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2-Year Outcomes After Iliofemoral Self-Expanding Transcatheter Aortic Valve Replacement in Patients With Severe Aortic Stenosis Deemed Extreme Risk for Surgery

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ABSTRACT

BACKGROUND We reported favorable 1-year outcomes in patients unsuitable for surgery who underwent self-expanding transcatheter aortic valve replacement (TAVR) compared with an objective performance goal. Longer-term outcomes in these patients are not known.

OBJECTIVES This study sought to evaluate the 2-year safety and efficacy in patients with severe aortic stenosis (AS) at extreme risk of surgery treated with self-expanding TAVR.

METHODS We performed a prospective, multicenter, controlled, nonrandomized investigation of self-expanding TAVR in patients with severe AS and prohibitive surgical risk. We report the 2-year clinical outcomes in these patients.

RESULTS A total of 489 extreme-risk patients were treated transfemorally with a self-expanding aortic bioprosthesis at 41 centers. The rate of all-cause mortality or major stroke was 38.0% at 2 years (all-cause mortality, 36.5%; major stroke, 5.1%). The rates of all-cause mortality, cardiovascular mortality, and major stroke were 36.6%, 26.2%, and 5.1%, respectively, at 2 years. Between 1 and 2 years, the incremental all-cause mortality, cardiovascular mortality, and major stroke rates were 12.3%, 7.9%, and 0.8%, respectively. Multivariable predictors of all-cause mortality at 2 years included the presence of coronary artery disease and admission from an assisted living center. A Society of Thoracic Surgeons score >15% was also predictive of 2-year all-cause mortality. At 2 years, 94% of patients had New York Heart Association functional class I or II symptoms. The frequency of moderate or severe paravalvular regurgitation (4.3% at 1 year; 4.4% at 2 years) was unchanged between the first and second year.

CONCLUSIONS Patients with severe AS at extreme surgical risk treated with self-expanding TAVR continued to show good clinical outcomes and hemodynamic valve performance at 2 years. The presence of comorbid conditions rather than valve performance affected 2-year outcomes in these patients. (Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement; NCT01240902) (J Am Coll Cardiol 2015;66:1327–34) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

NYHA = New York Heart Association

STS-PROM = Society for Thoracic Surgery Predicted Risk of Mortality

TAVR = transcatheter aortic valve replacement

Patients with severe symptomatic aortic stenosis (AS) deemed unsuitable for surgery have an estimated 50.0% mortality at 1 year without valve replacement (1). Transcatheter aortic valve replacement (TAVR) using balloon-expandable (1) and self-expanding (2) bioprostheses has become standard of care in these patients, who often have significant comorbidities, frailties, and disabilities that affect their long-term prognosis (3). Late outcomes after TAVR have been reported (4-7), but there is limited information about late survival in patients deemed to be at extreme risk of surgery (8,9).

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The CoreValve US Extreme Risk Pivotal Trial evaluated patients deemed unsuitable for surgery by 2 cardiac surgeons and 1 interventional cardiologist (2). A total of 489 patients underwent implantation with self-expanding TAVR by means of an iliofemoral access approach (2). Despite significant concomitant morbidities, the rate of 1-year all-cause mortality and major stroke at 1 year was superior to a rigorously defined objective performance goal (2). The self-expanding aortic bioprosthesis provided sustained improvement in the aortic valve effective orifice area, a reduction in the aortic valve gradient, and an overall improvement in New York Heart Association (NYHA) functional class (2). Our objective in this study was to evaluate the 2-year clinical outcomes in these patients.

