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Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery

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Objectives This study sought to evaluate the safety and efficacy of the CoreValve transcatheter heart valve (THV) for the treatment of severe aortic stenosis in patients at extreme risk for surgery.

Background Untreated severe aortic stenosis is a progressive disease with a poor prognosis. Transcatheter aortic valve replacement (TAVR) with a self-expanding bioprosthesis is a potentially effective therapy.

Methods We performed a prospective, multicenter, nonrandomized investigation evaluating the safety and efficacy of self-expanding TAVR in patients with symptomatic severe aortic stenosis with prohibitive risks for surgery. The primary endpoint was a composite of all-cause mortality or major stroke at 12 months, which was compared with a pre-specified objective performance goal (OPG).

Results A total of 41 sites in the United States recruited 506 patients, of whom 489 underwent attempted treatment with the CoreValve THV. The rate of all-cause mortality or major stroke at 12 months was 26.0% (upper 2-sided 95% confidence bound: 29.9%) versus 43.0% with the OPG ($p < 0.0001$). Individual 30-day and 12-month events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively). Procedural events at 30 days included life-threatening/disabling bleeding (12.7%), major vascular complications (8.2%), and need for permanent pacemaker placement (21.6%). The frequency of moderate or severe paravalvular aortic regurgitation was lower 12 months after self-expanding TAVR (4.2%) than at discharge (10.7%; $p = 0.004$ for paired analysis).

Conclusions TAVR with a self-expanding bioprosthesis was safe and effective in patients with symptomatic severe aortic stenosis at prohibitive risk for surgical valve replacement. (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 2014;63:1972–81) © 2014 by the American College of Cardiology Foundation

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Degenerative aortic valve disease resulting in severe stenosis is the most common form of valvular heart disease in developed countries (1). Surgical aortic valve replacement (SAVR) remains the therapy of choice for most patients with severe aortic stenosis, and this therapy is associated with an improvement in both symptoms and survival (2). A significant number of patients with severe aortic stenosis, however, are not candidates for SAVR, due to pre-existing comorbidities, frailty, and disabilities (3). Patients denied surgery have a dismal prognosis, with an estimated mortality rate of 50% within 1 year after surgical evaluation (4).

Transcatheter aortic valve replacement (TAVR) is an alternative to SAVR in selected patients with aortic stenosis (5,6). Balloon-expandable TAVR in patients deemed unsuitable for surgery reduced 12-month mortality compared with medical therapy, albeit with a higher 30-day incidence of major stroke, vascular complication, and paravalvular regurgitation (4), each of which was associated with late mortality (4,7). The CoreValve self-expanding transcatheter bioprosthetic heart valve (Medtronic, Inc., Minneapolis, Minnesota) has been widely used worldwide (8,9), but a rigorous, prospective evaluation of this device in patients recognized to be at an extreme risk for surgery has not been performed.

The CoreValve Extreme Risk Pivotal Trial evaluated patients who were deemed to have an extreme risk for SAVR and were treated with this self-expanding transcatheter heart valve (THV). Our objective was to evaluate the clinical safety and efficacy of self-expanding TAVR in patients at extreme risk for SAVR.

Methods

Patient selection. Patients with New York Heart Association (NYHA) class II or greater symptoms related to aortic valve disease were eligible for the trial. Severe aortic stenosis was defined as an aortic valve area $\leq$0.8 cm^2 or aortic valve index $\leq$0.5 cm^2/m^2 and either a mean aortic valve gradient >40 mm Hg or a peak aortic valve velocity >4.0 m/s at rest or with a dobutamine stress if the left ventricular ejection fraction was <50%. Patients were considered at extreme risk if 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a 50% or greater risk for mortality or irreversible morbidity at 30 days with SAVR.

Principal exclusion criteria were an active gastrointestinal hemorrhage within the prior 3 months, a major stroke within the prior 6 months, or a life expectancy <1 year due to comorbidities. Anatomic exclusion criteria included an aortic annular diameter <18 mm or >29 mm, moderate to severe or severe mitral regurgitation, or a dilated ascending aorta. A complete list of all inclusion and exclusion criteria is found in the Online Appendix (Online Table 1S).

A case summary was created for each patient that included comorbidities and independent imaging review by a central laboratory and was presented by the clinical site heart team to a national screening committee (Online Table 2S). At least 2 senior cardiac surgeons and 1 interventional cardiologist had to agree that the patient met study eligibility, risk, and imaging criteria for the trial.

Abbreviations and Acronyms

EuroSCORE = European System for Cardiac Operative Risk Evaluation

MACCE = major adverse cardiovascular and cerebral event(s)

NYHA = New York Heart Association

OPG = objective performance goal

SAVR = surgical aortic valve replacement

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

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

VARC = Valve Academic Research Consortium

Study device. The CoreValve system consists of 3 components: the THV, delivery catheter system, and compression loading system. The THV comprises a self-expanding nitinol frame that supports a trileaflet porcine pericardial valve. The valves available in this report included those with 23-, 26-, 29-, and 31-mm diameters treating patients with an annulus range from 18 to 29 mm (Fig. 1). The inflow portion of the frame is designed to conform to the annulus and to stabilize the frame at the annular location. The lowest 12 mm of the frame contains a porcine pericardial skirt to seal the annulus. The valve is located in a supra-annular position at the waist (constrained portion) of the valve frame. The outflow portion of the valve frame is constructed to support the valve commissures and orient the frame to facilitate laminar flow. All valve sizes are delivered using an 18-F catheter delivery system. The valve is deployed without rapid pacing and is partially repositionable until annular contact with the THV is made.

