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5-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in Low-Risk Patients With Aortic Stenosis

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ABSTRACT

BACKGROUND The Evolut Low Risk trial demonstrated that transcatheter aortic valve replacement (TAVR) was noninferior to surgery for the primary endpoint of all-cause mortality or disabling stroke at 2 years. Outcomes at 5 years have not been reported.

OBJECTIVES This study sought to evaluate 5-year clinical and hemodynamic outcomes with TAVR vs surgery in patients from the Evolut Low Risk trial.

METHODS We randomly assigned low-risk patients with severe aortic stenosis to TAVR or surgery. The primary endpoint was a composite of all-cause mortality or disabling stroke. Secondary endpoints included clinical, echocardiographic, and quality-of-life outcomes through 5 years.

RESULTS A total of 1,414 patients underwent an attempted implant (n = 730 TAVR, n = 684 surgery). The mean age was 74 years (range 51-88 years), and women accounted for 35% of patients. At 5 years the Kaplan-Meier estimate for the primary endpoint of all-cause mortality or disabling stroke was 15.5% for the TAVR group and 16.4% for the surgery group ($P = 0.47$). The Kaplan-Meier estimates in the TAVR and surgery groups for all-cause mortality were 13.5% and 14.9% ($P = 0.39$) and for disabling stroke were 3.6% and 4.0% ($P = 0.57$). Cardiovascular mortality was 7.2% in the TAVR group and 9.3% in the surgery group ($P = 0.15$). Noncardiovascular mortality in the TAVR group was 6.8% and 6.2% in the surgery group ($P = 0.73$). A site-level vital status sweep was performed for patients who were lost to follow-up or withdrew from the study. With the addition of these patients, the all-cause mortality rate at 5 years for patients undergoing TAVR was 14.7% and for surgery was 15.2% ($P = 0.74$). Over 5 years, valve reintervention rate was 3.3% for TAVR and 2.5% for surgery ($P = 0.44$). A sustained improvement in quality of life was observed in both treatment arms with mean Kansas City Cardiomyopathy Questionnaire summary score of 88.3 ± 15.8 in TAVR and 88.5 ± 15.8 in surgery.

CONCLUSIONS At 5 years, patients with severe aortic stenosis who were treated with either TAVR or surgery had comparable rates of all-cause mortality or disabling stroke. Valve durability and performance were excellent in both arms. This midterm evaluation reinforces the position of TAVR as noninferior to surgery in patients with severe aortic stenosis at low surgical risk (Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients; NCT02701283) (JACC. 2025;■:■-■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

KCCQ = Kansas City Cardiomyopathy Questionnaire

PPI = permanent pacemaker implantation

PVL = paravalvular regurgitation/leak

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) has become the predominant intervention for the treatment of severe, symptomatic aortic stenosis in the United States, regardless of surgical risk. Randomized studies have demonstrated excellent procedural and short-term outcomes in low-risk patients,[1,2] but longer-term data for supra-annular self-expanding valves are limited.[3] The Evolut Low Risk (Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients) trial randomized patients with severe trileaflet aortic stenosis to receive either TAVR or surgery. The primary endpoint for the study, a composite of all-cause mortality or stroke at 2 years using Bayesian methods, was 5.3% in the TAVR group and 6.7% in the surgery group.[4] The difference of −1.4% met the prespecified criterion for noninferiority using Bayesian adaptive statistical methods.[4] The findings from the Bayesian analysis were subsequently confirmed at 2 years using the full data set[1] and were sustained out to 3 and 4 years.[5,6] Patients in the Evolut Low Risk trial have now completed 5-year follow-up, and we herein provide an analysis of the 5-year clinical outcomes.

METHODS

TRIAL DESIGN AND OVERSIGHT. The Evolut Low Risk trial (NCT02701283) is a multinational, prospective, randomized, interventional trial comparing the safety and efficacy of TAVR with surgery in patients with severe aortic stenosis who are low-risk for surgery. The trial was conducted at 86 sites in Australia, Canada, France, Japan, the Netherlands, New Zealand, and the United States (see the Supplemental Appendix for the full list of trial sites and investigators). The protocol was developed by the sponsor (Medtronic) in collaboration with the principal investigators and executive committee, and it received approval from the Institutional Review Board or medical ethics committee at each site. The trial was funded by Medtronic, which also oversaw clinical site selection, data monitoring, and statistical analyses. A steering committee provided oversight of the scientific content and execution of the trial. An independent clinical events committee adjudicated endpoint-related adverse events (aortic valve rehospitalization was not adjudicated by the clinical events committee), with safety results reviewed by an independent data and safety monitoring board (Baim Institute for Clinical Research). Echocardiographic endpoints were assessed by an independent echocardiographic core laboratory (Mayo Clinic, Rochester, Minnesota). Additional details of trial oversight and core laboratories are included in the Supplemental Appendix. Written informed consent was provided by all patients.