TABLE 1 Baseline Clinical Characteristics and Comorbidities (N = 489)

Age, yrs	83.2 ± 8.7
Men, %	47.9 (234/489)
Society of Thoracic Surgeons Predicted Risk of Mortality, %	10.3 ± 5.5
<10	55.6 (272/489)
10–15	27.2 (133/489)
>15	17.2 (84/489)
Logistic euroSCORE, %	22.6 ± 17.1
New York Heart Association functional class III/IV	91.8 (449/489)
Diabetes mellitus	41.5 (203/489)
Insulin controlled	18.4 (90/489)
Cardiac history	
Previous stroke	13.7 (67/488)
Coronary artery disease	81.8 (400/489)
Previous coronary artery bypass graft	39.5 (193/489)
Previous percutaneous coronary intervention	37.0 (181/489)
Previous balloon artic valvuloplasty	20.4 (100/489)
Prohibitive anatomy	
Severe aortic calcification	17.2 (84/488)
Hostile mediastinum	11.9 (58/488)
Comorbidities	
Severe chronic lung disease	23.5 (115/489)
Home oxygen	29.9 (146/489)
Charlson Comorbidity Index	5.3 ± 2.3
Frailty	
Anemia with previous transfusion	22.8 (108/473)
Albumin <3.3 g/dl	18.2 (88/484)
5-m gait speed >6 s	84.2 (283/336)
Disabilities	
Assisted living	27.6 (135/489)
≥2 Katz ADL deficits	20.9 (102/489)
Wheelchair bound	16.6 (81/489)

Values are mean ± SD or frequency, % (n/N).
ADL = activities of daily living; euroSCORE = European System for Cardiac Operative Risk Evaluation.

METHODS

PATIENT ENROLLMENT AND STUDY DESIGN. Detailed patient enrollment criteria, inclusion and exclusion criteria, and study methods have been reported elsewhere (2). In brief, patients with severe symptomatic AS defined as having at least NYHA functional class II symptoms, an aortic valve area ≤0.8 cm^2 (or aortic valve index ≤0.5 cm^2/m^2), and a mean aortic valve gradient >40 mm Hg or a peak aortic

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valve velocity >4.0 m/s were eligible. Patients were considered to be at extreme risk if they were determined to have a 50.0% or greater risk for mortality or irreversible morbidity at 30 days with surgical replacement (2). Baseline assessment included calculation of risk using the Society of Thoracic Surgery Predictors of Mortality (STS-PROM) (10) and logistic euroSCORE (European System for Cardiac Operative Risk Evaluation) (11), the Charlson Comorbidity Index (12), and assessments of frailty using 5-m gait speed (13) and disability using the Katz Activities of Daily Living (14).

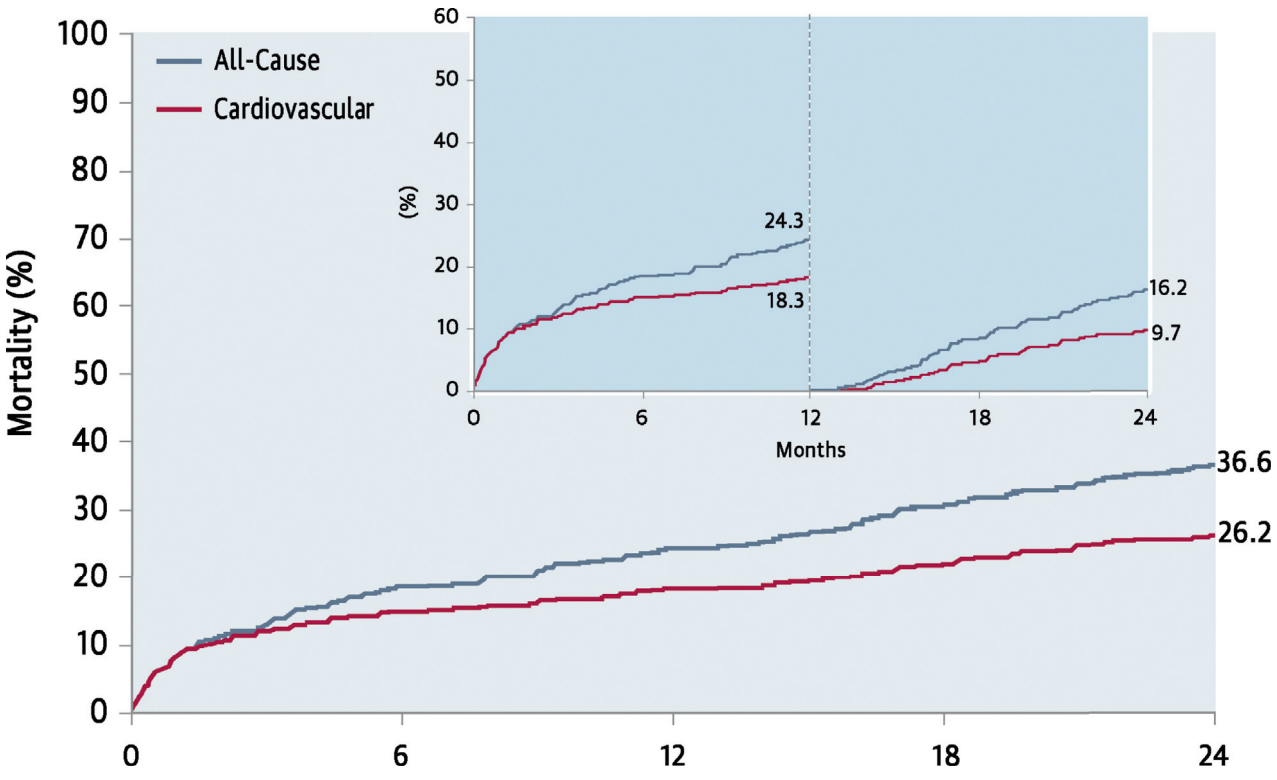
The CoreValve US Extreme Risk Pivotal Trial was a prospective, multicenter, controlled, nonrandomized, single-arm clinical study performed at 41 clinical sites in the United States (2). The responsible institutional review boards approved the study protocol, and written informed consent was obtained from all patients. The sponsor (Medtronic, Minneapolis,