Procedural details. The size of the selected bioprosthesis was determined based on a pre-enrollment computed tomography angiogram. Aspirin 325 mg and clopidogrel 300 to 600 mg were given prior to the procedure. Following general anesthesia or deep conscious sedation and attainment of arterial access, anticoagulation with intravenous heparin or bivalirudin was given to achieve an activated

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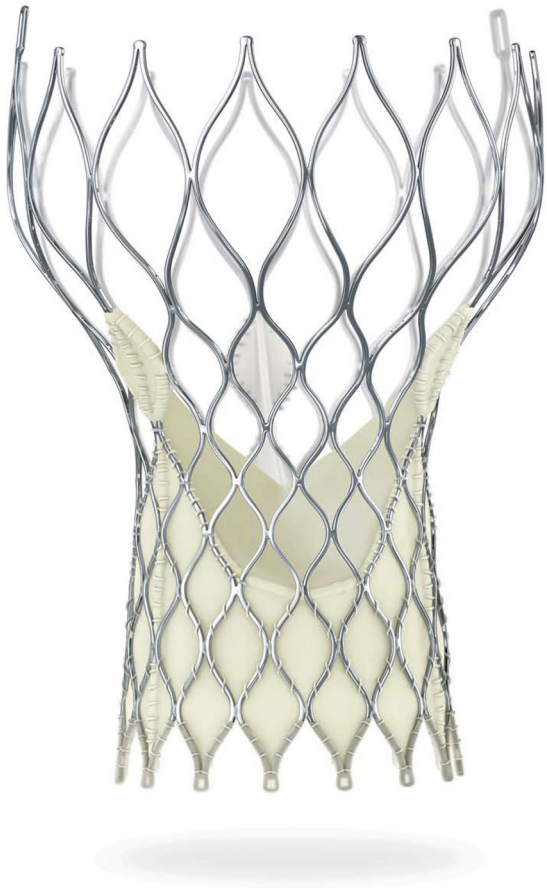

Figure 1 CoreValve Transcatheter Heart Valve

The self-expanding nitinol frame serves to anchor the transcatheter heart valve at the level of the aortic annulus. The supra-annular trileaflet porcine pericardial valve is hand sewn to the nitinol frame.

clotting time of at least 250 s. Through an 18-F sheath, aortic valvuloplasty was performed using a balloon undersized to the aortic annulus and rapid ventricular pacing to a target systolic pressure <60 mm Hg. The self-expanding THV was then advanced across the aortic valve. Contrast injections were performed through a pigtail catheter positioned in the noncoronary sinus to guide positioning of the inflow portion of the frame 2 to 6 mm inferior to the noncoronary basal annulus. After valve deployment, the delivery catheter was removed and valve performance was evaluated using transthoracic or transesophageal echocardiography, aortography, and invasive measurements of transaortic valve gradients and left ventricular end-diastolic pressures. Valve repositioning using a vascular snare, balloon post-dilation, or placement of an additional bioprosthetic valve was used to treat significant residual aortic regurgitation after deployment. The 18-F sheath was then removed using percutaneous or surgical techniques. Dual antiplatelet therapy with aspirin 81 mg daily and clopidogrel 75 mg daily was recommended for 3 months after the procedure, followed by aspirin at least 81 mg daily or clopidogrel 75 mg daily indefinitely. In the event that warfarin was indicated for other reasons, aspirin at least 81 mg daily and warfarin were administered indefinitely.

Study design. The CoreValve Extreme Risk Pivotal Trial was a prospective, multicenter, controlled, nonrandomized single-arm clinical study performed at 41 clinical sites in the United States (Online Table 3S). The responsible institutional review boards approved the study protocol, and written informed consent was obtained from all patients. The trial was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

The clinical study was designed and funded by the study sponsor (Medtronic). 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 (Online Table 2S) adjudicated all major adverse clinical events. The data and safety monitoring board was responsible for study oversight. The CoreValve US steering committee reviewed the primary manuscript and made the decision to submit the manuscript for publication.

Analysis populations. The intended treatment population included all patients accepted by the screening committee who were then enrolled in the study by the clinical site. The attempted implant population included patients with a documented valve implant attempt via an iliofemoral approach. The attempted implant population was prespecified as the primary analysis group.

A detailed assessment of the patient baseline comorbidities was performed using the Society for Thoracic Surgery Predicted Risk of Mortality (STS-PROM) (10), European System for Cardiac Operative Risk Evaluation (EuroSCORE) (10), and Charlson comorbidity index (11). Frailty markers included a 5-m gait speed test (12) and grip strength testing (13). Disability was assessed using Katz activities of daily living (14) and mini-mental test for dementia (15).

