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Self-Expanding Transcatheter Aortic Valve Replacement or Surgical Valve Replacement in High-Risk Patients

5-Year Outcomes

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ABSTRACT

BACKGROUND The CoreValve US Pivotal High Risk Trial was the first randomized trial to show superior 1-year mortality of transcatheter aortic valve replacement (TAVR) compared with surgical aortic valve replacement (SAVR) among high operative mortality–risk patients.

OBJECTIVES The authors sought to compare TAVR to SAVR for mid-term 5-year outcomes of safety, performance, and durability.

METHODS Surgical high-risk patients were randomized (1:1) to TAVR with the self-expanding bioprosthesis or SAVR. VARC-1 (Valve Academic Research Consortium I) definitions were applied. Severe hemodynamic structural valve deterioration was defined as a mean gradient ≥40 mm Hg or a change in gradient ≥20 mm Hg or new severe aortic regurgitation. Five-year follow-up was planned.

RESULTS A total of 797 patients were randomized at 45 U.S. centers, of whom 750 underwent an attempted implant (TAVR = 391, SAVR = 359). The overall mean age was 83 years, and the STS score was 7.4%. All-cause mortality rates at 5 years were 55.3% for TAVR and 55.4% for SAVR. Subgroup analysis showed no differences in mortality. Major stroke rates were 12.3% for TAVR and 13.2% for SAVR. Mean aortic valve gradients were 7.1 ± 3.6 mm Hg for TAVR and 10.9 ± 5.7 mm Hg for SAVR. No clinically significant valve thrombosis was observed. Freedom from severe SVD was 99.2% for TAVR and 98.3% for SAVR ($p = 0.32$), and freedom from valve reintervention was 97.0% for TAVR and 98.9% for SAVR ($p = 0.04$). A permanent pacemaker was implanted in 33.0% of TAVR and 19.8% of SAVR patients at 5 years.

CONCLUSIONS This study shows similar mid-term survival and stroke rates in high-risk patients following TAVR or SAVR. Severe structural valve deterioration and valve reinterventions were uncommon.(Medtronic CoreValve U.S. Pivotal Trial; NCT01240902). (J Am Coll Cardiol 2018;■:■-■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

NYHA = New York Heart Association

PVL = paravalvular leak

SAVR = surgical aortic valve replacement

STS PROM = Society of Thoracic Surgeons Predictors of Mortality

SVD = structural valve deterioration

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is now a recognized alternative to surgical aortic valve replacement (SAVR) with 1- to 3-year mortality and stroke outcomes that are equivalent. Specifically, the PARTNER IA trial (Placement of AoRTic TraNscathetER Valve Trial) with a balloon-expandable annular valve showed TAVR to be noninferior to SAVR in high-risk patients in the short and mid term (1,2). Congruously, the CoreValve US Pivotal High Risk Trial with a self-expanding supra-annular valve showed TAVR to be superior to SAVR for the primary endpoint of all-cause mortality at 1 (3) and 2 (4) years with a numerical, but not statistical, advantage remaining at 3 years (5). These trials have resulted in a Class I, Level of Evidence: A recommendation for patients with symptomatic severe aortic stenosis (AS) and high surgical mortality risk to undergo either TAVR or SAVR (6). We now report the final 5-year outcomes for high-risk patients in this trial.

METHODS

STUDY DESIGN. Details of the CoreValve US Pivotal High Risk Trial design have been previously reported (3). This was a multicenter, prospective, randomized trial performed at 45 centers in the United States. Patients with severe, symptomatic (New York Heart Association [NYHA] functional class II or greater) aortic stenosis were randomized in a 1:1 manner to TAVR or SAVR, stratified by clinical site and recommended transcatheter vascular access site. An independent clinical events committee adjudicated all major adverse events based on the initial VARC-1 (Valve Academic Research Consortium) definitions (7). Each institutional review board approved the protocol, and all patients provided written consent to participate in the trial.

The primary endpoint was all-cause mortality at 1 year in the as-treated patients. Pre-defined secondary endpoints at 5 years included major adverse cardiovascular and cerebrovascular events (death, myocardial infarction, stroke, or valve reintervention) and the individual components, change in NYHA functional class, quality of life using a summary of the Kansas City Cardiomyopathy Questionnaire (KCCQ), 12-item Short Form General Health Survey (SF-12), echocardiography indices of effective orifice area, mean gradient and aortic regurgitation (AR) (both total and paravalvular leak [PVL]), cardiovascular deaths and stroke. The definition of these pre-specified secondary endpoints have been previously reported (3).

The definition of moderate and severe hemodynamic structural valve deterioration (SVD) was that of Capodanno et al. (8). Severe SVD was defined as a mean gradient ≥40 mm Hg or a change in gradient ≥20 mm Hg or new severe AR. Moderate SVD was defined as an AV gradient ≥20 mm Hg but <40 mm Hg, a change in mean gradient from discharge or 1 month of ≥10 mm Hg but <20 mm Hg or moderate new central AR.