TABLE 2 Clinical Outcomes at 1 and 2 Years After Self-Expanding TAVR

	1 Year	2 Years
Death from any cause or major stroke	127 (26.0)	185 (38.0)
Death		
Any cause	119 (24.3)	178 (36.6)
Cardiovascular	88 (18.3)	122 (26.2)
Stroke	31 (7.0)	37 (8.6)
Major	19 (4.3)	22 (5.1)
Minor	14 (3.2)	17 (4.1)
Myocardial infarction	9 (2.0)	12 (2.8)
Reintervention	8 (1.8)	8 (1.8)
Life-threatening or disabling bleeding	85 (18.0)	96 (21.1)
Major vascular complications	41 (8.4)	41 (8.4)
Valve thrombosis	0.0	0.0
Endocarditis	5 (1.3)	6 (1.6)
Device embolization/migration	1 (0.2)	1 (0.2)
Permanent pacemaker	124 (26.4)	132 (28.8)

Values are number of patients with event (Kaplan-Meier estimated rates).
TAVR = transcatheter aortic valve replacement.

CENTRAL ILLUSTRATION Long-Term Outcomes After TAVR: Kaplan-Meier Estimates of All-Cause and Cardiovascular Mortality Through 2 Years



Yakubov, S.J. et al. J Am Coll Cardiol. 2015; 66(12):1327–34.

(Inset) Landmark survival analysis of all-cause and cardiovascular mortality for the first year after TAVR for all patients **(left)** and during the second year after TAVR for patients alive at 1 year **(right)**. TAVR = transcatheter aortic valve replacement.

Minnesota), funded the study and, along with the study Steering Committee, designed the study. The study sponsor was responsible for selection of the clinical sites, monitoring of the data, and management of the case report forms and statistical analyses. An independent Clinical Events Committee adjudicated all major adverse clinical events. The primary author (S.J.Y.) and Co-Principal Investigators of the CoreValve US Pivotal Trials (J.J.P. and D.H.A.) drafted the initial manuscript. All authors contributed to this manuscript and made the decision to submit it for publication.

STUDY ENDPOINTS. The attempted iliofemoral implant population was the primary analysis group (2). All-cause mortality or stroke was assessed at 2 years. Major and minor strokes were defined using Valve Academic Research Consortium 1 criteria (15). Valve Academic Research Consortium 1 criteria also were used to define major adverse cardiovascular and cerebral events that comprised all-cause death, myocardial infarction, all stroke, and reintervention to alter, adjust, or replace a previously implanted valve (15). Symptom status at 2 years was assessed using the NYHA functional classification system.