Study endpoints. The primary endpoint was the rate of all-cause mortality or major stroke 12 months after the procedure in the attempted implant population. Major and minor stroke were defined using Valve Academic Research Consortium (VARC)-1 criteria (16) (Online Table 4S). Criteria for major adverse cardiovascular and cerebral events (MACCE) comprising all-cause death, myocardial infarction, all stroke, and reintervention to alter, adjust, or replace a previously implanted valve, along with additional secondary endpoints, are found in the Online Appendix (Online Table 4S). Symptom status was assessed using the NYHA classification system. Device success was defined using the VARC-1 criteria (Online Table 4S) (16). Procedure success was defined as device success in the absence of in-hospital MACCE.

Echocardiographic analysis. Serial echocardiograms were collected at screening, post-procedure (within 24 to 48 h), hospital discharge, and 1, 6, and 12 months after THV

implantation and were interpreted by a central laboratory (Mayo Echocardiography Core Laboratory, Rochester, Minnesota). Prosthetic valve dysfunction and periprocedural aortic regurgitation were determined using VARC-1 criteria (16).

Statistical analysis. For estimation of the rate of death or major stroke in patients with aortic stenosis at prohibitive risk for surgery treated with standard therapy, an objective performance goal (OPG) of 43% for all-cause mortality or major stroke was determined from 2 sources. A weighted meta-analysis performed of 7 contemporary balloon aortic valvuloplasty studies (17–23) yielded a rate of 12-month all-cause mortality or major stroke of 42.7% (95% confidence interval: 34.0% to 51.4%). The meta-analysis estimate was then adjusted based on the lower 95% confidence boundary of 43% in the standard therapy arm of inoperable patients in PARTNER (Placement of Aortic Transcatheter Valve Trial) B (4). The rate of all-cause mortality or major stroke with TAVR was estimated to be 36.5% (33.0% plus 1 SE of 3.5%) based on the treatment group of the PARTNER B trial (4).

The study had one primary objective, which was to demonstrate that the combined all-cause mortality or major stroke rate at 12 months was <43.0% after treatment with the self-expanding THV. A sample size of 438 was required to obtain a 1-sided alpha of 0.025; power = 0.80 and assumed a 36.5% Kaplan-Meier rate of death or major stroke for patients treated with the THV in the as-treated population. Accounting for an approximate 10% attrition rate, a total of 506 patients were recruited in the study.

Categorical variables were compared with the use of the Fisher exact test. Continuous variables were presented as mean ± SD and compared with the use of Student *t* test. Kaplan-Meier estimates were used to construct the survival curves based on all available follow-up for the time-to-event analysis. All testing used a 2-sided alpha level of 0.05. All statistical analyses were performed with SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Patient enrollment. From February 2011 to August 2012, 41 centers in the United States recruited 506 patients for treatment with the CoreValve THV (Fig. 2). Prior to treatment, 11 patients exited from the study: 4 patients died, 3 withdrew consent, and 4 were withdrawn by the treating physicians. An additional 6 patients did not complete the procedure with iliofemoral access: 4 underwent left subclavian TAVR and 2 underwent direct aortic implantation. All 489 remaining patients were included in the attempted implant analysis population.

Patient demographics. Patient demographics for the attempted implant population are in Table 1. Patients were elderly (83.2 ± 8.7 years), commonly women (52.1%), and severely symptomatic (NYHA class III or IV 91.8%). The STS-PROM was 10.3% ± 5.5% and was >15% in 17.2% of patients. A history of atrial fibrillation was present in 46.8% of patients.