The trial randomized patients in a 1:1 fashion to either TAVR with a supra-annular, self-expanding valve (CoreValve, Evolut R, or Evolut PRO; Medtronic) or surgery with a bioprosthetic valve between March 2016 and May 2019. Patients are being followed for 10 years. Inclusion criteria included severe trileaflet aortic valve stenosis, a low predicted risk of death (<3%) following surgical aortic valve replacement as assessed by a local multidisciplinary heart team, and anatomic suitability for both TAVR and surgery. There was no minimum age for inclusion. The trial protocol was approved by the Institutional Review Board at each site and the trial was conducted in accordance with Good Clinical Practice principles and the Declaration of Helsinki. Full details of the trial design, oversight, and randomization procedure have been described previously.[4]

TRIAL ENDPOINTS. The primary endpoint was a nonhierarchical composite of all-cause mortality or disabling stroke at 2 years postprocedure in the as-treated population using Bayesian adaptive statical methods.[4] The primary endpoint was evaluated for noninferiority followed by hierarchical superiority if

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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the primary objective and secondary objectives were met. Clinical endpoints reported in this analysis include 5-year rates of all-cause mortality or disabling stroke as well as valve performance as determined using Doppler echocardiographic assessment, paravalvular regurgitation (PVL) at 30 days and 5 years, quality of life as assessed using Kansas City Cardiomyopathy Questionnaire (KCCQ), and NYHA functional class. Prespecified safety endpoints included 5-year rates of stroke, new permanent pacemaker implantation (PPI), prosthetic valve endocarditis, prosthetic valve thrombosis, and aortic valve rehospitalization. Post hoc analyses at 5 years included the composite of all-cause mortality, disabling stroke, or aortic valve hospitalization; the severity of prosthesis-patient mismatch (according to Valve Academic Research Consortium 3 criteria)[7]; a landmark analysis of the association of 30-day PPI with mortality (patients who died or exited before 30 days were excluded). Stroke was defined and adjudicated as described previously.[4] A vital status sweep was performed at the site level for patients in whom 5-year mortality data were not known. Each site collected vital status data via means such as civil registry records search, review of medical records, and telephone calls where allowable and approved. Centers for Medicare are Medicaid Services linkage or use of the national death index was not performed given protocol constraints.

STATISTICAL ANALYSIS. The as-treated population consisted of all randomized patients with an attempted implant procedure, grouped according to the planned procedure. Evaluations of safety events and quality-of-life outcomes were conducted in the as-treated population. The implanted population consisted of all the as-treated patients based on the final valve that was implanted during the index procedure (transcatheter or surgical aortic valve). The annual echocardiographic measurements were assessed in the implanted population. Echocardiographic measurements, including severity of prosthetic valve regurgitation, were reported based on protocol-scheduled echocardiographic assessment at the 5-year study visit. Patients who required reintervention on the index valve were not included in postreintervention echocardiographic assessments. Continuous variables were presented as mean ± SD, and categorical variables were presented as frequencies and percentages. Kaplan-Meier estimates were used to report adverse event rates and compared using the log-rank test, and the difference (95% CI) between treatment arms was reported. Proportions of moderate or severe PVL and prosthesis-patient mismatch were reported with risk differences (95% CI). No adjustments were made for multiplicity, and no statistical technique was used to impute missing data. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