ECHOCARDIOGRAPHIC ANALYSIS. Echocardiograms were collected at 1 and 2 years and were interpreted by a central laboratory (Mayo Echocardiography Core Laboratory, Rochester, Minnesota). Prosthetic valve dysfunction and periprocedural aortic regurgitation were determined using Valve Academic Research Consortium 1 criteria (15). Aortic valve orifice area and mean gradient were compared at 1 and 2 years.

STATISTICAL ANALYSIS. Categorical variables were compared using the Fisher exact test. Continuous variables were presented as mean ± SD and compared with the Student *t* test. The Kaplan-Meier estimate and its 95% confidence interval were summarized for each subgroup. The difference between subgroups was compared using Cox regression with subgroup as a factor and the time to event endpoint as the outcome. All testing used a 2-sided alpha level of 0.05. Multivariable predictors of 2-year all-cause mortality were identified from univariable predictors with $p < 0.05$. Stepwise multivariable analyses were performed. The significance-level thresholds for entry and exit of independent variables were set at 0.10. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

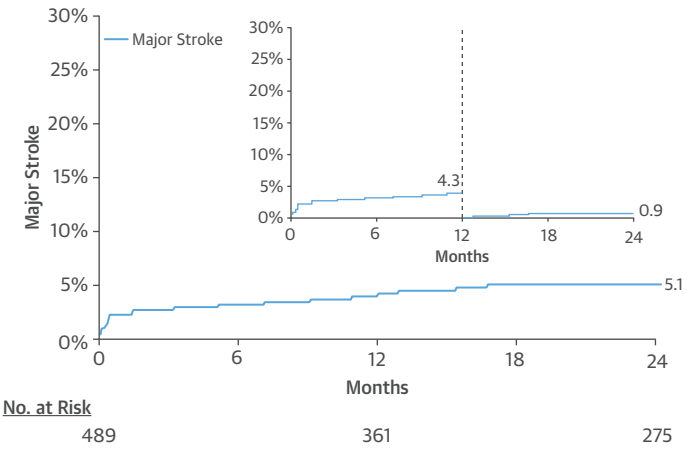
RESULTS

PATIENT FLOW AND DEMOGRAPHICS. A total of 489 patients underwent attempted iliofemoral self-expanding TAVR at 41 U.S. centers between February 2011 and August 2012; 486 patients were implanted with a self-expanding bioprosthesis (2). Between 1 and 2 years, 58 patients died, and 2 patients withdrew from the study. Two-year follow-up was available for 289 of 307 patients (94.1%).

Clinical characteristics for the attempted implant population are shown in Table 1. The mean age was 83.2 ± 8.7 years; 47.9% were men; 81.8% had coronary artery disease, and 27.6% were in an assisted living facility. The mean STS-PROM was 10.3% ± 5.5% and >15% in 17.2% of patients. Nearly 92% of patients experienced NYHA functional class III or IV symptoms.

CLINICAL OUTCOMES. Two-year clinical outcomes are shown in Table 2. The Kaplan-Meier rate of 2-year all-cause mortality or major stroke in the attempted iliofemoral implant population was 38.0% with a 2-sided upper 95% confidence interval of 42.6%. Two-year Kaplan-Meier rates were 36.6% for all-cause mortality and 26.2% for cardiovascular mortality (Central Illustration); the incremental rates between year 1 and year 2 were 12.3% for all-cause mortality and 7.9% for cardiovascular mortality. Causes of death during year 2 are listed in the Online Table 1. The rate of major stroke at 2 years was 5.1% (Figure 1), with a difference in the rates at 1 and 2 years of 0.8%. Univariable predictors for 2-year all-cause mortality are shown in Table 3 (Figures 2A to 2C). Multivariable predictors of all-cause mortality at 2 years included the presence of coronary artery disease ($p = 0.002$), and admission from an assisted living center

FIGURE 1 Kaplan-Meier Estimates of Major Stroke Through 2 Years



(Inset) Landmark analysis for the first year after TAVR for all patients **(left)** and during the second year after TAVR for patients alive at 1 year **(right)**. TAVR = transcatheter aortic valve replacement.