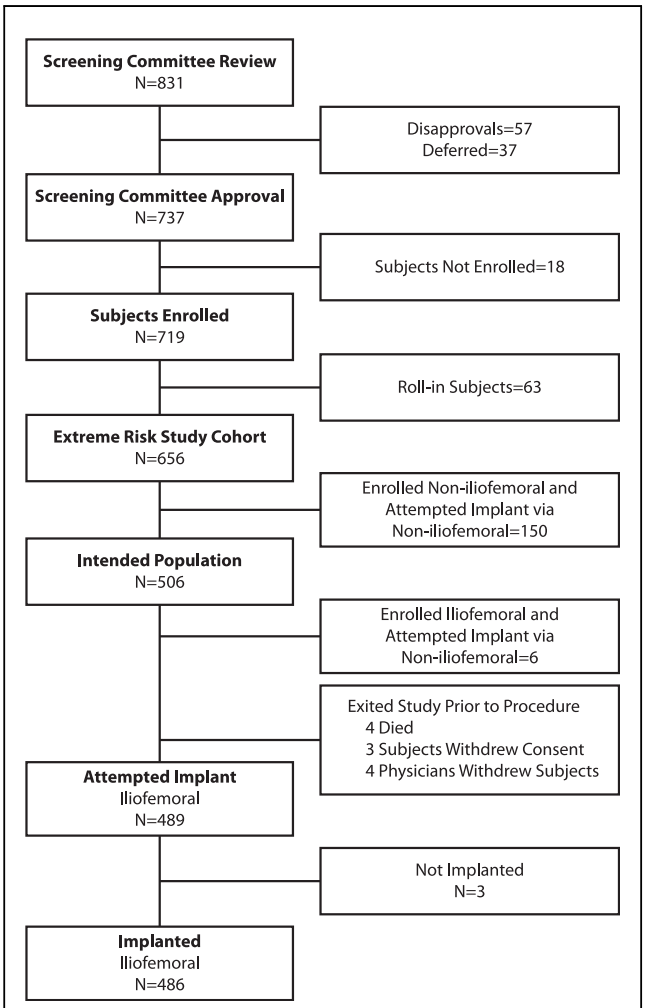

Figure 2 Study Flow Diagram

Anatomic factors precluding SAVR are in Table 1. Significant comorbidities and frailty indexes are in Table 2. Using STS criteria, severe lung disease was present in 23.5% of patients, and home oxygen therapy was used in 29.9% of patients. A total of 58.7% of patients had severe comorbidities using the Charlson comorbidity index. The average 5-m gait speed was >6 s in 84.2% of patients, and the grip strength was below the age- and sex-matched threshold in 67.7% of patients. Disability assessments prior to the procedure are in Table 3. Two or more deficits in activities of daily living were present in 20.7% of patients and 3 or more deficits were found in 13.9% of patients.

Procedural outcomes. A total of 486 of 489 patients (99.4%) underwent the THV implantation procedure. Most patients (94.4%) were given general anesthesia. Balloon pre-dilation was performed in 478 patients (98.4%), and post-dilation after the THV implantation was performed in 101 patients (20.8%). The distribution of implanted valve sizes were 23 mm (2.5%), 26 mm (35.0%),

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Table 1 Patient Baseline Demographics (N = 489)

Age, yrs	83.2 ± 8.7
Female	255 (52.1)
NYHA functional class	
II	40 (8.2)
III	313 (64.0)
IV	136 (27.8)
STS-PROM	10.3 ± 5.5
<10%	272 (55.6)
10%–15%	133 (27.2)
>15%	84 (17.2)
Logistic EuroSCORE, %	22.6 ± 17.1
Diabetes mellitus	203 (41.5)
Controlled by insulin	90 (18.4)
Creatinine level >2 mg/dl	22 (4.5)
Chronic kidney disease class 4/5	63/484 (13.0)
History of hypertension	441 (90.2)
Peripheral vascular disease	171/486 (35.2)
Prior stroke	67/488 (13.7)
Prior TIA	47/488 (9.6)
Cardiac risk factors	
Coronary artery disease	400 (81.8)
Prior coronary artery bypass surgery	193 (39.5)
Prior percutaneous coronary intervention	181 (37.0)
Prior balloon valvuloplasty	100 (20.4)
Pre-existing pacemaker/defibrillator	127 (26.0)
Previous myocardial infarction	151 (30.9)
Congestive heart failure	473 (96.7)
Prior atrial fibrillation/atrial flutter	228/487 (46.8)
Factors unfavorable for surgical aortic valve surgery	
Aorta calcification	
Severe	84/488 (17.2)
Porcelain	24/488 (4.9)
Chest wall deformity	27 (5.5)
Hostile mediastinum	58/488 (11.9)

Values are mean ± SD, n (%), or n/N (%). Denominator = 489 unless otherwise indicated.
EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association; STS-PROM = Society for Thoracic Surgery Predicted Risk of Mortality; TIA = transient ischemic attack.

Table 2 Comorbidities and Frailty (N = 489)

Comorbidities	
STS chronic lung disease severity	
None	201 (41.1)
Mild	98 (20.0)
Moderate	75 (15.3)
Severe	115 (23.5)
Home oxygen	146 (29.9)
FEV1 <1,000 ml	116 (23.7)
DLCO <50%	109 (22.3)
Liver cirrhosis	15 (3.1)
Connective tissue disease	13/487 (2.7)
Immunosuppressive therapy	62 (12.7)
Charlson comorbidity index	5.3 ± 2.3
None (score = 0)	0 (0.0)
Mild (score = 1 or 2)	41 (8.4)
Moderate (score = 3 or 4)	161 (32.9)
Severe (score = 5)	287 (58.7)
Frailty	
Anemia with transfusion	108/473 (22.8)
Body mass index <21 kg/m^2	42 (8.6)
Albumin <3.3 g/dl	88/484 (18.2)
Unplanned weight loss	61 (12.5)
Fall in past 6 months	88 (18.0)
5-m gait speed, s, mean ± SD (n)	14.8 ± 28.0 (336)
Patients with average >6 s	283/336 (84.2)
Grip strength below threshold (13)	329/486 (67.7)

Values are n (%), n/N (%), or mean ± SD.
DLCO = diffusing capacity of lung carbon monoxide; FEV1 = forced expiratory volume in 1 second; other abbreviation as in Table 1.

29 mm (58.4%), and 31 mm (4.1%). Two or more CoreValve THVs were implanted in 17 patients (3.5%). The average procedure time was 66.1 ± 39.0 min. The median length of stay was 7 days. The device success rate was 84.6% as defined by VARC-1, and the procedural success rate was 77.6% (Online Table 5S).

Clinical endpoints. The Kaplan-Meier rate of the primary endpoint of 12-month all-cause mortality or major stroke in the attempted implant population was 26.0% with an upper 2-sided 95% CI of 29.9% (Table 4). The upper 95% CI was significantly lower than the pre-specified OPG of 43% ($p < 0.0001$), and therefore this study met its primary endpoint (Fig. 3). The Kaplan-Meier rates of all-cause mortality at 30 days and 12 months were 8.4% and 24.3%, respectively; and the rates of major stroke at 30 days and 12 months were 2.3% and 4.3%, respectively. The causes of mortality through 12 months are in Online Table 6S. A permanent pacemaker implantation was required in 104 patients (21.6%) by 30 days and 123 patients (26.2%) at 1 year, most often due to atrioventricular block. All MACCE endpoints for the attempted implant population are reported in Table 4.