PATIENT SELECTION. Patient selection has been previously described in detail (3). Eligible patients

US Pivotal High Risk Trial. Dr. Gleason has received institutional grant support from Medtronic and Boston Scientific; and has served on medical advisory boards for Abbott and Cytosorbents Corporation. Dr. Reardon has received fees from Medtronic for providing educational services. Dr. Popma has received institutional research grants from Medtronic, Abbott, Edwards Lifesciences, Boston Scientific, and Direct Flow Medical; and has served on a medical advisory board for Boston Scientific, Cordis Corporation, and Edwards Lifesciences. Dr. Deeb has served on an advisory board for Medtronic; as a proctor for Medtronic and Terumo; as a consultant for Edwards Lifesciences and Terumo; and as a research investigator for Edwards Lifesciences, Medtronic, and Gore Medical. Dr. Yakubov has received institutional research grants from Boston Scientific and Medtronic; has served on a steering committees for Medtronic CoreValve trials; and has received proctor fees from Medtronic. Dr. Kleiman has received educational and research grants from Medtronic. Dr. Chetcuti has served as a proctor for Medtronic; has served as a consultant for Jena; and has received grant support from Medtronic, Edwards Lifesciences, and Gore. Dr. Hermiller has received fees for educational services from Medtronic. Dr. Merhi has served on the steering committee of the Medtronic Low Risk Trial. Dr. Zorn has received consulting and proctoring fees from Medtronic and Edwards Lifesciences. Dr. Tadros has received consulting fees, proctoring fees, and research support from Medtronic and St. Jude Medical (Abbott). Dr. Hughes has served as a consultant and speaker for Medtronic. Dr. Harrison has received institutional grants from Medtronic, Boston Scientific, Direct Flow Medical, St. Jude Medical (Abbott), and Edwards Lifesciences; and has served on a medical advisory board for Direct Flow Medical and on the data safety monitoring board for CardiAQ. Dr. Conte has served on an advisory board for Medtronic; and has served as a consultant to Boston Scientific and Sorin. Dr. Mumtaz has served as a consultant to Abbott, Atricure, Edwards Lifesciences, Japanese Organization for Medical Device Development, Medtronic, Millipede, and Terumo. Dr. Oh has been the director of the Echocardiography Core Lab for CoreValve/Evolut R; and a consultant for Medtronic. Dr. Huang is an employee and shareholder of Medtronic. Dr. Adams has received other support from Medtronic during the conduct of the study, and from NeoChord and Medtronic outside the submitted work; and has received patent royalties from Edwards Lifesciences and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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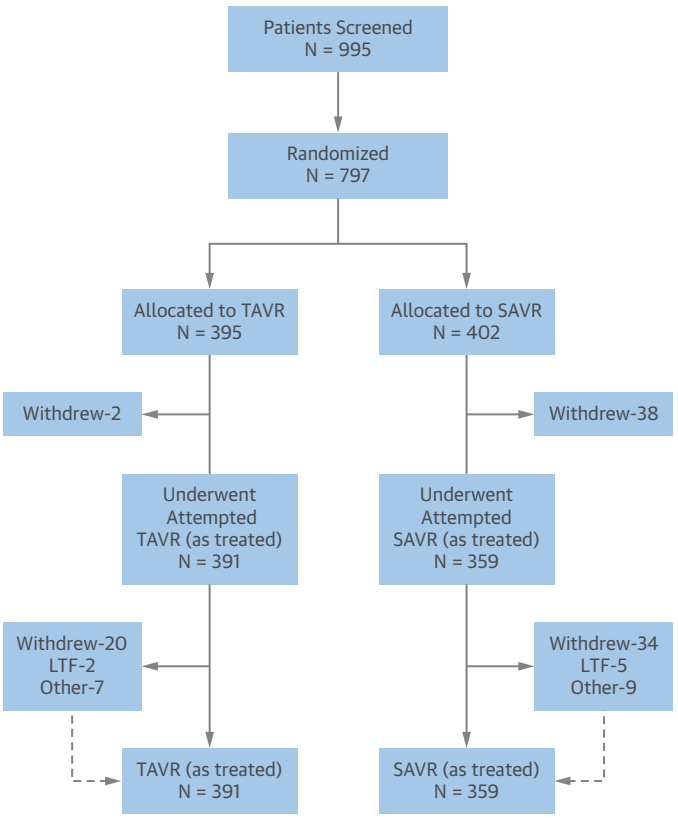
were reviewed by a national screening committee comprising cardiac surgeons and interventional cardiologists. High surgical risk was defined as an estimated 30-day risk of surgical mortality and major morbidity of at least 15%, but <50%. The Society of Thoracic Surgeons Predictor of Mortality (STS PROM) score, frailty, disabilities, and other comorbidities were considered during patient screening.

STUDY DEVICE. Patients randomized to TAVR underwent implantation of the CoreValve System (Medtronic, Dublin, Ireland) comprising a supra-annular porcine pericardial valve sewn within a self-expanding nitinol frame, an 18-F equivalent delivery catheter system, and a compression loading tool. The valve was available in 23-, 26-, 29-, and 31-mm sizes to fit aortic annuli from 18 to 29 mm in diameter (the 31-mm valve was added in the latter half of the trial enrollment period).

PROCEDURES. Study procedures and details of the transcatheter implant procedure have been previously published (3,9). Surgical valve selection was left to the operator's discretion. Echocardiographic data presented are site-reported. All patients with a presumed neurological event were seen by a neurologist, and appropriate imaging was obtained. All neurological events were adjudicated by a neurologist from the clinical events committee. Clinical outcomes and hemodynamic assessments at 5 years were prespecified.