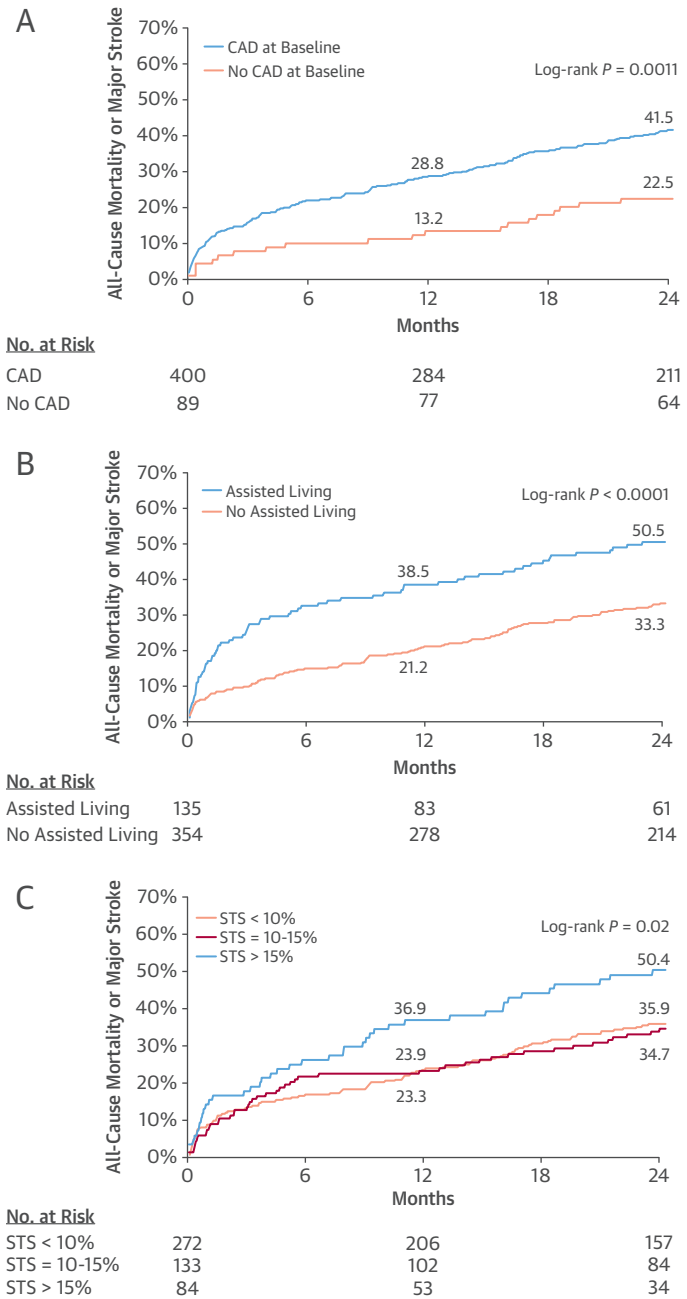
TABLE 3 All-Cause Mortality or Major Stroke for Select Subgroups