At 12 months, the Kaplan-Meier rate of the primary endpoint in the intended population was 27.0% (upper 2-sided 95% CI: 30.9%). The all-cause mortality rate was

Table 3 Disability Assessments (N = 489)

Disability Factor	
Dementia, based on MMSE score	
None (≥25)	352/488 (72.1)
Mild (21–24)	112/488 (23.0)
Moderate (10–20)	23/488 (4.7)
Severe (<10)	1/488 (0.2)
Does not live independently	135 (27.6)
ADL	
Does not bathe independently	106 (21.7)
Does not dress independently	85 (17.4)
Does not toilet independently	44 (9.0)
Does not transfer independently	91 (18.6)
Incontinent	32 (6.5)
Does not feed independently	12 (2.5)
Deficit >2 ADLs	101 (20.7)
Deficit >3 ADLs	68 (13.9)

Values are n/N (%) or n (%).
ADL = activities of daily living; MMSE = mini–mental state examination.

Table 4 Clinical Outcomes at 30 Days and 12 Months*

Outcome	30 Days (N = 489)	12 Months (N = 489)
Death from any cause or major stroke	48 (9.8)	127 (26.0)
Death		
From any cause	41 (8.4)	119 (24.3)
Cardiovascular	41 (8.4)	88 (18.3)
Stroke	19 (4.0)	31 (7.0)
Major	11 (2.3)	19 (4.3)
Minor	9 (1.9)	14 (3.2)
TIA	3 (0.6)	5 (1.1)
MACCE	60 (12.3)	143 (29.2)
Myocardial infarction	6 (1.2)	9 (2.0)
Periprocedural	6 (1.2)	6 (1.2)
Spontaneous	0 (0)	3 (0.7)
Reintervention	5 (1.1)	8 (1.8)
Major or life-threatening bleeding	179 (36.7)	206 (42.8)
Life-threatening or disabling	62 (12.7)	83 (17.6)
Major	121 (24.9)	136 (28.5)
Major vascular complications	40 (8.2)	41 (8.4)
Acute kidney injury	57 (11.8)	57 (11.8)
Cardiogenic shock	13 (2.7)	13 (2.7)
Cardiac perforation	9 (1.8)	9 (1.8)
Device migration	0	1 (0.2)
Device embolization	0	0

Values are n (%). *All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number in the study group.

MACCE = major adverse cardiovascular and cerebrovascular event(s); other abbreviation as in Table 1.

24.6% and the major stroke rate was 4.6% in the intended population.

NYHA class improved significantly from baseline to 12-month follow-up (Δ 1.6 ± 0.9; $p < 0.0001$). At baseline, the majority of patients (91.3%) were in NYHA class III or IV, and at each subsequent follow-up, the majority of patients were in NYHA class I or II (Fig. 4). Fewer than 15% of patients had no change in their functional status from baseline to 1 month, 6 months, or 12 months (13.9%, 7.3%, and 6.3%, respectively). The proportion of patients who were alive and had a worsening in functional status following TAVR was <1% at any follow-up visit.

Echocardiographic findings. Serial echocardiographic findings by the core laboratory are in Table 5. The mean aortic valve gradient was reduced from 47.3 ± 14.6 mm Hg at baseline to 8.9 ± 4.1 mm Hg (Δ 39.8 ± 14.8 mm Hg; $p < 0.0001$ for paired echocardiograms), and the effective orifice area was significantly increased from 0.7 ± 0.2 cm^2 to 1.9 ± 0.5 cm^2 at the 12-month follow-up (Δ 1.2 ± 0.6 mm Hg; $p < 0.0001$ for paired echocardiograms) (Fig. 5). The left ventricular ejection fraction was 54.5% ± 14.4% at baseline and increased to 57.3% ± 11.6% at the 12-month follow-up. The frequencies of total, paravalvular, and central aortic regurgitation are presented in Table 5. Transvalvular regurgitation was uncommon at any time point after CoreValve THV placement. The frequency of moderate paravalvular aortic regurgitation was lower 12 months after self-expanding TAVR (4.2%) than at discharge (9.7%; $p = 0.004$ for paired analyses) (Fig. 6A). In patients with moderate paravalvular aortic regurgitation at discharge and paired echocardiograms at 12 months, 82.8% showed an improvement of the moderate paravalvular regurgitation (Fig. 6B). For patients with less than moderate paravalvular regurgitation at discharge and paired echocardiograms at 12 months, 2.9% worsened to moderate paravalvular regurgitation. Late mortality was associated with total severe aortic regurgitation at the time of discharge (Fig. 7).