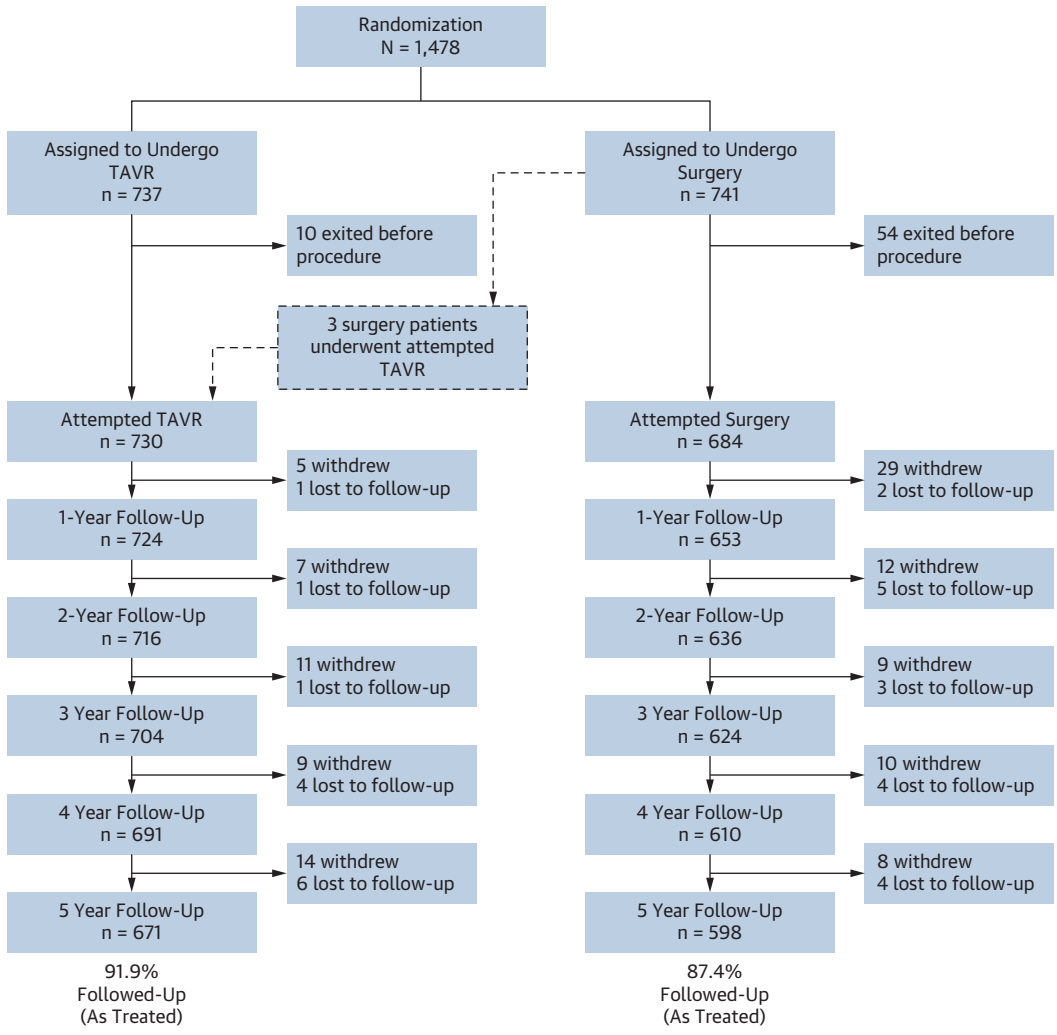
RESULTS

PATIENTS. A total of 1,478 patients were randomized to TAVR (n = 737) or surgery (n = 741). Accounting for patients who exited the study before undergoing a procedure (TAVR [n = 10], surgery [n = 54]), aortic valve replacement was attempted in 1,414 patients (TAVR [n = 730] and surgery [n = 684]) (**Figure 1**). Three patients randomized to surgery were crossed over to the TAVR group before their index procedure at the operator's discretion and were therefore included in the TAVR group. In addition, 1 patient who underwent an attempted surgical aortic valve replacement converted to TAVR during the index procedure and 4 patients who underwent an attempted TAVR procedure were converted to surgical aortic valve replacement during the index procedure. Over the 5-year follow-up period, 59 patients in the TAVR group exited the trial (withdrew [n = 46]; lost to follow-up [n = 13]) and 86 patients in the surgery group exited the trial (withdrew [n = 68]; lost to follow-up [n = 18]), resulting in 671 TAVR patients and 598 surgery patients with evaluable status at 5 years. Baseline patient characteristics were comparable between the TAVR (age: 74.1 ± 5.8 years; Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM]: 2.0% ± 0.7%) and surgery groups (age: 73.7 ± 5.9 years; STS-PROM: 1.9% ± 0.7%) (Supplemental Table 1).

5-YEAR CLINICAL OUTCOMES. The TAVR group and surgery groups had similar outcomes for key endpoints at 5 years (**Table 1**). Kaplan-Meier estimates for the composite of all-cause mortality or disabling stroke at 5 years were 15.5% in the TAVR group and 16.4% in the surgery group (difference: −1.0%; 95% CI: −5.1% to 3.2%; $P = 0.47$) (**Central Illustration**). The all-cause mortality rate was 13.5% in the TAVR group and 14.9% in the surgery group (difference: −1.4%; 95% CI: −5.4% to 2.5%; $P = 0.39$). The rate of disabling stroke was 3.6% in the TAVR group and 4.0% in the surgery group (difference: −0.4%; 95% CI: −2.7% to 1.9%; $P = 0.57$) (**Central Illustration**).

Cardiovascular mortality was 7.2% in the TAVR group and 9.3% in the surgery group (difference: −2.1%; 95% CI: −5.3% to 1.1%; $P = 0.15$) (**Central Illustration**). The rate of noncardiovascular deaths was 6.8% in the TAVR group and 6.2% in the surgery group (difference: 0.6%; 95% CI: −2.3% to 3.5%; $P = 0.73$) (**Central Illustration**). Causes of death

FIGURE 1 Consort Diagram



Data were available for 671 (91.9%) patients in the TAVR arm and 598 (87.4%) patients in the surgical arm at 5 years. Patients who died were counted as known status for each time point. TAVR = transcatheter aortic valve replacement.

in the TAVR and surgery groups between years 4 and 5 are shown in Supplemental Tables 2 and 3.

Rates of myocardial infarction at 5 years for the TAVR and surgery groups were 6.0% and 3.6%, respectively (difference: 2.4%; 95% CI: −0.1% to 5.0%; $P = 0.06$). Management approach of coronary ischemia is listed in Supplemental Table 4. The rate of atrial fibrillation was 16.3% in the TAVR group and 41.2% in the surgery group (difference: −24.9%; 95% CI: −30.3% to −19.6%; $P < 0.001$). Excluding patients with preexisting pacemakers or implantable cardioverter-defibrillators, the rate of new PPI was 27.0% in the TAVR group and 11.3% in the surgery group (difference: 15.7%; 95% CI: 11.0%-20.4%; $P < 0.001$). For patients with a pacemaker prior to TAVR, the 5-year mortality was 22.7% (95% CI: 9.6%-48.1%); for patients who required a pacemaker after TAVR (within the first 30 days), the 5-year mortality was 16.6% (95% CI: 10.9%-24.9%); for patients who did not require a pacemaker in the first 30 days after TAVR, the 5-year mortality was 12.1% (95% CI: 9.5%-15.2%) (Supplemental Figure 1). For the TAVR vs surgery groups, both clinical valve thrombosis (0.3% vs 0.2%; difference: 0.1%; 95% CI: −0.4% to 0.7%;