	No. of Patients	All-Cause Mortality or Major Stroke	p Value*
Sex			0.16
Male	255	35.1 (29.2-40.9)	
Female	234	41.2 (34.9-47.6)	
Age, yrs			0.41
≤85	263	36.7 (30.9-42.5)	
>85	226	39.6 (33.2-46.0)	
New York Heart Association functional class			
II	40	30.0 (15.8-44.2)	
III	313	38.3 (32.9-43.7)	0.35
IV	136	39.8 (31.6-48.1)	0.31
Left ventricular ejection fraction, %			0.09
≥40	404	36.4 (31.7-41.1)	
<40	83	45.8 (35.1-56.5)	
STS score, %			
<10	272	35.9 (30.1-41.6)	
10-15	133	34.7 (26.6-42.8)	0.84
>15	84	50.4 (39.7-61.2)	0.01
Hypertension			0.25
Yes	441	39.0 (34.4-43.6)	
No	48	29.2 (16.3-42.0)	
Diabetes			0.41
Yes	203	40.0 (33.3-46.8)	
No	286	36.6 (31.0-42.3)	
Chronic lung disease/COPD			0.36
Yes	288	40.1 (34.4-45.8)	
No	201	35.0 (28.4-41.6)	
Peripheral vascular disease			0.17
Yes	171	41.7 (34.3-49.1)	
No	315	35.8 (30.4-41.1)	
Previous stroke			0.57
Yes	67	40.3 (28.6-52.0)	
No	421	37.8 (33.1-42.4)	
Previous myocardial infarction			0.07
Yes	151	43.8 (35.8-51.7)	
No	338	35.4 (30.3-40.6)	
Coronary artery disease			0.0015
Yes	400	41.5 (36.7-46.4)	
No	89	22.5 (13.8-31.1)	
Assisted living			<0.0001
Yes	135	50.5 (42.1-59.0)	
No	315	33.3 (28.3-38.2)	

Values are n or Kaplan-Meier rates (95% confidence interval). *Proportional hazard models.

COPD = chronic obstructive pulmonary disease; STS = Society of Thoracic Surgeons.

FIGURE 2 Kaplan-Meier 2-Year All-Cause Mortality or Major Stroke Estimates for Select Subgroups

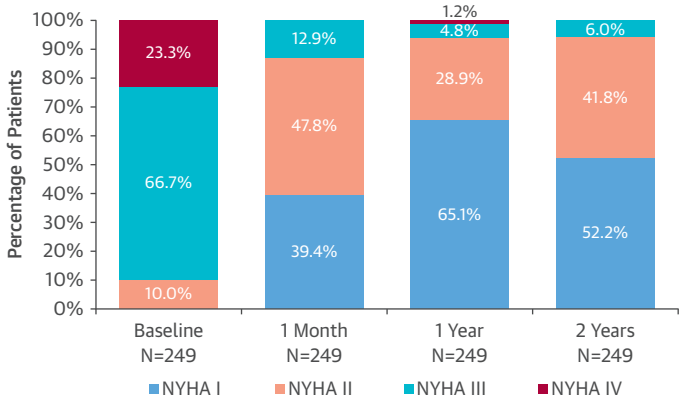


All-cause mortality to 2 years by **(A)** the presence of CAD; **(B)** residing in an assisted living facility before undergoing TAVR; and **(C)** by STS risk severity. CAD = coronary artery disease; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

(p = 0.0001). An STS-PROM score >15% was also predictive of 2-year all-cause mortality (p = 0.07). Coronary artery disease was defined as the presence of at least 1-vessel disease or having previous coronary artery bypass grafting or a previous percutaneous coronary intervention.

Improvement in symptom status was still present at 2 years after self-expanding TAVR. Compared with baseline symptoms, 92.0% of patients improved at 2 years by at least 1 NYHA functional class, and 58.0%

FIGURE 3 NYHA Functional Classification Through 2 Years

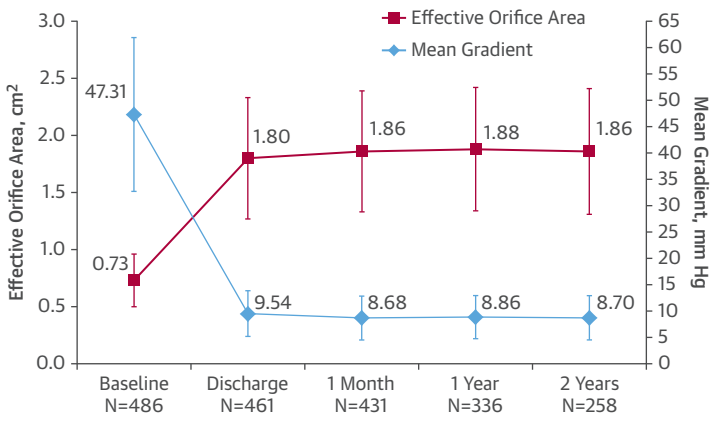


Symptom status for 249 patients with matched datasets at all time points are presented. NYHA = New York Heart Association.

improved by at least 2 classes (Figure 3). An additional 8 patients (2.4%) required a permanent pacemaker between the first and second year after TAVR (Table 2). There was no effect on 2-year survival for patients with or without a pacemaker (38.5% vs. 35.0%; log-rank p = 0.55).