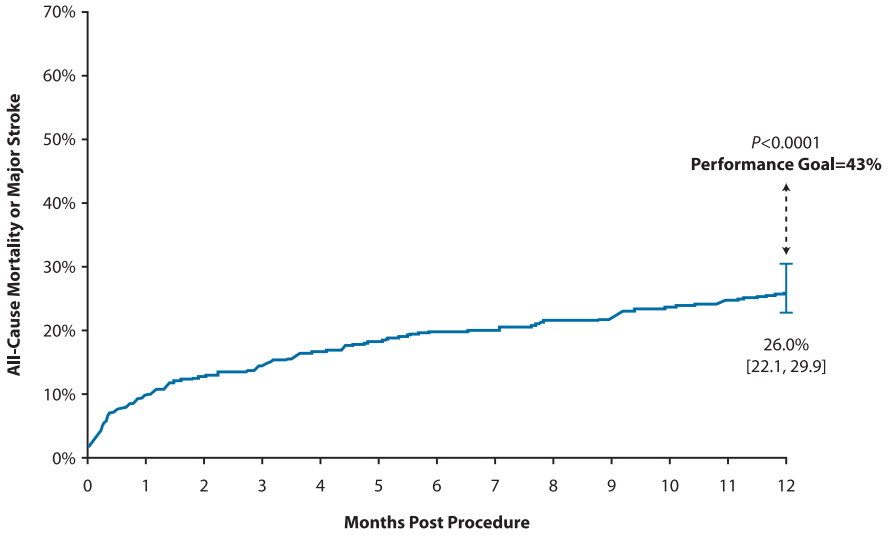

Figure 3 Cumulative Event Curve for All-Cause Mortality or Major Stroke

Event rates were calculated with Kaplan-Meier methods. **Brackets** indicate 95% confidence interval.

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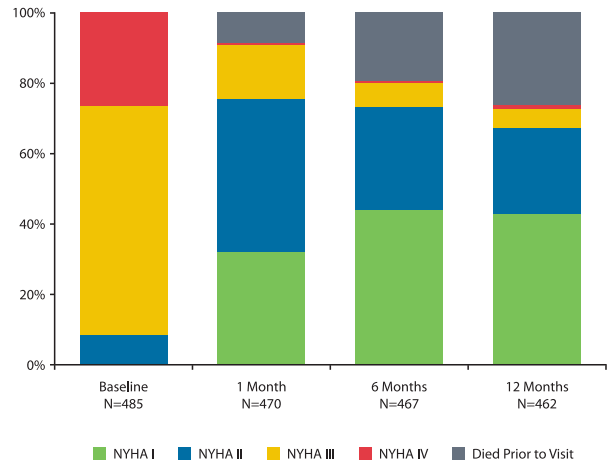

Figure 4 NYHA Classification Over Time

Symptom status according to New York Heart Association (NYHA) class is shown at baseline and at 30 days, 6 months, and 1 year among patients undergoing attempted transcatheter aortic valve replacement.

Discussion

Our main finding was that treatment of severe aortic stenosis with the CoreValve self-expanding bioprosthesis in patients deemed extreme risk for conventional surgery reduced the frequency of all-cause mortality or major stroke at 12 months compared with an OPG (26.0% vs. 43.0%; $p < 0.0001$). This 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 NYHA functional class.

Risk assessment. Patient selection for TAVR has relied upon an interdisciplinary heart team who collectively determine patient risk for aortic valve surgery (24,25). These decisions are often based on subjective assessments that incorporate factors beyond those captured in traditional surgical risk assessment tools (26), such as STS-PROM (10) or logistic EuroSCORE (27). In the current study, patients were judged by the clinical site heart team to have a 50% or greater risk for 30-day mortality or irreversible morbidity with conventional SAVR, a risk that was confirmed by a national screening committee. Our detailed assessment of surgical comorbidities, frailty, and disability provided further objective evidence of poor suitability for surgery in these extreme-risk patients. STS-defined severe pulmonary disease was present in nearly 25% of patients, severe comorbidity using the Charlson index was present in nearly 60% of patients, slow gait speed or wheelchair bound was present in approximately 85% of patients, and 27.6% of patients did not live independently.

Mortality and major stroke. The 30-day mortality rate of 8.4% in our study is comparable to the 30-day mortality rate of 6.7% in inoperable patients treated with the transfemoral SAPIEN (Edwards Lifesciences, Irvine, California) THV in the Transcatheter Valve Therapy Registries (28), considering the extreme comorbidity, frailty, and disability profiled in our patients. The 12-month mortality rate of 24.3% in this study is also comparable to the 12-month mortality of 30.7% in the PARTNER B trial (4). Moreover, the incidence of major stroke at 30 days was lower

Table 5 Serial Echocardiography Findings in Patients Undergoing CoreValve Transcatheter Heart Valve Implantation