TABLE 1 5-Year Clinical Outcomes

	TAVR (n = 730)	Surgery (n = 684)	HR (95% CI)	*P* Value (Log-Rank)
All-cause mortality or disabling stroke	108 (15.5)	104 (16.4)	0.90 (0.69-1.18)	0.47
All-cause mortality	94 (13.5)	93 (14.9)	0.88 (0.66-1.17)	0.39
Cardiovascular death	49 (7.2)	57 (9.3)	0.75 (0.51-1.11)	0.15
Noncardiovascular death	45 (6.8)	36 (6.2)	1.08 (0.70-1.67)	0.73
All-cause mortality with vital status sweep	106 (14.7)	99 (15.2)	0.96 (0.73-1.26)	0.74
All-stroke	66 (9.5)	54 (8.6)	1.11 (0.77-1.59)	0.58
Disabling stroke	24 (3.6)	25 (4.0)	0.85 (0.49-1.49)	0.57
Aortic valve hospitalization	93 (13.9)	91 (15.1)	0.89 (0.67-1.19)	0.44
Major vascular complication	30 (4.1)	26 (3.9)	1.07 (0.64-1.82)	0.79
Myocardial infarction	40 (6.0)	22 (3.6)	1.63 (0.97-2.75)	0.06
Permanent pacemaker implant	185 (27.0)	69 (11.3)	2.70 (2.04-3.55)	<0.001
Atrial fibrillation	114 (16.3)	278 (41.2)	0.32 (0.25-0.39)	<0.001
Valve endocarditis	9 (1.4)	15 (2.5)	0.52 (0.23-1.20)	0.12
Reintervention	21 (3.3)	14 (2.5)	1.30 (0.66-2.56)	0.44
Total valve thrombosis	6 (0.9)	4 (0.6)	1.36 (0.38-4.82)	0.63
Clinical[a]	2 (0.3)	1 (0.2)	1.84 (0.17-20.24)	0.61
Subclinical[b]	4 (0.6)	3 (0.5)	1.20 (0.27-5.37)	0.81

Values are n (%) unless otherwise indicated. [a]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-segment elevation myocardial infarction, or hemodynamic impairment associated with a worsening heart failure. [b]Defined as those without evident clinical sequelae causing a hemodynamic impediment meeting the following criteria: increase in aortic regurgitation resulting in a severity of moderate or severe, a postdischarge mean gradient of ≥20 mm Hg that increased by >50%, or a decrease in the Doppler velocity index by >50%.

TAVR = transcatheter aortic valve replacement.

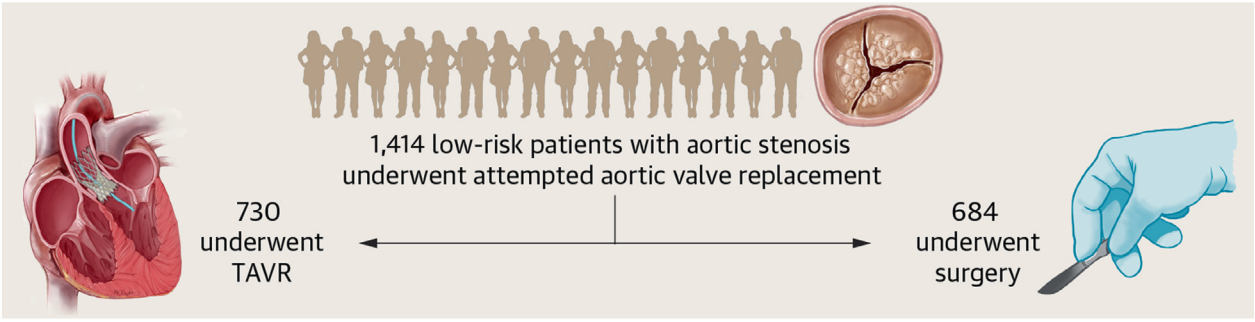
$P = 0.61$) and subclinical valve thrombosis (0.6% vs 0.5%; difference: 0.1%; 95% CI: −0.8% to 1.0%; $P = 0.81$) remained low at 5 years (**Table 1**).