ECHOCARDIOGRAPHIC FINDINGS. Aortic valve orifice area (1.88 cm^2 at 1 year and 1.86 cm^2 at 2 years; p = 0.43) and mean gradient (8.86 mm Hg at 1 year and 8.70 mm Hg at 2 years; p = 0.13) were unchanged at 2 years (Figure 4). The rates of moderate paravalvular aortic regurgitation were similar at 1 and 2 years (Figure 5).

FIGURE 4 Valve Hemodynamics Over Time



Mean aortic valve gradient **(blue)** and effective orifice area **(red)** remain consistent through 2 years. **Error bars** represent SDs.

DISCUSSION

Our study shows that the good survival and low stroke rates at 1 year associated with the self-expanding TAVR in patients deemed unsuitable for surgery were sustained 2 years after the procedure (Central Illustration, Figure 1). Our study also showed that the improvement in aortic valve effective orifice area and reduction in the aortic valve gradient was maintained and that improvement in functional class persisted in patients undergoing self-expanding TAVR. We also found that the degree of paravalvular regurgitation remained unchanged over the second year after the procedure. Longer-term mortality was most influenced by the presence of coronary artery disease and disability requiring assisted living.

MORTALITY AND MAJOR STROKE. Left untreated in patients deemed unsuitable for surgery, severe AS is associated with an all-cause mortality rate of 50.0% at 1 year (1) and 68.0% at 2 years (8). Both balloon-expandable (1) and self-expanding bioprostheses (2) improve survival in these patients. We previously reported a rate of 1-year all-cause mortality and major stroke of 26.0% (95% upper confidence bound: 29.9%) in extreme-risk patients undergoing self-expanding TAVR, which was significantly lower than an objective performance goal of patients with medical therapy alone (43.0%; p < 0.0001) (2). We now report an increase in all-cause mortality from 24.3% at 1 year to 36.6% at 2 years with an incremental increase in all-cause mortality in the second year of 12.3%, similar to the second-year mortality rate in the PARTNER B (Placement of Aortic Transcatheter Valve Trial B) of 18.2% (6). Late deaths in the PARTNER B were attributable to extensive comorbidities, as reflected in a worsened outcome in patients with an STS-PROM >15.0% (8). Our study also found a relationship between STS-PROM >15% and late mortality, and we identified that severe disability, as assessed by admission from an assisted living facility also worsened prognosis with a untoward 2-year mortality rate (50.5% vs. 33.3% in patients admitted from home for TAVR: p < 0.001).

Strokes occur in approximately 3.0% to 4.0% of patients after TAVR (16). With careful neurological examination before and after TAVR, we reported low major stroke rates at 30 days (2.3%) and 1 year (4.3%) (2). The current study also found a low (1.6%) stroke rate in the second year after TAVR, similar to the 2.6% increase in stroke in the second year in PARTNER B (6). Although we did not characterize the type of stroke in our study, hemorrhagic strokes occurred most often after 30 days in the PARTNER B (8). Due to

the occasional occurrence of atrial fibrillation after TAVR and the higher risk of bleeding complications in the elderly population, a careful balance is needed to optimize anticoagulation in this population of patients.