	Baseline	Post-Procedural	Discharge	1 Month	6 Months	12 Months
n	481	456	443	418	364	330
Mean aortic gradient, mm Hg	47.3 ± 14.6	9.6 ± 4.4	9.6 ± 4.3	8.7 ± 4.2	9.1 ± 3.9	8.9 ± 4.1
Effective orifice area, cm^2	0.73 ± 0.23	1.87 ± 0.55	1.80 ± 0.52	1.86 ± 0.56	1.88 ± 0.55	1.88 ± 0.54
Total aortic regurgitation, n	477	460	450	419	367	329
None	56 (11.7)	64 (13.9)	53 (11.88)	38 (9.1)	73 (19.9)	70 (21.3)
Trivial	174 (36.5)	174 (37.8)	155 (40.0)	137 (32.7)	123 (33.5)	134 (40.7)
Mild	205 (43.0)	162 (35.2)	180 (40.0)	180 (43.0)	134 (36.5)	104 (31.6)
Moderate	41 (8.6)	51 (11.1)	54 (12.0)	59 (14.1)	36 (9.8)	21 (6.4)
Severe	1 (0.2)	9 (2.0)	8 (1.8)	5 (1.2)	1 (0.3)	0
Paravalvular regurgitation, n		449	440	412	364	327
None	—	83 (18.5)	70 (15.9)	64 (15.5)	89 (24.5)	95 (39.1)
Trivial	—	161 (35.9)	145 (33.0)	130 (31.6)	124 (34.1)	123 (37.6)
Mild	—	158 (35.2)	178 (40.5)	171 (41.5)	120 (33.0)	95 (29.1)
Moderate	—	40 (8.9)	40 (9.1)	45 (10.9)	31 (8.5)	14 (4.3)
Severe	—	7 (1.6)	7 (1.6)	2 (0.5)	0	0
Transvalvular regurgitation, n		445	439	411	362	325
None	—	323 (72.6)	309 (70.4)	266 (64.7)	263 (72.7)	238 (73.2)
Trivial	—	92 (20.7)	103 (23.5)	107 (26.0)	74 (20.4)	64 (19.7)
Mild	—	25 (5.6)	21 (4.8)	32 (7.8)	23 (6.4)	23 (7.1)
Moderate	—	4 (0.9)	5 (1.1)	6 (1.5)	2 (0.6)	0
Severe	—	1 (0.2)	1 (0.2)	0	0	0

Values are n, mean ± SD, or n (%).

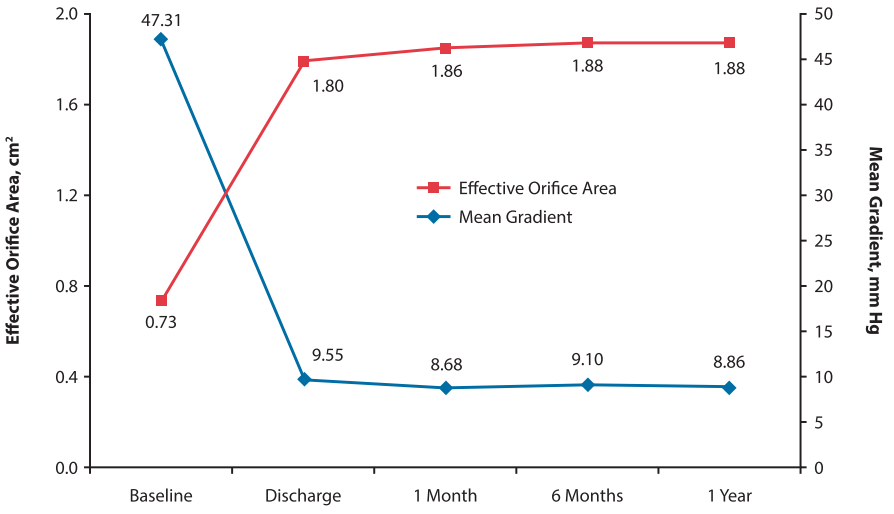

Figure 5 **Changes in Mean Aortic Valve Gradient Over Time**

The mean aortic valve gradient is displayed in mm Hg **(red)** and the mean effective orifice area is displayed in cm^2 **(blue)** at each follow-up.

(2.3%) than that reported in the PARTNER B trial (5.0%) (4). This may be attributable to the lower profile of the CoreValve device (18-F) compared with the 22-F and 24-F diameter SAPIEN devices (4), resulting in less trauma during advancement of the THV around the aortic arch.

Aortic regurgitation. Moderate or severe paravalvular regurgitation occurs in 9% to 16% of patients after TAVR, depending on the time point of measurement, implantation depth, valve sizing, extent of calcification, and clinical site versus core laboratory review (29–31). The presence of moderate or severe aortic regurgitation post-TAVR increased mortality at 30 days and 1 year in several studies (29–31). The results of our study demonstrated a relatively low rate of moderate or severe paravalvular aortic valve regurgitation (4.3%) identified by the core laboratory 1 year after CoreValve THV placement. The severity of moderate aortic regurgitation improved over time in patients with paired discharge and 1-year echocardiograms (Fig. 6B), potentially attributable to the use of pre–computed tomography assessment of aortic annular diameter prior to the procedure (32,33), higher placement of the THV within the aortic annulus, and use of post-dilation in the presence of significant paravalvular regurgitation during the procedure. The improvement of moderate regurgitation in our patients suggests that there is ongoing remodeling of the annular-bioprosthesis interface with the self-expanding device.