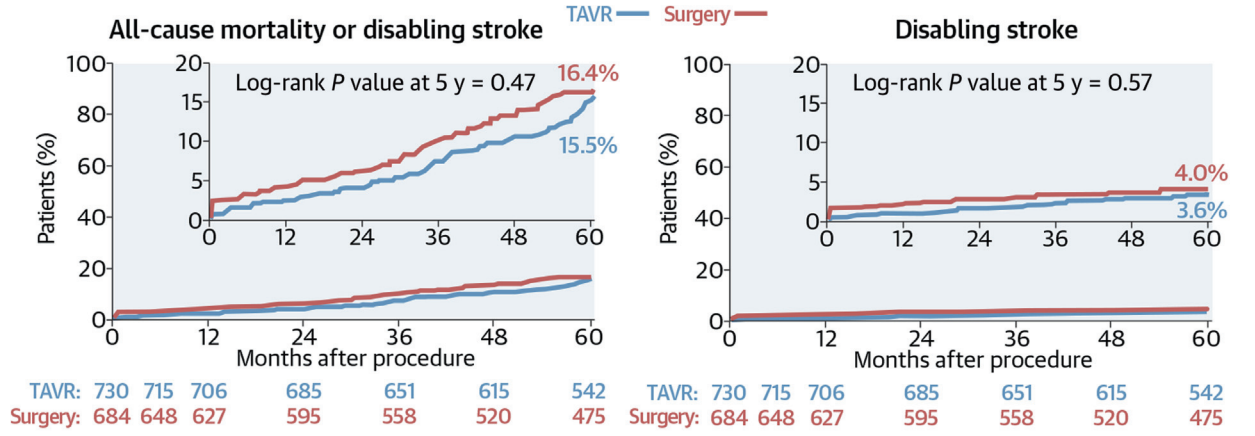
Early (0-2 years) and late (2-5 years) clinical outcomes are shown in Supplemental Table 5. No significant interactions in the treatment effect were observed for all-cause mortality or disabling stroke among the various demographic subgroups (Supplemental Figure 2). A vital status sweep performed by sites successfully identified 40 of 60 (66.7%) TAVR patients and 45 of 89 (51.0%) surgical patients who had withdrawn from the study, were lost to follow-up, or for whom 5-year mortality status was unknown. The mortality rate of patients identified in this site-performed vital status sweep was 51% (43 of 85). Including the vital status sweep data, the all-cause mortality rate at 5 years for patients undergoing TAVR was 14.7% and for surgery was 15.2% ($P = 0.74$) (Supplemental Table 6).

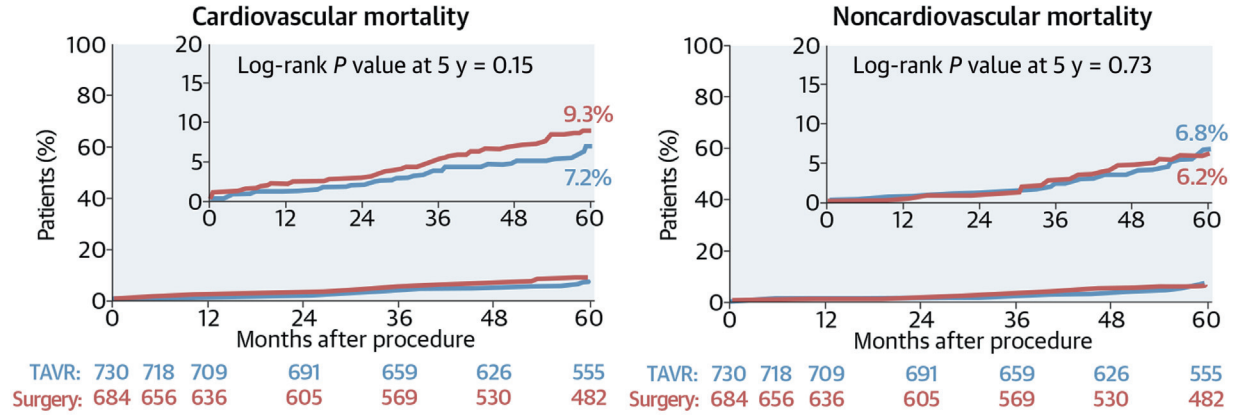
ECHOCARDIOGRAPHIC OUTCOMES. At 5 years, the mean aortic valve gradient was significantly lower after TAVR than surgery (10.7 mm Hg vs 12.8 mm Hg; difference: −2.1; 95% CI: −3.0 to −1.2; $P < 0.001$) (**Table 2**, **Figure 2A**) and mean effective orifice area was significantly larger, 2.1 cm^2 TAVR vs 1.9 cm^2 surgery (difference: 0.2; 95% CI: 0.1-0.3; $P < 0.001$) (**Figure 2A**). The mean Doppler velocity index was significantly higher for TAVR vs surgery (0.51 ± 0.15 vs 0.46 ± 0.12; $P < 0.001$) (Supplemental Figure 3). At 5 years, total prosthetic valve regurgitation of mild or greater severity was present in 80 of 470 patients (17.0%) in the TAVR group and in 22 of 388 patients (5.7%) in the surgery group; PVL of mild or greater severity was present in 67 of 457 patients (14.7%) in the TAVR group and in 2 of 379 patients (0.5%) in the surgery group (risk difference: 14.1%; 95% CI: 10.8-17.5; $P < 0.001$) (**Table 2**). For patients who underwent TAVR and had mild PVL at 30 days, most (110 of 154) improved over time (Supplemental Table 7). The mortality rate at 5 years for TAVR patients with mild PVL at 30 days was 14.1% (Supplemental Figure 4). This was similar to the 13.0% mortality rate at 5 years for patients with no/trace PVL at 30 days ($P = 0.67$).