STATISTICAL ANALYSIS. The analysis cohort comprised all patients who underwent an attempted TAVR or SAVR (as-treated). Categorical variables were compared using the Fisher exact test or chi-square test. Continuous variables are presented as mean ± SD and were compared using an independent samples *t*-test. Kaplan-Meier estimates were used to construct the survival graphs based on all available follow-up data for the time-to-event analysis. Adverse event rates are reported as Kaplan-Meier estimates, and differences in rates between the transcatheter and surgical groups were evaluated using the log-rank test. Cox proportional hazards models were used for 5-year mortality univariable and multivariable modeling analyses. Variables selected for inclusion in the univariable models were selected based on clinical relevance. Potential multivariable predictors of mortality were identified from univariable predictors with p value ≤0.05. A stepwise procedure was performed to determine the final model (entry and stay criteria of 0.10). The univariable and multivariable model development was performed separately for overall (TAVR and SAVR), TAVR only, and SAVR only cohorts. For the overall cohort, treatment (TAVR vs. SAVR) was forced into multivariable Cox proportional hazards model. The multivariable model was repeated in each treatment group. All testing used a 2-sided alpha level of 0.05. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, North Carolina).

FIGURE 1 Randomization and Analysis Cohorts



Patient flow chart for the SAVR and TAVR treatment groups. LTF = lost to follow-up; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

RESULTS

PATIENTS. A total of 995 patients were screened for the trial, of whom 795 were enrolled and 750 underwent an attempted implantation (**Figure 1**). Of these, 391 had attempted TAVR, and 359 had attempted SAVR. In the TAVR cohort, 30 patients left the trial, and in the SAVR cohort, 83 left the trial; however, they were still included in the as-treated analysis cohort. The median follow-up was 49.9 (range 0 to 65) months for the TAVR patients and 41.0 (range 0 to 68) months for the SAVR patients. Baseline characteristics are reported in Online Table 1. The mean age and

TABLE 1 Clinical Outcomes After 1 and 5 Years

	1 Year		5 Years		
	TAVR (n = 391)	SAVR (n = 359)	TAVR (n = 391)	SAVR (n = 359)	Log-Rank p Value*
All-cause mortality	55 (14.1)	67 (18.9)	208 (55.3)	184 (55.4)	0.50
Cardiovascular	41 (10.6)	45 (12.9)	134 (39.7)	115 (39.5)	0.80
AV hospitalization	61 (16.5)	45 (13.9)	120 (37.5)	83 (31.5)	0.08
Death or AV hospitalization	101 (25.8)	99 (27.9)	258 (67.7)	212 (62.8)	0.38
MACCE	80 (20.5)	96 (27.0)	229 (60.5)	211 (62.5)	0.19
Stroke	33 (8.7)	42 (12.5)	56 (17.5)	62 (21.0)	0.13
Major	22 (5.8)	23 (6.9)	38 (12.3)	38 (13.2)	0.49
Minor	11 (3.0)	20 (6.0)	21 (6.7)	27 (9.1)	0.14
Transient ischemic attack	6 (1.6)	5 (1.6)	12 (4.1)	13 (6.3)	0.51
All-cause mortality or major stroke	63 (16.1)	79 (22.2)	216 (57.2)	193 (57.4)	0.41
Myocardial infarction	7 (1.9)	5 (1.5)	10 (3.1)	9 (3.3)	0.93
Reintervention	8 (2.2)	0 (0.0)	10 (3.0)	2 (1.1)	0.04
Major bleeding	119 (31.0)	133 (37.4)	132 (35.9)	144 (43.3)	0.05
Major vascular complication	25 (6.4)	7 (2.0)	27 (7.1)	7 (2.0)	0.001
Endocarditis	2 (0.6)	4 (1.3)	5 (1.8)	5 (1.7)	0.78
Valve thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Pacemaker implantation†	86 (22.4)	40 (11.9)	112 (33.0)	55 (19.8)	<0.001
New pacemaker implantation‡	85 (28.8)	36 (13.3)	105 (38.6)	50 (22.3)	<0.001

Values are n (%) where n is the number of patients with an event and Kaplan-Meier estimates as percentage at the specific time point, and do not equal the number of patients with events divided by the total number of patients in each treatment group. *p Value comparing event rates at 5 years in the TAVR and SAVR groups. †Includes patients with a pacemaker at baseline. ‡Excludes patients with a pacemaker at baseline.

AV = aortic valve; MACCE = major adverse cardiovascular and cerebrovascular event; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

STS PROM were 83.2 years and 7.3% (range 1.0% to 21.0%) for TAVR and 83.3 years and 7.5% (range 2.0% to 23.0%) for SAVR, respectively. The groups were well matched by all comorbidities.

