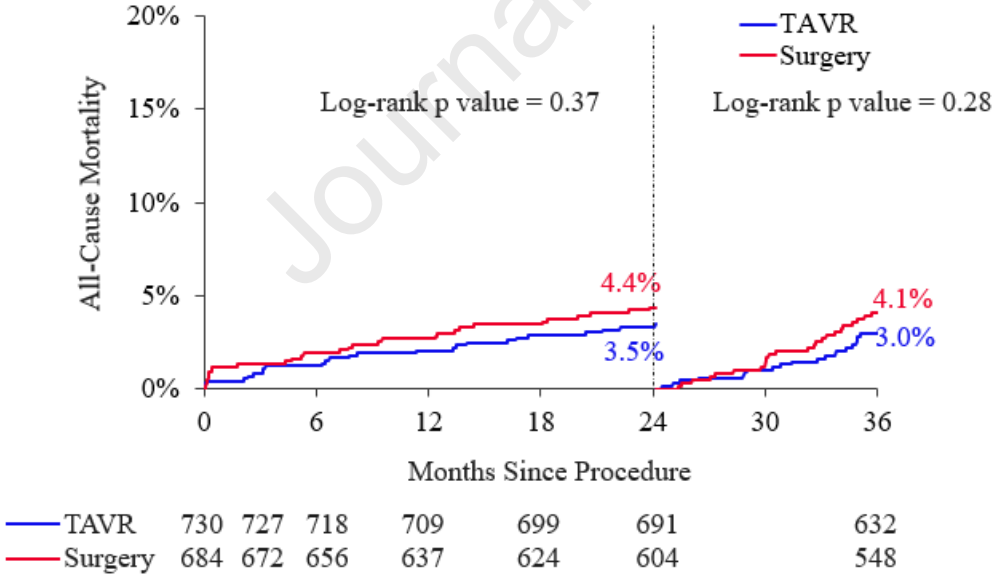
Supplemental Figure 1: At 3 years, data were available for 704 patients (96.4%) in the TAVR group and 624 patients (91.2%) in the surgery group. Patients who died were counted as known status for each time point. TAVR = transcatheter aortic valve replacement.

Supplemental Figure 2: Landmark Analyses: Primary Endpoint and Components

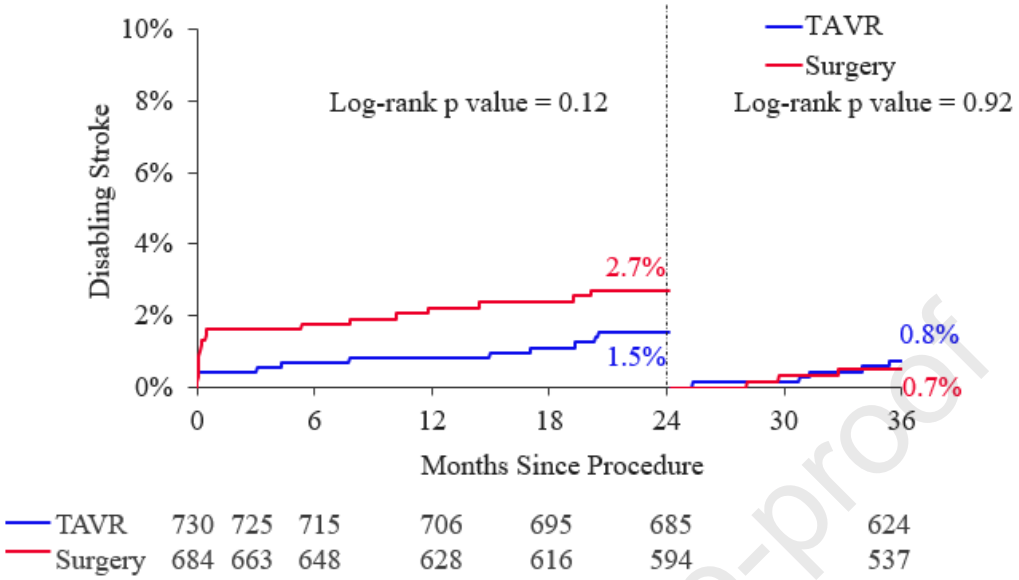
Supplemental Figure 2A: Primary Endpoint Landmarked at 2 Years