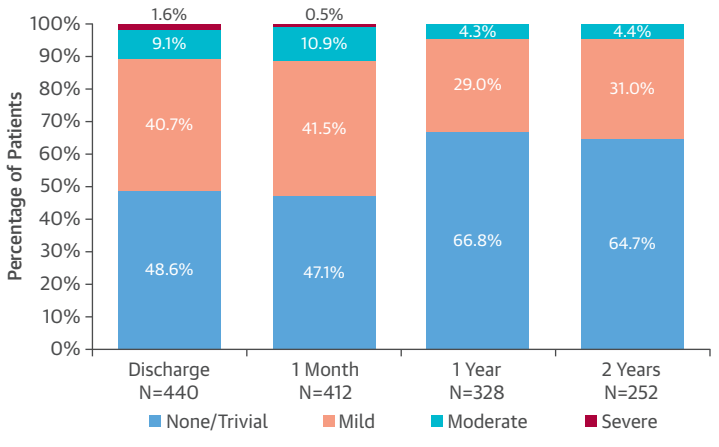
We observed a durable improvement in symptom status associated with self-expanding TAVR in our patients, with 94.0% of patients reporting NYHA functional class I or II symptoms at 2 years. This symptomatic improvement at 2 years in inoperable patients treated with TAVR was also found in the PARTNER B with 83.1% of patients having NYHA functional class I or II symptoms (8).

PARAVALVULAR AORTIC REGURGITATION. Significant residual paravalvular regurgitation is an important prognostic finding after TAVR (17,18). Predictors of paravalvular regurgitation include implantation depth, aortic valve area (17), annular size (17–19), presence of severe calcification (17,20,21), and the use of computed tomography imaging to guide valve sizing (22,23). We previously reported paired analyses that showed a reduction in the frequency of moderate or severe paravalvular regurgitation during the first year after self-expanding TAVR (from 10.7% at discharge to 4.2% at 1 year; p = 0.004) (2). We hypothesized that the mechanism of this improvement resulted from annular remodeling due to appropriate valve sizing on the basis of multidetector computed tomography imaging (19,24). In the current report, we found that the frequency of moderate paravalvular regurgitation remained stable from 1 to 2 years (4.3% to 4.4%, respectively) (**Figure 5**). Longer-term studies in a larger number of patients are needed to understand the complex relationship between moderate paravalvular regurgitation and late mortality.

HEMODYNAMIC FINDINGS. We found no evidence of valve degeneration in the second year after self-expanding TAVR in our study, and there were no cases of valve thrombosis. There was no significant change in the aortic valve effective orifice area or increase in the aortic valve gradients in the second year after self-expanding TAVR. This is similar to hemodynamic reports by others (4,8). Although the 2-year timeframe is short for the identification of structural deterioration of the self-expanding bioprosthesis, it is reassuring that there is no evidence of early failure in this population of patients.

STUDY LIMITATIONS. We did not pre-specify an objective performance goal for the composite of all-cause mortality or major stroke in our study beyond 1 year, and there is no active control group for our extreme-risk patients. Our predictor model for later term mortality was not pre-specified, and identified predictors should be considered exploratory for larger analyses. The presence of coronary artery disease was based on a simple definition and did not include detailed ischemia scoring or specific vessel stenosis.

FIGURE 5 Degree of Paravalvular Regurgitation



The 2-year follow-up of paravalvular regurgitation in surviving patients.

CONCLUSIONS

In patients with AS at extreme risk with surgical aortic valve replacement, iliofemoral placement of a self-expanding transcatheter bioprosthesis was shown to safe and effective through 2 years. Longer-term mortality was most influenced by the presence of coronary artery disease and disability. Hemodynamic improvements in aortic valve area and mean gradients were maintained at 2 years, and the rates of moderate or severe paravalvular regurgitation remained unchanged over the second year after the procedure. We conclude that self-expanding TAVR is beneficial in patients with AS without surgical options.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with severe AS facing a high risk of death or major complications with surgical valve replacement who undergo TAVR with self-expanding prostheses exhibit sustained improvement in valve function and clinical outcomes after 2 years.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The main determinants of clinical outcomes during the first 2 years after TAVR in patients with severe, symptomatic AS at high risk of early operative mortality are comorbid medical conditions.

TRANSLATIONAL OUTLOOK: More work is needed to define the specific diseases, conditions, and other factors contributing to frailty and disability as they relate to long-term outcomes after TAVR. These efforts could lead to the development and validation of a clinical risk prediction instrument to guide selection of patients for this procedure.

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KEY WORDS extreme risk, self-expanding, severe aortic stenosis, transcatheter aortic valve replacement

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