Conduction system disturbances. Conduction system disturbances may occur following CoreValve TAVR, due to mechanical trauma applied by the extended frame length to the membranous septum in the region of the atrioventricular conduction system and left bundle branch (34,35). Accordingly, the need for a permanent pacemaker placement after CoreValve implantation has been reported from 25.8%

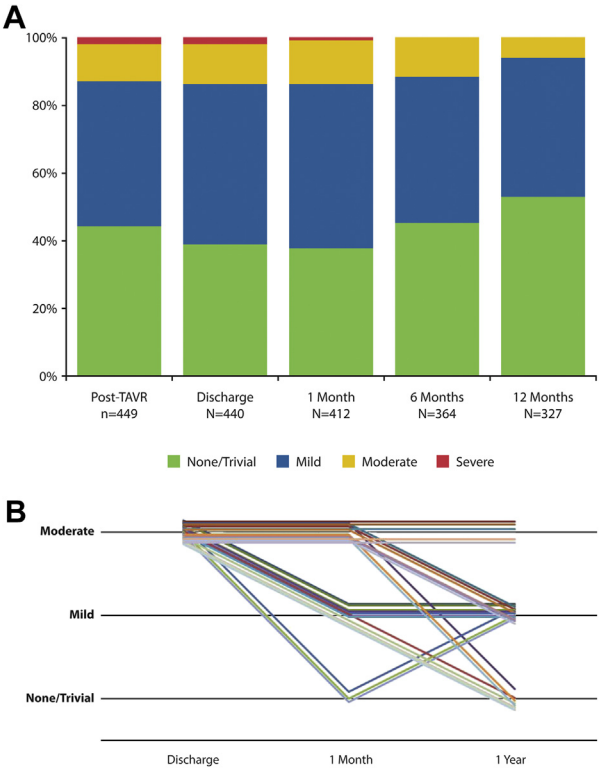

Figure 6 **Changes in Paravalvular Regurgitation Over Time and Regurgitation Grades Over Time in Patients With Moderate Paravalvular Regurgitation at Discharge**

(A) The percentage of patients by degree of paravalvular aortic regurgitation at each follow-up interval. **(B)** Echocardiograms were presented for 29 patients with paired echocardiographic studies at discharge and 12-month follow-up.
TAVR = transcatheter aortic valve replacement.

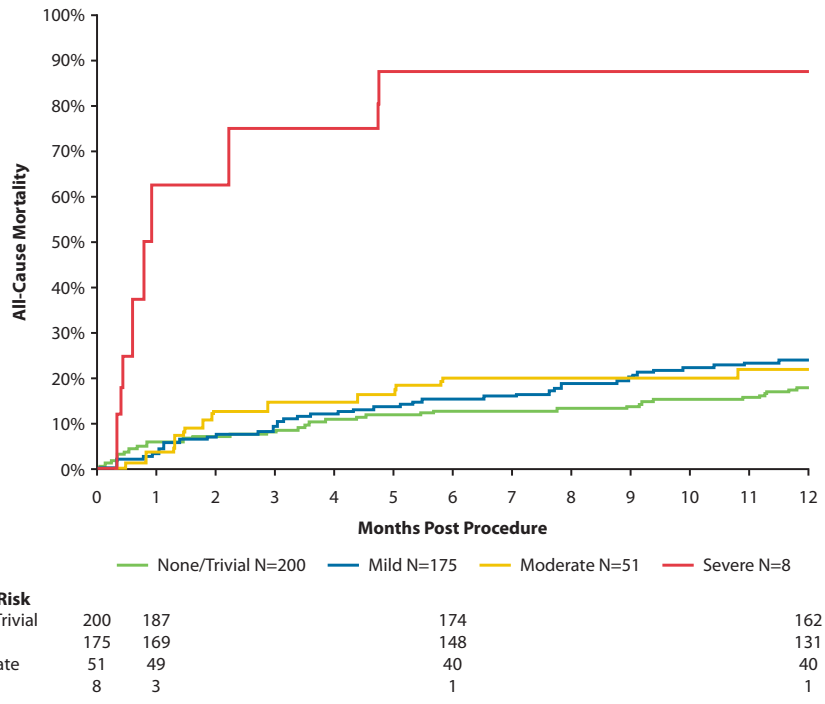

Figure 7 **Mortality Over Time by Grade of Paravalvular Aortic Regurgitation**

There was a significant relationship in the presence of severe paravalvular regurgitation at discharge and late mortality.

to 33.0% (36,37). Although placement of a permanent pacemaker does not seem to affect late mortality (38), we used "best practices" to reduce the occurrence of conduction disturbances during TAVR, including smaller pre-dilation balloons, valve sizing based on computed tomography, and higher positioning of the CoreValve THV with avoidance of the conduction system (39,40). In the current study, the rate of permanent pacemaker implantation was 21.6% at 30 days post-procedure. Lower permanent pacemaker rates may be attributable to the revised implantation methods that were part of this study.

Study limitations. The primary endpoint of the study was compared with an OPG of medically treated patients rather than a randomized study with medical therapy due to the lack of continued clinical equipoise with TAVR and medical therapy (4). Only severe aortic regurgitation was associated with late mortality in this study, but the small number of patients with moderate aortic regurgitation precludes any definitive conclusions about the relationship between moderate aortic regurgitation and late mortality with the self-expanding THV. TAVR was a new procedure for all of the clinical sites participating in this trial, and better procedural outcomes may be expected with more experience in patient selection and operator technique.

Conclusions

Based on the findings of this study, TAVR using the self-expanding CoreValve THV should be considered an alternative to medical therapy in patients with severe aortic stenosis who are deemed extreme risk for surgery.

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Key Words: aortic stenosis ■ transcatheter aortic valve replacement ■ outcomes.

APPENDIX

For supplemental material and tables, please see the online version of this article.