Supplemental Figure 2B: All-Cause Mortality Landmarked at 2 Years



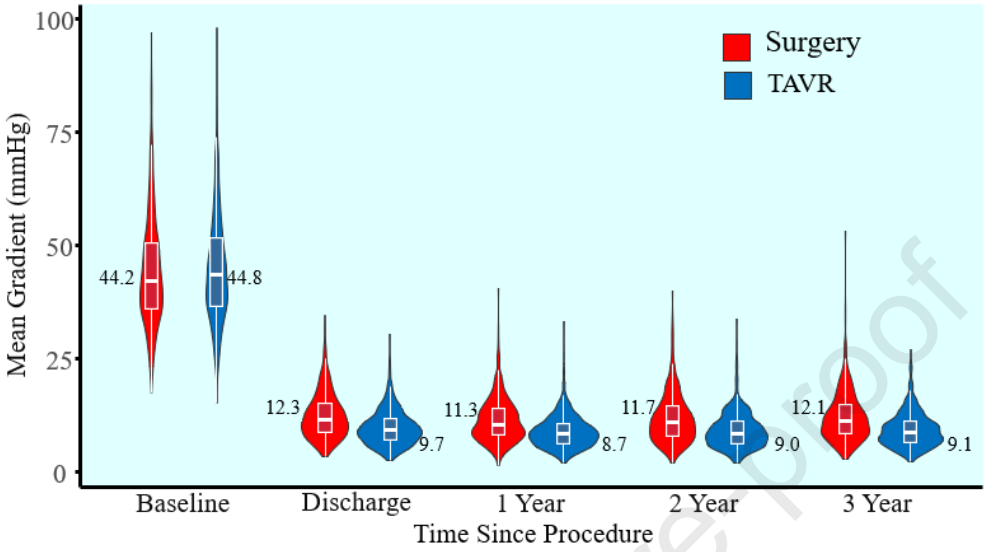
Supplemental Figure 2C: Disabling Stroke Landmarked at 2 Years



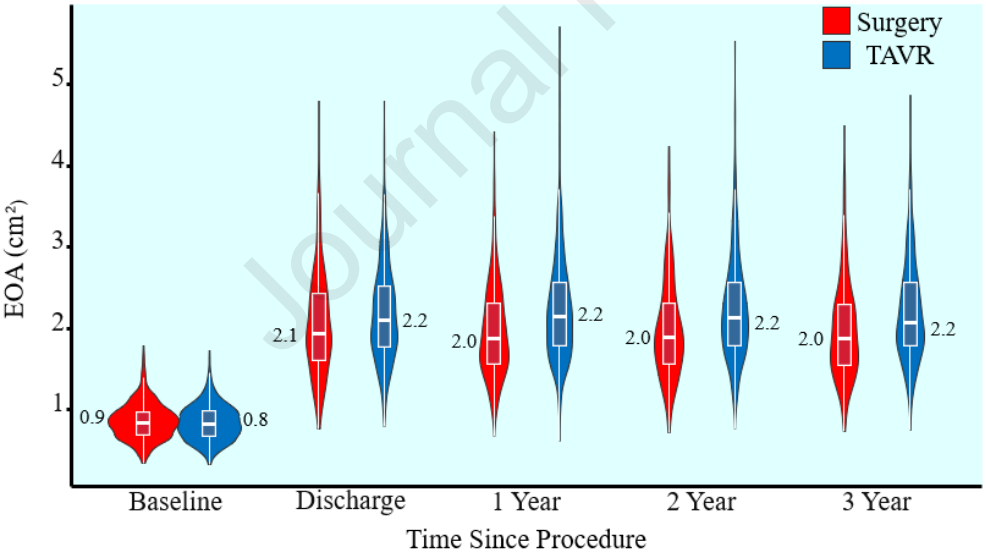
Supplemental Figure 2: Landmark Analyses. Kaplan-Meier estimates and log-rank p values for the primary endpoint (A), all-cause mortality (B), and disabling stroke (C) landmarked at 2 years. TAVR = transcatheter aortic valve replacement.