SAFETY OUTCOMES. All-cause mortality at 5 years was 55.3% for TAVR and 55.4% for SAVR (p = 0.50) (**Table 1, Central Illustration**). Cardiovascular death rates also did not differ at 5 years, with 39.7% for TAVR and 39.5% for SAVR (p = 0.80) (**Table 1, Figure 2**). The mean days alive and out of the hospital at 5 years was 1,241.4 ± 627.1 days for the TAVR group and 1,109.8 ± 683.3 days for the SAVR group (p = 0.006). There were no statistical differences in all-cause mortality at 5 years between TAVR and SAVR across 9 subgroups; age over 85 years, sex, body mass index, STS PROM score, left ventricular ejection fraction, hypertension, prior coronary artery bypass grafting, peripheral vascular disease, or diabetes mellitus (Online Figure 1). Landmarked analysis of all-cause mortality also showed no difference between TAVR and SAVR out to 5 years (p = 0.64) (Online Figure 2). Of note, the 5-year all-cause Kaplan-Meier mortality rates specifically for iliofemoral access patients were 54.6% for TAVR (n = 324) and 55.1% for SAVR (n = 302); p = 0.57, and the 5-year all-cause Kaplan-Meier mortality rates for non-iliofemoral access patients were 58.6% for TAVR (n = 67) and 56.9% for SAVR (n = 57); p = 0.68. Moreover, there were no differences in all-cause mortality at 5 years when comparing TAVR to SAVR for the intention-to-treat cohort: 54.9% versus 55.8%, respectively; p = 0.41.

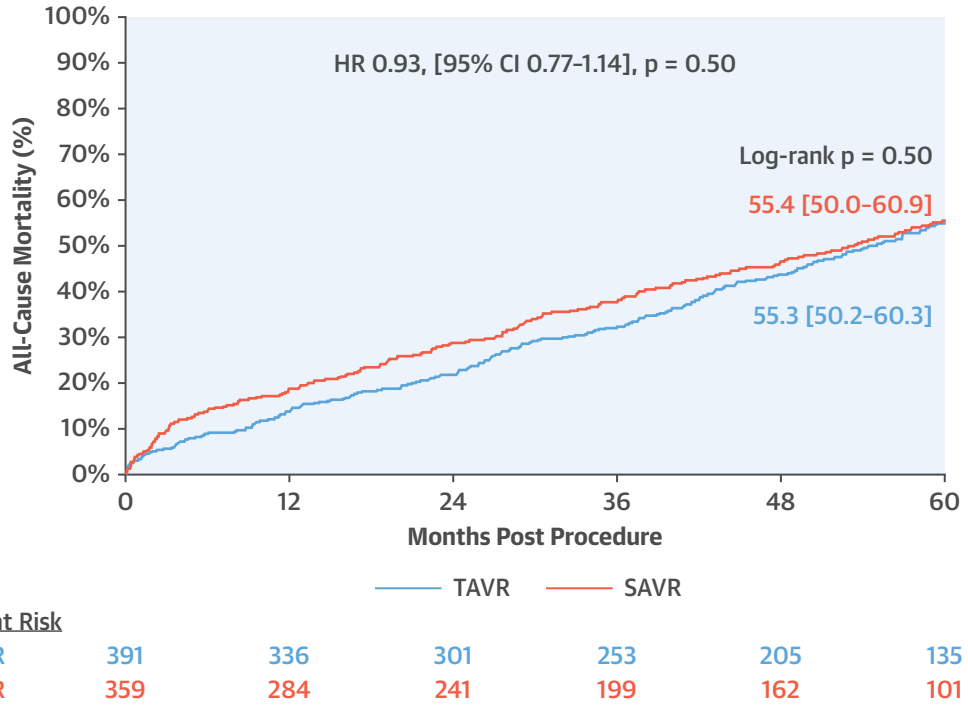
There were no differences between the TAVR and SAVR groups for additional safety outcomes except that more TAVR than SAVR patients underwent reinterventions (3.0% vs. 1.1%; p = 0.04) and had a permanent pacemaker implanted (33.0% vs. 19.8%; p < 0.001) by 5 years post-procedure (**Table 1**). There were no differences in 5-year mortality for the TAVR patients with or without a new permanent pacemaker within 30 days of procedure (46.5% vs. 53.2%; p = 0.37) (Online Figure 3). No clinical valve thrombosis was observed by transthoracic echocardiography in either group.

PREDICTORS OF 5-YEAR MORTALITY. Predictors of all-cause mortality at 5 years for all patients in the study, regardless of treatment, included age over 85 years, an STS PROM score >7%, NYHA functional class III or IV symptoms, home oxygen, malnutrition (albumin <3.3 gm/dl), recent falls, moderate or more mitral valve regurgitation, and post-procedural acute kidney injury (**Table 2**). Age over 85 years, an STS PROM score >7%, baseline moderate or more mitral valve regurgitation, and mild AR at 1 month post-procedure were positive predictors of 5-year mortality in the TAVR group. Predictors of mortality in the SAVR group included home oxygen and post-procedural acute kidney injury.

STROKE. Because more strokes were seen in the TAVR arm of the PARTNER IA trial with retrospective analysis (2), we incorporated a stringent neurological assessment with the National Institutes of Health Stroke Scale at baseline, post-procedure, and at every visit or with every potential neurological event for the CoreValve U.S. Pivotal High Risk Trial. At 5 years, there were no differences in the rate of any stroke for TAVR and SAVR (17.5% vs. 21.0%, respectively; p = 0.13) or major stroke (12.3% vs. 13.2%, respectively; p = 0.49) (**Table 1**). The rate of transient ischemic attacks also did not differ between groups. Similar to the mortality outcomes, the 5-year stroke rates specifically for iliofemoral access patients were 17.3% for TAVR and 18.7% for SAVR; p = 0.53, and the 5-year stroke rates for non-iliofemoral access patients were 18.4% for TAVR and 33.5% for SAVR; p = 0.02.