REINTERVENTION. Aortic valve reintervention occurred in 21 patients (3.3%) after TAVR and 14 patients (2.5%) after surgery by 5 years (difference: 0.8%; 95% CI: −1.2% to 2.9%; $P = 0.44$) (**Table 1**). For patients requiring reintervention, aortic regurgitation (valvular or paravalvular), stenosis, and endocarditis were the primary indications. Five patients who had TAVR underwent reintervention due to PVL and 2 patients who had surgery underwent reintervention due to PVL. In both groups, most patients who required reintervention were treated with surgery. Mortality after surgical reintervention was similar

CENTRAL ILLUSTRATION **5-Year Outcomes After Transcatheter or Surgical Aortic Valve Replacement**







Transcatheter and surgical aortic valve replacement had comparable rates of all-cause mortality or disabling stroke with sustained outcomes over 5 years

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Kaplan-Meier estimates are shown for the composite of all-cause mortality or disabling stroke, disabling stroke, cardiovascular mortality, and noncardiovascular mortality through 5 years. The inset in each panel shows the same data on an enlarged y axis. TAVR = transcatheter aortic valve replacement.

TABLE 2 Echocardiographic Outcomes at the 5-Year Visit for the Index Valve[a]

	TAVR (n = 727)	Surgery (n = 686)	Risk Difference (95% CI)	*P* Value
Mean gradient, mm Hg	10.7 ± 6.6 (467)	12.8 ± 6.9 (387)		<0.001
Effective orifice area, cm^2	2.1 ± 0.6 (399)	1.9 ± 0.6 (313)		<0.001
Doppler velocity index	0.51 ± 0.15 (440)	0.46 ± 0.12 (366)		<0.001
Paravalvular regurgitation				<0.001
None/trace	85.3 (390/457)	99.5 (377/379)		
Mild	14.2 (65/457)	0.5 (2/379)		
Moderate	0.4 (2/457)	0.0 (0/379)		
Severe	0.0 (0/457)	0.0 (0/379)		
≥Mild	14.7 (67/457)	0.5 (2/379)	14.1 (10.8-17.5)	<0.001

Values are mean ± SD (n) or % (n/N), unless otherwise indicated. [a]Echocardiographic measurements were reported based on protocol-scheduled echocardiographic assessment at the 5-year study visit; patients who required reintervention on the index valve were not included in subsequent echocardiographic assessments.

TAVR = transcatheter aortic valve replacement.

between treatment arms and resulted in 2 deaths in each treatment arm (Supplemental Table 8).

QUALITY-OF-LIFE OUTCOMES. At 5 years, overall KCCQ summary scores remained high and were similar after TAVR and surgery (88.3 ± 15.8 vs 88.5 ± 15.8; difference: −0.2; 95% CI: −2.2 to 1.8; $P = 0.83$) (**Figure 2B**). Most patients in each arm remained asymptomatic from a heart failure standpoint (NYHA functional class I) at 5 years (Supplemental Figure 5). Rates of patients who were alive and well (alive and KCCQ summary score >75) were similar between the TAVR and surgery groups (70.6% and 69.3%).