Supplemental Figure 3: Aortic Valve Mean Gradient and Effective Orifice Area

Supplemental Figure 3A. Mean Gradient

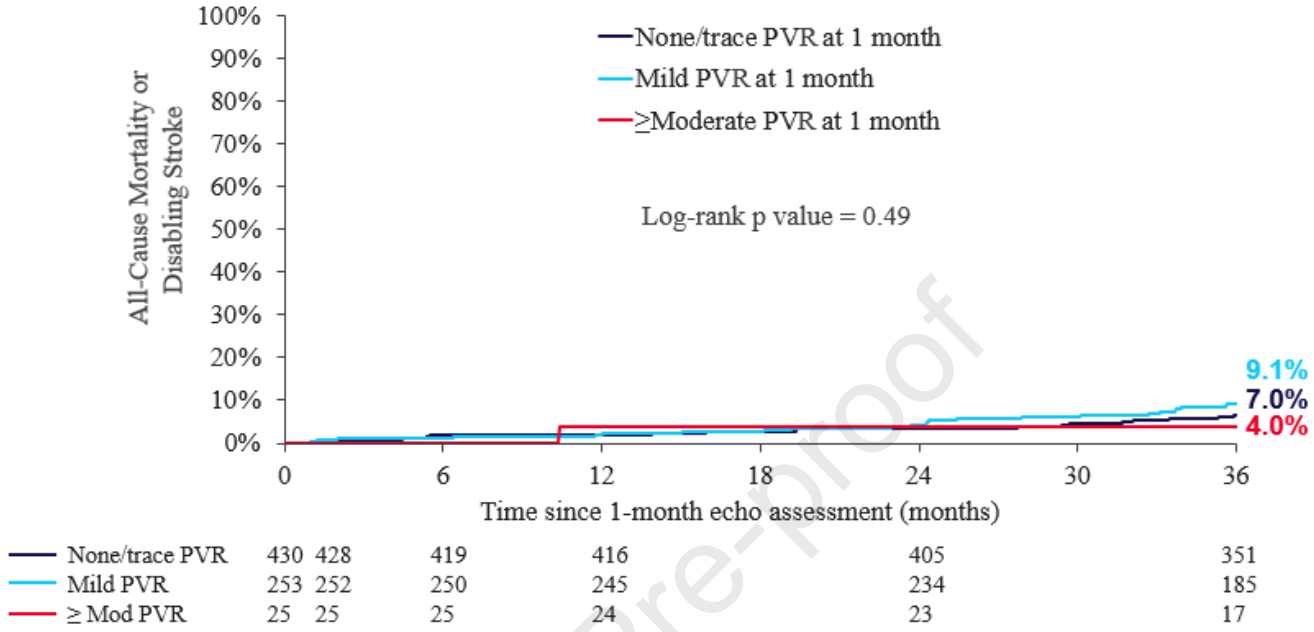


Supplemental Figure 3B. Effective Orifice Area



Supplemental Figure 3. Aortic Valve Mean Gradient and Effective Orifice Area. Violin plots of (A) aortic valve mean gradient and (B) effective orifice area by study visit through 3 years for the TAVR and surgery groups as reported by the echocardiography core laboratory. Within each plot, the horizontal line represents the median, and the upper and lower bounds of the boxes represent the 25th and 75th percentiles, respectively. White vertical lines represent the 1.5x interquartile range, and black vertical lines represent minimum and maximum. Mean is presented in text. TAVR = transcatheter aortic valve replacement

Supplemental Figure 4: Landmark Analysis: Impact of Paravalvular Regurgitation on Three Year Mortality or Disabling Stroke



Supplemental Figure 4. Impact of paravalvular regurgitation at the 1-month echocardiogram on midterm clinical outcomes. Patients in the TAVR group were stratified by none/trace PVL vs mild PVL vs ≥ moderate PVL at the 1-month echocardiography assessment and then followed through 3 years to assess impact on all-cause mortality or disabling stroke. The analysis was landmarked at the 1-month echocardiography date. Clinical outcomes are presented as Kaplan Meier estimates. Paravalvular regurgitation was based on echocardiography core laboratory assessment. PVR = paravalvular regurgitation