QUALITY OF LIFE. NYHA symptoms improved similarly in both groups, with a mean of 1.3 classes in both groups (TAVR range −3.0 to 2.0: SAVR range −3.0 to 1.0) at 5 years. The KCCQ overall summary score

CENTRAL ILLUSTRATION **Self-Expanding-TAVR Versus SAVR in High-Risk Patients: All-Cause Mortality to 5 Years**



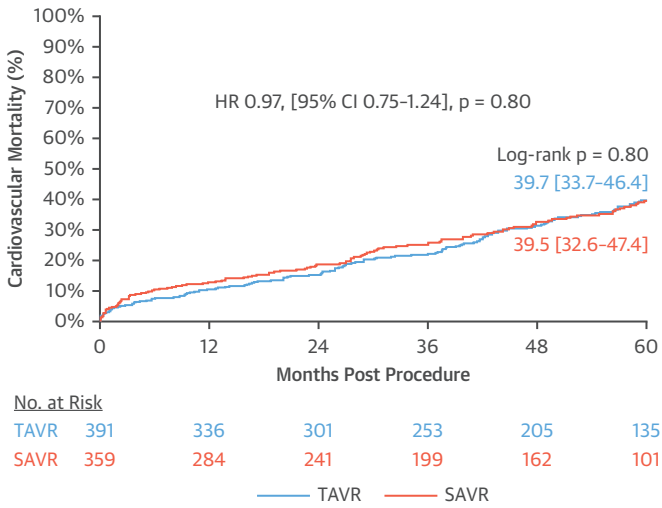
Gleason, T.G. et al. J Am Coll Cardiol. 2018;■(■):■-■.

Kaplan-Meier curves on all-cause mortality estimates to 5 years. CI = confidence interval; HR = hazard ratio; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

improved faster after TAVR at 1 month (Online Figure 4) but was similar between TAVR and SAVR when scored from years 1 to 5 with a slight decrease in both groups as patients reached 5 years (TAVR 66.5 ± 21.3 vs. SAVR 66.0 ± 20.4; p = 0.86). Similar patterns were observed in the physical summary and mental summary scores of the SF-12 Health Survey (Online Figure 4).

HEMODYNAMICS AND SVD. Serial echocardiograms through 5 years showed TAVR to be superior to SAVR for effective orifice area and mean gradient at all time points (**Figure 3**) while being inferior for total AR (**Figure 4**), which was primarily due to PVL. Mild and greater AR at 1 month assessed by the echocardiographic core laboratory was associated with an increased all-cause and cardiovascular mortality at 5 years (**Figure 5A**). Considering the composite of cardiovascular mortality or reintervention (**Figure 5B**), the moderate/severe group had the greatest incidence of reintervention. There were no patients that developed severe AR, and 6 TAVR and no SAVR patients had moderate AR.

FIGURE 2 **Kaplan-Meier Cardiovascular Mortality Estimates to 5 Years**



Cardiovascular mortality to 5 years for patients in the TAVR and SAVR groups. 95% confidence intervals (CI) shown in brackets. HR = hazard ratio; other abbreviations as in **Figure 1**.

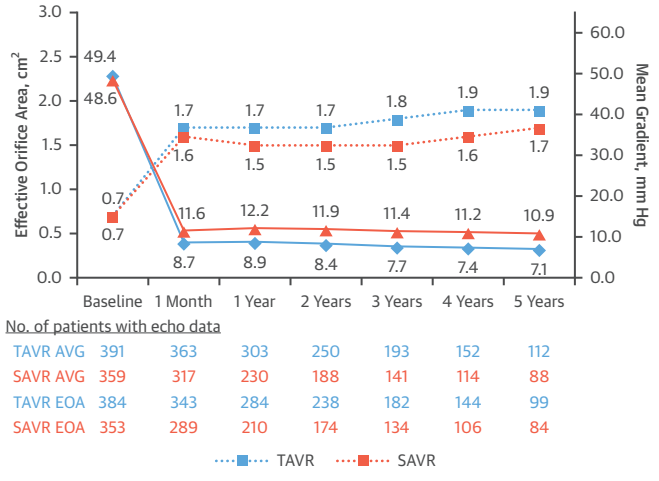
TABLE 2 Multivariable Predictors of 5-Year All-Cause Mortality*

	Hazard Ratio (95% CI)	p Value†
All patients (TAVR and SAVR)		
TAVR vs. SAVR	0.95 (0.77-1.17)	0.621
Age >85 yrs	1.26 (1.01-1.57)	0.044
Body surface area, m^2	0.50 (0.31-0.83)	0.007
STS PROM >7%	1.23 (0.98-1.53)	0.068
NYHA functional class III/IV symptoms	1.36 (0.97-1.90)	0.078
Home oxygen	1.76 (1.30-2.36)	< 0.001
Albumin < 3.3 g/dl	1.46 (1.11-1.92)	0.007
Falls in the past 6 months	1.27 (0.98-1.65)	0.072
Baseline ≥moderate MR	1.45 (1.06-1.99)	0.020
Acute kidney injury‡	1.86 (1.35-2.55)	< 0.001
TAVR patients		
Age >85 yrs	1.49 (1.11-2.01)	0.009
STS PROM >7%	1.36 (1.01-1.83)	0.045
Baseline ≥moderate MR	2.06 (1.33-3.19)	0.001
Mild AR at 1 month‡	1.45 (1.07-1.98)	0.017
Moderate or severe AR at 1 month‡	0.82 (0.47-1.44)	0.487
SAVR patients		
Diabetes mellitus	0.66 (0.49-0.90)	0.009
Home oxygen	1.77 (1.18-2.65)	0.006
Acute kidney injury§	1.78 (1.20-2.65)	0.004

*Excludes patients who died or had follow-up duration ≤30 days post-procedure. †Univariable predictors with a p value ≤0.05 were entered into a Cox proportional hazards model using a stepwise entry and exit criteria of 0.10. ‡Patients with no or trace AR as reference. §Within 7 days.