DISCUSSION

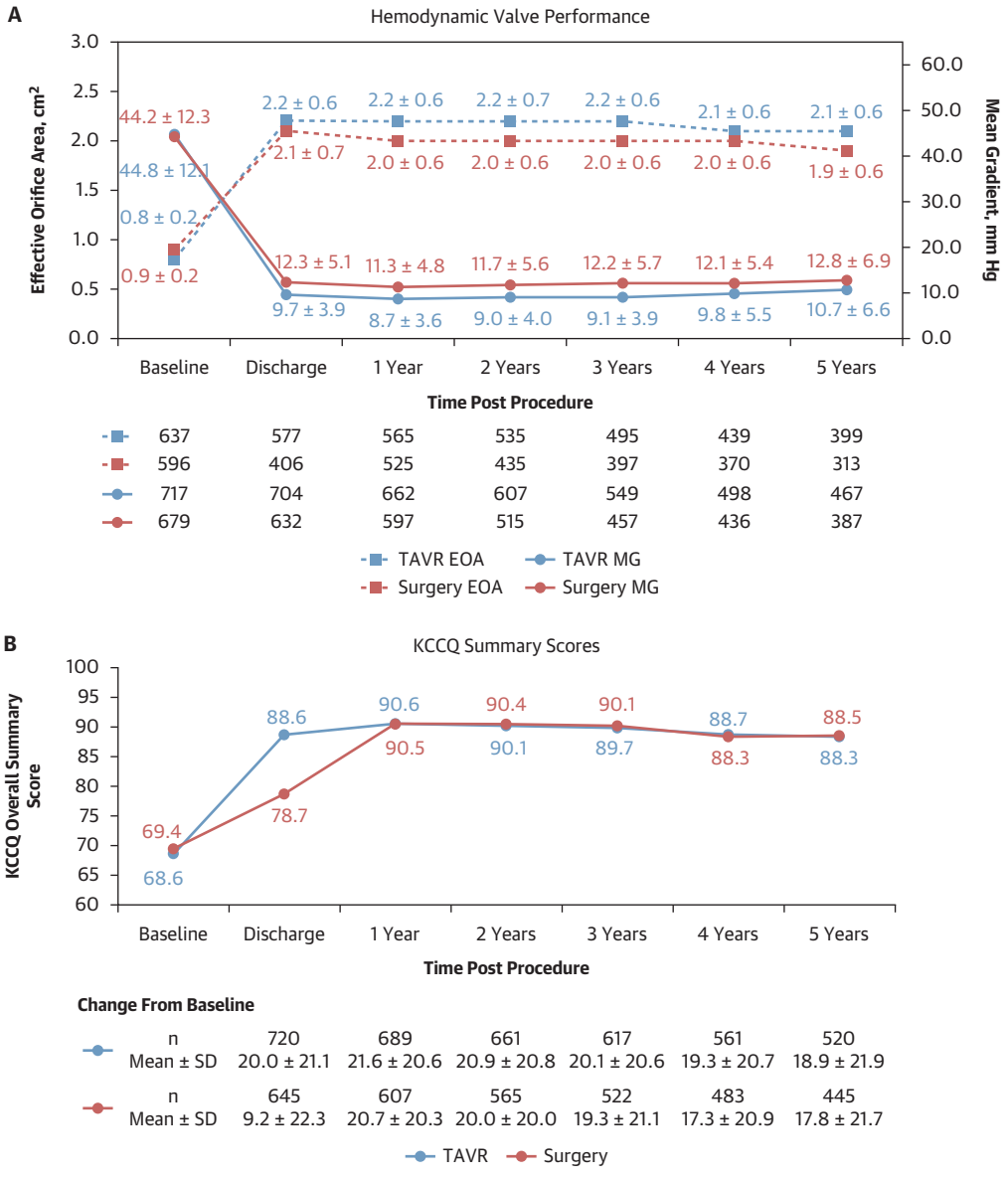
At 5 years, the results from the Evolut Low Risk trial demonstrated sustained outcomes for the primary endpoint of all-cause mortality or disabling stroke that were similar between the TAVR and surgical groups. At 5 years, cardiovascular mortality was 7.2% in TAVR and 9.3% in surgery; noncardiovascular mortality was 6.8% in TAVR and 6.2% in surgery; and disabling stroke was 3.6% in TAVR and 4.0% in surgery. This sustained performance at 5 years for patients undergoing TAVR with a supra-annular self-expanding valve continues to show TAVR as a durable therapy for this lower-risk patient population.

There were differences in some secondary endpoints including better hemodynamics as well as a lower rate of atrial fibrillation in the TAVR group. Patients who underwent surgery had a lower rate of new pacemaker placement and less mild paravalvular regurgitation. At 5 years there was no significant difference in the rate of aortic valve rehospitalization, endocarditis, myocardial infarction, reintervention, or valve thrombosis between groups. Data at 4 years for this study had shown an increasing delta in the primary outcome of all-cause mortality or disabling stroke ($P = 0.05$).[5] This analysis demonstrates that changes between years 2 and 4 were driven predominantly by more noncardiovascular deaths in the surgical arm, whereas between years 4 and 5 there were more noncardiovascular deaths in the TAVR arm. These results now suggest that there is no significant difference in 5-year mortality or the composite of death or disabling stroke between TAVR and surgery.

The benefits of TAVR at all surgical risk levels have been demonstrated in randomized clinical trials[8-15] and led to 2020 American College of Cardiology/American Heart Association guidelines recommending surgery for patients <65 years of age and with life expectancy of 20 years, surgery or TAVR for patients 65 to 80 years, and TAVR for those >80 years of age.[16] The present trial, in which >93% of patients in both groups were >65 years of age (the youngest patient treated with TAVR was 54 years), demonstrates that with this supra-annular self-expanding valve, the initial results remain consistent and durable out to 5 years. The primary endpoint of all-cause mortality or disabling stroke at 2 years using Bayesian adaptive statistical methods was 5.3% in the TAVR group and 6.7% in the surgery group, and at 5 years the Kaplan-Meier estimate for the primary outcome was 15.5% in the TAVR group and 16.4% in the surgical group.[4]

Given the younger age of this patient cohort, valve durability remains a primary concern beyond the initial implant and recovery from the index procedure. These results at 5 years demonstrate sustained valve performance, including low rates of valve thrombosis, excellent hemodynamics, and low rates of valvular reintervention. After TAVR, the primary indication for reintervention was aortic regurgitation. Although TAVR explant and surgical aortic valve replacement increases mortality risk in previous retrospective studies,[17,18] within this study outcomes

FIGURE 2 5-Year Hemodynamic Performance and Quality of Life



(A) Aortic valve mean gradient and effective orifice area in the TAVR and surgery groups from baseline to 5 years. (B) KCCQ overall summary scores and change from baseline for patients in the TAVR and surgical arms from baseline to 5 years. EOA = effective orifice area; KCCQ = Kansas City Cardiomyopathy Questionnaire; MG = mean gradient; TAVR = transcatheter aortic valve replacement.

were similar for patients who required surgical reintervention regardless of whether the first valve was transcatheter or surgical.