AR = aortic valve regurgitation; CI = confidence interval; MR = mitral valve regurgitation; NYHA = New York Heart Association functional class; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

FIGURE 3 Forward Flow Hemodynamics Through 5 Years for Patients in the Transcatheter and Surgical Groups



Site-reported aortic valve effective orifice area **(dotted lines)** and mean gradient **(solid lines)** over time for patients in the TAVR **(blue lines)** and SAVR **(orange lines)** groups. Transcatheter valve replacement was associated with significantly larger effective orifice area, and significantly smaller mean gradients at each time point compared with surgery (all $p < 0.01$). AVG = aortic valve gradient; EOA = effective orifice area; other abbreviations as in Figure 1.

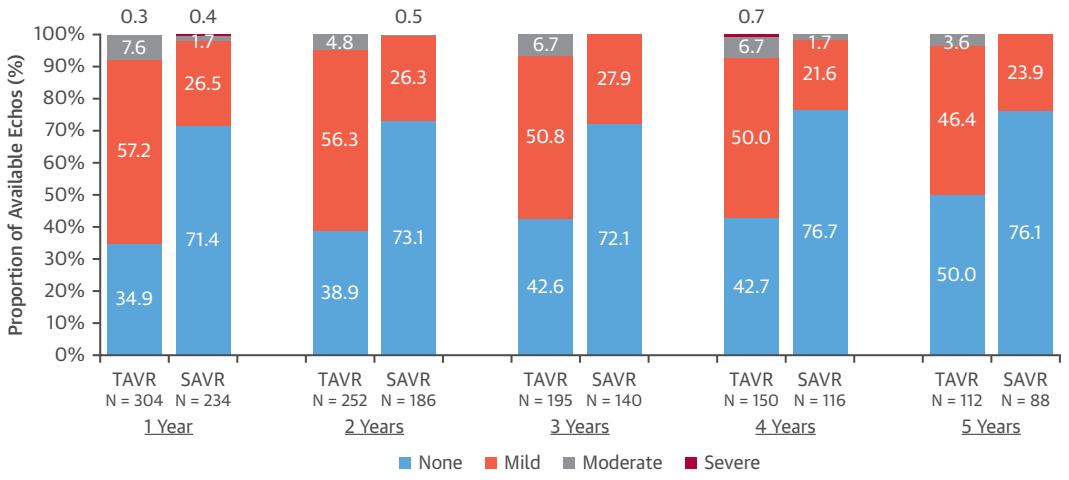
The overall incidence of SVD and components of moderate and severe SVD are show in Table 3. Severe SVD was observed in 3 patients (0.8%) in the TAVR group and 6 patients (1.7%) in the SAVR group ($p = 0.32$). Significantly fewer TAVR patients (9.2%) had moderate SVD compared with 26.6% of SAVR patients ($p < 0.001$). Most of the SAVR patients met the criteria for moderate hemodynamic SVD if they had a mean gradient of ≥20 mm Hg at any time during follow-up.

DISCUSSION

There were several key findings from this final 5-year report in high-risk patients with severe aortic stenosis including: the incidence of all-cause mortality (Central Illustration), cardiovascular mortality, and stroke was similar between the TAVR and SAVR groups; and the presence of severe SVD was low in both treatment groups. With this early-generation self-expanding valve, the presence of mild or more AR in the TAVR groups remained greater than the SAVR group to 5 years. Both treatment groups experienced similar improvements in quality of life scores over time, although the improvements seen in the short term decreased slightly over time as this patient cohort reached 88 years of age.

This is the first randomized trial to our knowledge to report mid-term 5-year hemodynamic outcomes with this self-expanding valve in high-risk patients compared with surgery. Long-term durability has been a major concern for all biological replacement valves. Durability has historically been defined as survival without the need for reoperation (10). However, more recent guidelines suggest that SVD should be defined by clinically determined measures rather than reoperation or echo criteria alone, suggesting the need for reoperation (11). Using the recent definitions by Capodanno et al. (8) from the European cardiovascular community, the incidence of severe SVD was rare and similar between treatment groups. Moderate SVD was more common in the SAVR versus the TAVR patients (26.6% vs. 9.2%; $p < 0.001$), although much of this difference was attributable to higher gradients seen in certain SAVR patients that may not have been indicative of true SVD but of other factors such as the size of the valve implanted and patient-prosthetic mismatch. Because this definition includes gradients measured at any time, a post-procedural gradient of 19 mm Hg (not uncommon following surgical implantation with a 21-mm valve) that is later documented as 20 mm Hg would meet the criteria for moderate SVD. A better definition of moderate SVD may be the combination of an elevated

FIGURE 4 **AR Through 5 Years**



Total aortic regurgitation reported by the investigational sites through 5 years for patients in the TAVR and SAVR groups. AR = aortic regurgitation; other abbreviations as in Figure 1.

gradient over 20 mm Hg *and* a minimum increase in gradient of over 10 mm Hg.

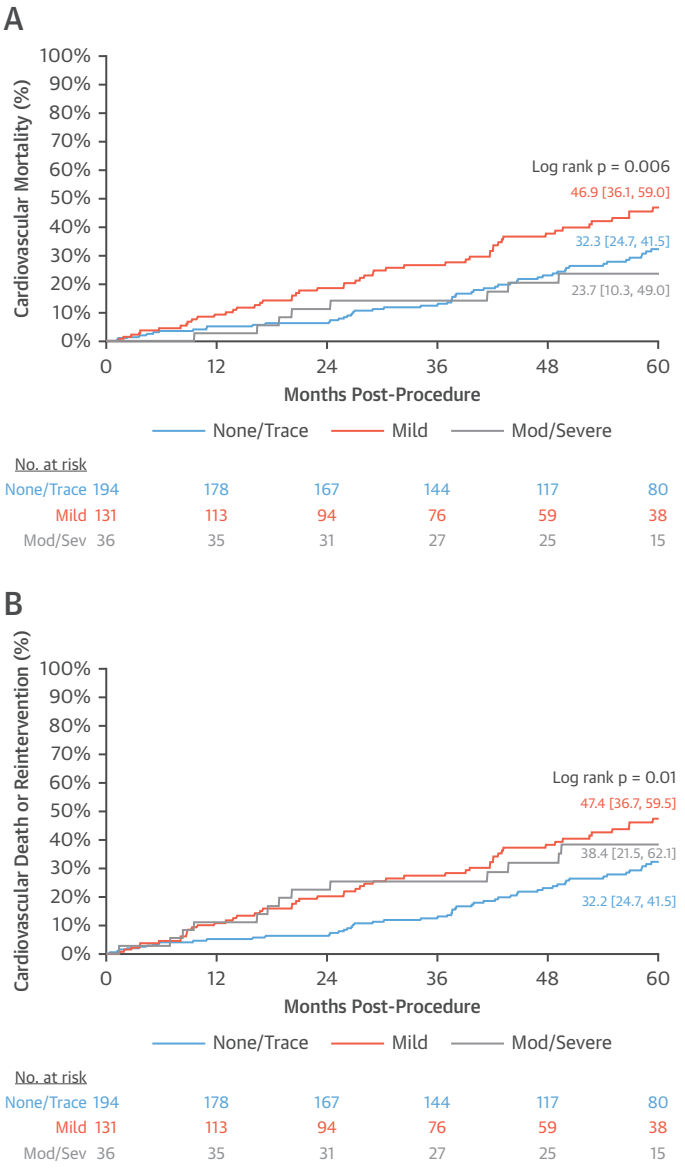
These results are very encouraging because they corroborate the 5-year outcomes of the PARTNER IA trial (1), underscoring the safety and efficacy of TAVR at mid-term follow-up. Early concerns that transcatheter aortic valves would not have the same mid-term durability as surgical bioprostheses has been tempered by these 2 pivotal trials. However, surgical bioprostheses typically do not begin to experience significant SVD until 8 years post-operatively and beyond, and importantly, SVD has been inversely related to age (10,12-14). Thus, with a mean age of 83 years in our study, and considering death as a competing risk, there remain inadequate data available to compare valve deterioration between transcatheter and surgical bioprostheses in the long term. Moreover, the long-term clinical impact of the transcatheter valve stent frames specifically with respect to pannus or pseudointimal scar formation, coronary obstruction, or other potential deleterious effects of the frames themselves remains unknown. This residual unknown may be particularly relevant to low-risk, intermediate-risk, and some high-risk patients that have long-term life expectancy once their AS is corrected. As longer-term data accrue from the ongoing intermediate- and low-risk randomized trials, we will gain a better understanding of the relative roles of TAVR and SAVR with respect to long-term durability and clinical impact.

The trial was conducted at U.S. sites that were all relatively new to TAVR while requiring at least 5 years of SAVR experience from each surgeon. The transcatheter heart valve used was also a first-generation device. Second- and third-generation devices of this self-expanding valve are now available and in routine use (15-18).

The 1- and 2-year outcome reports of the CoreValve US Pivotal High Risk Trial revealed a superior all-cause mortality rate with TAVR as compared with SAVR (3,4). Analysis of the timing and causes of death in this trial revealed that TAVR survival was only superior during the 1- to 4-month recovery period largely influenced by the inability of this high-risk group to recover from the physiological insult of surgery with SAVR (19). By 4 months, when the patient had recovered from their surgery, the instantaneous hazard of death was similar between TAVR and SAVR. Once this point of recovery is reached in an AS patient, longer-term survival should be affected largely by how well the AS was corrected and the patient's comorbidities. Both TAVR and SAVR relieve AS very well, and if the intrinsic risk levels are well matched, as would be expected in a randomized trial, then longer-term survival should be similar in the absence of other factors impacting mortality unless the stent frames of transcatheter valves have a long-term impact that is not yet realized or appreciated.