One of the benefits of TAVR is early improvement in quality of life, as assessed by the KCCQ score. Although patients undergoing surgery have a slower improvement in KCCQ scores, by 1 year the overall improvement is similar between the 2 groups. The quality-of-life improvement was sustained through 5 years for both groups. Similarly, 1-year improvements in NYHA functional classification were maintained out to 5 years, with >75% of patients in both treatment arms continuing to be asymptomatic (NYHA functional class I). Patients are increasingly interested in more than just periprocedural mortality and ~70% of patients in each treatment group met

the criteria for being alive and well (alive and KCCQ summary score >75) at 5 years.

STUDY LIMITATIONS. Limitations of this trial have been previously reported.[1,4,6] Echocardiographic-defined outcomes were measured at discrete intervals as per the protocol, and as such, it is possible for a patient with valve deterioration to be intervened on but not have the echocardiographic measurements captured within the 5-year visit window. Another limitation of this and other randomized TAVR studies is loss to follow-up, with disproportionate loss in the control arm.[19] To help account for this, a site-level vital status sweep was performed for patients who were lost to follow-up or withdrew. The percentage of patients for whom a known vital status was obtained differed between the 2 groups (TAVR: 66.7% and surgery: 51.0%). Centers for Medicare and Medicaid Services linkage or use of the national death index was not performed given protocol constraints and country-specific privacy regulations prohibited data collection by some sites. The mortality rate in patients who withdrew or were lost to follow-up was higher than in those who did not exit the study, and protocol updates are planned to allow for better capture of these patients at future follow-ups. Procedural and device-related advancements have occurred since this study completed enrollment. In particular, modifications to the implant technique[20] and valvular improvements have decreased the incidence of PPI after TAVR as compared with the data presented here.[21] Another limitation of these data is that it represents a time point at 5 years. Within the United States, outcomes beyond 1 year are routinely collected only within randomized trials. Given the importance of longer-term outcomes and valve durability in low-risk patients, continued follow-up of data from the low-risk trials must be frequently reported. Patients in the Evolut Low Risk trial will be followed for 10 years.

CONCLUSIONS

Patients with severe aortic stenosis who were treated with either a supra-annular self-expanding TAVR or surgery showed comparable rates of all-cause mortality and disabling stroke at 5 years, strengthening TAVR as a safe, effective, and durable alternative to surgery for patients, regardless of their surgical risk.

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REFERENCES

1. Forrest JK, Deeb GM, Yakubov SJ, et al. 2-Year outcomes after transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll Cardiol*. 2022;79:882-896.

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

3. Thyregod HGH, Jørgensen TH, Ihlemann N, et al. Transcatheter or surgical aortic valve implantation: 10-year outcomes of the NOTION trial. *Eur Heart J*. 2024;45:1116-1124.

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

5. Forrest JK, Deeb GM, Yakubov SJ, et al. 4-Year outcomes of patients with aortic stenosis in the

Evolut Low Risk Trial. *J Am Coll Cardiol*. 2023;82:2163–2165.

6. Forrest JK, Deeb GM, Yakubov SJ, et al. 3-Year outcomes after transcatheter or surgical aortic valve replacement in low-risk patients with aortic stenosis. *J Am Coll Cardiol*. 2023;81:1663–1674.

7. Généreux P, Piazza N, Alu MC, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77:2717–2746.

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

9. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798.

10. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2015;66:113–121.

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

12. Reardon MJ, Kleiman NS, Adams DH, et al. Outcomes in the randomized CoreValve US Pivotal High Risk Trial in patients with a Society of Thoracic Surgeons risk score of 7% or less. *JAMA Cardiol*. 2016;1:945–949.

13. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement in low-risk patients at five years. *N Engl J Med*. 2023;389:1949–1960.

14. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.

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

16. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77(4):450–500.

17. Jawitz OK, Gulack BC, Grau-Sepulveda MV, et al. Reoperation after transcatheter aortic valve replacement: an analysis of the Society of Thoracic Surgeons database. *JACC Cardiovasc Interv*. 2020;13:1515–1525.

18. Bowdish ME, Habib RH, Kaneko T, Thourani VH, Badhwar V. Cardiac surgery after transcatheter aortic valve replacement: trends and outcomes. *Ann Thorac Surg*. 2024;118:155–162.

19. Barili F, Brophy JM, Ronco D, et al. Risk of bias in randomized clinical trials comparing transcatheter and surgical aortic valve replacement: a systematic review and meta-analysis. *JAMA Network Open*. 2023;6. e2249321-e2249321.

20. Grubb KJ, Gada H, Mittal S, et al. Clinical impact of standardized TAVR technique and care pathway: insights from the Optimize PRO study. *JACC Cardiovasc Interv*. 2023;16:558–570.

21. Harvey JE, Puri R, Grubb KJ, et al. Decreasing pacemaker implantation rates with Evolut supra-annular transcatheter aortic valves in a large real-world registry. *Cardiovasc Revasc Med*. 2024;69:1–9.

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