Clinical stroke adjudicated retrospectively was more common in the TAVR arm of the PARTNER IA

FIGURE 5 Cardiovascular Mortality Rates From 30 Days to 5 Years in TAVR Patients Based on Severity of AR at 1 Month Post-Procedure



(A) Kaplan-Meier estimates of cardiovascular mortality and **(B)** cardiovascular mortality or intervention (time to first event) to 5 years for patients in the transcatheter group based on echocardiographic core laboratory assessment of total aortic regurgitation at 1 month post-procedure. Excludes patients who died before 30 days or with follow-up <30 days. Differences in time-to-event distributions were evaluated using the log-rank test. Abbreviations as in Figures 1 and 4. Values are HR [95% CI].

trial (2), and at the time, this appropriately raised awareness of the need for better neurological assessments with both TAVR and SAVR. Previous studies have shown that stroke tends to be systematically underreported in the valve replacement literature as most distinctly demonstrated by the DENOVO (Determining Neurologic Outcomes from Valve Operations) trial (20). To acquire better neurological outcomes data, the CoreValve High Risk Trial relied on well-defined prospective neurological evaluations including National Institutes of Health Stroke Scale assessments at baseline, post-procedure, at every follow-up visit, and with any new neurological event. With use of prospective neurologist adjudication, neurological events including all stroke, major stroke, minor stroke and transient ischemic attacks were similar between TAVR and SAVR all the way to the 5-year mark (Table 1).

The incidence of clinically significant (mild or more) AR was higher in TAVR than SAVR in this trial, consistent with rates seen in other randomized trials (2,3,21,22). Cardiovascular mortality was higher for patients with mild AR at 1 month but, surprisingly, not for none/trace or moderate/severe (Figure 5A). The lack of apparent impact on mortality for moderate AR in this current trial may be a result of the low incidence of moderate AR seen and thus a consequence of a type II statistical error. The composite of cardiovascular death or reintervention showed that the patients with moderate/severe AR early on, had a higher incidence of interventions, while there was negligible effect on the other AR groups by adding the intervention procedures (Figure 5B). More TAVR than SAVR patients were implanted with a permanent pacemaker over the 5 years (33.0% vs. 19.8%), yet this did not appear to increase mortality at least out to 5 years.

Since the completion of the trial both second-generation (the Evolut R valve that is repositionable) and third-generation (the Evolut PRO valve [Medtronic, Minneapolis, Minnesota] that is repositionable and has an external wrap at the inflow to help mitigate PVL) self-expanding valves have been released for commercial use. In a relatively small Evolut PRO trial, the incidence of milder PVL at 30 days was 27.6%, with the remaining patients having trace to none (15). The pacemaker rate in this trial was also lower at 11.8% (15). How the results of the trial would improve if executed in a similar group of patients treated in the current era with these newer-generation devices is difficult to predict. Although, in addition to technological advances, TAVR operator experience in patient selection, planning, and implantation has also markedly improved since the patient enrollment period for this trial.

STUDY LIMITATIONS. The data and analysis of this study can only be applied to similar patients who

TABLE 3 SVD

	TAVR (n = 390)	SAVR (n = 354)	p Value
SVD	9.5 (37/390)	26.6 (94/354)	<0.001
Moderate hemodynamic SVD	9.2 (36/390)	26.6 (94/354)	<0.001
Mean gradient at any time of ≥20 mm Hg, but <40 mm Hg	5.4 (21/390)	25.7 (91/354)	<0.001
Change in mean gradient from discharge/1 month of ≥10, but < 20, mm Hg	1.5 (6/390)	5.4 (19/354)	0.004
Moderate Central AR (new from discharge)	3.3 (13/390)	0.8 (3/354)	0.022
Severe hemodynamic SVD	0.8 (3/390)	1.7 (6/354)	0.322
Mean gradient ≥40 mm Hg	0.3 (1/390)	1.1 (4/354)	0.197
Change in mean gradient from discharge/1 month of ≥20 mm Hg	0.5 (2/390)	0.8 (3/354)	0.673
Severe central AR (new from discharge)	0.3 (1/390)	0.0 (0/354)	>0.999

Values are % (n/N).
SVD = structural valve deterioration; other abbreviations as in Tables 1 and 2.

would meet the eligibility criteria of this randomized trial. Because event rates were relatively low across all outcome measures studied, the possibility of type I and type II statistical errors exists. Moreover, the transcatheter self-expanding bioprosthesis implanted in this trial is not representative of current TAVR technologies given the technological advances that have occurred to date.

CONCLUSIONS

The 5-year outcomes of the trial show a similar safety profile, functional recovery, and freedom from severe SVD for both TAVR and SAVR, consistent with earlier-term reports. These outcomes support TAVR as a reasonable alternative to SAVR in the high-risk population and its current Class I indication.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: TAVR with the self-expanding valve in high-risk patients at 5 years has a similar survival and safety profile as SAVR. Functional outcomes are good in both groups. Significant SVD was very unusual in both groups. TAVR is a reasonable alternative to SAVR in the elderly high-risk group.

TRANSLATIONAL OUTLOOK: Long-term data regarding structural valve deterioration and the impact of stent frames of transcatheter aortic valves are still necessary to establish TAVR's utility and appropriateness in patients with extended life expectancy.

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

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