Self-expanding transcatheter aortic valve replacement using alternative access sites in symptomatic patients with severe aortic stenosis deemed extreme risk of surgery

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Objectives: The CoreValve Extreme Risk US Pivotal Trial enrolled patients with symptomatic severe aortic stenosis deemed unsuitable for surgical aortic valve replacement. Implants were attempted using transfemoral access (n = 489) or an alternative access (n = 150). In present analysis, we sought to examine the safety and efficacy of CoreValve transcatheter aortic valve replacement using alternative access.

Methods: The present study included 150 patients with prohibitive iliofemoral anatomy who were treated with the CoreValve transcatheter heart valve delivered by way of the subclavian artery (n = 70) or a direct aortic approach (n = 80). The echocardiograms were read by an independent core laboratory. The primary endpoint was all-cause mortality or major stroke at 12 months.

Results: The preoperative aortic valve area was $0.72 \pm 0.27 \text{ cm}^2$ and mean aortic valve gradient was $49.5 \pm 17.0 \text{ mm Hg}$. After the transcatheter aortic valve replacement, the effective aortic valve area was $1.82 \pm 0.64 \text{ cm}^2$ at 1 month and $1.85 \pm 0.51 \text{ cm}^2$ at 12 months. The mean aortic valve gradient was $9.7 \pm 5.8 \text{ mm Hg}$ at 30 days and $9.5 \pm 5.7 \text{ mm Hg}$ at 12 months. The death or major stroke rate was 15.3% at 30 days and 39.4% at 12 months. The individual rate of all-cause mortality and major stroke was 11.3% and 7.5% at 30 days and 36.0% and 9.1% at 12 months.

Conclusions: These data demonstrate that the CoreValve transcatheter heart valve delivered by an alternative access provides a suitable alternative for treatment of extreme risk patients with symptomatic severe aortic stenosis, who have prohibitive iliofemoral anatomy and no surgical options. (J Thorac Cardiovasc Surg 2014;148:2869-76)

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Transcatheter aortic valve replacement (TAVR) is an accepted therapy in patients poorly suited for surgical aortic valve replacement (SAVR).¹⁻³ Although most TAVR procedures are performed using the transfemoral approach,^{1,4} some

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A complete listing of the investigators, institutions, and research organizations participating in the CoreValve Extreme Risk US Pivotal Trial are listed in Table E1. Received for publication April 9, 2014; revisions received June 25, 2014; accepted for publication July 5, 2014; available ahead of print Aug 22, 2014.

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Abbreviations and Acronyms

NYHA	= New York Heart Association
PARTNER	= Placement of Aortic Transcatheter Valve (trial)
SAVR	= surgical aortic valve replacement
STS	= Society of Thoracic Surgeons
STS-PROM	= Society of Thoracic Surgeons-Predicted Risk of Mortality
TAVR	= transcatheter aortic valve replacement
THV	= transcatheter heart valve

patients have anatomy unsuitable for placement of a large femoral sheath.

In such patients, alternative access with the balloon-expandable SAPIEN (Edwards Life Sciences, Irvine, Calif) transcatheter heart valve (THV) has been primarily performed using a transapical approach.² This technique was not allowed in the Placement of Aortic Transcatheter Valve (PARTNER) B inoperable trial but was used in the PARTNER A trial in patients deemed at high risk of SAVR.

In patients with prohibitive iliofemoral vessels, the CoreValve self-expanding THV (Medtronic, Inc, Minneapolis, Minn) has been used with alternative access sites, including the subclavian artery⁵⁻⁷ and a direct aortic approach with a medial partial sternotomy or right thoracotomy.⁸⁻¹⁰ The CoreValve Extreme Risk US Pivotal Trial evaluated patients deemed to have a prohibitive risk for surgery and treated with this self-expanding THV using the transfemoral access. A separate arm of the study was designed for patients deemed unsuitable for iliofemoral access and requiring alternative access procedures. Our objective was to evaluate the clinical safety and efficacy of self-expanding TAVR in patients at extreme risk for SAVR in whom alternative access sites were used owing to preclusive iliofemoral anatomy.

METHODS**Patient Selection**

The patient selection criteria for the CoreValve Extreme Risk US Pivotal Trial have been previously described in detail.⁴ In brief, patients with severe aortic stenosis and symptoms related to aortic valve disease were eligible for the study. Severe aortic stenosis was defined as an aortic valve area of ≤ 0.8 cm² or an aortic valve index of ≤ 0.5 cm²/m² and either a mean aortic valve gradient >40 mm Hg or a peak aortic valve velocity >4.0 m/s. Patients were considered at extreme risk if 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a $\geq 50\%$ risk of mortality or irreversible morbidity at 30 days with SAVR. This risk was confirmed by 2 cardiac surgeons and 1 interventional cardiologist on a National Screening Committee.

The anatomic exclusion criteria included an aortic annular diameter <18 mm or >29 mm, moderate to severe mitral stenosis or severe mitral regurgitation, or a dilated ascending aorta.⁴ Computed tomographic angiography of the thoracic and abdominal aorta and common and external

iliac and femoral arteries was performed to determine the vessel caliber, presence of calcification, and tortuosity. Patients with permissive femoral and iliac arteries were enrolled in the CoreValve Extreme Risk US Pivotal Trial Iliofemoral Arm. In the event that iliofemoral access was not suitable for placement of an 18F sheath, the patients were considered for alternative access.

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 the present report included those with 23-, 26-, 29-, and 31-mm diameters, treating patients with an annulus range from 18 to 29 mm. 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 (Figure E1). All valve sizes are delivered using an 18F catheter delivery system. The valve is deployed without rapid pacing and is partially repositionable until annular contact with the THV has been made.

Study Design

The CoreValve Extreme Risk US Pivotal Trial was a prospective, multicenter, controlled, nonrandomized, single-arm clinical study performed at 41 clinical sites in the United States (Table E1). The responsible institutional review boards approved the study protocol, and all patients provided written informed consent. The trial was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice Guidelines, and the Declaration of Helsinki (ClinicalTrials.gov identifier, NCT01240902).

This study was designed and funded by the study sponsor (Medtronic, Inc). The study sponsor was responsible for the selection of the clinical sites, monitoring the data, management of the case report forms, and statistical analyses. An independent Clinical Events Committee (Table E2) 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 report and made the decision to submit it for publication.

Subclavian Access

An open surgical approach was used to isolate the subclavian artery, and an 18F sheath was advanced to the aorta over a stiff 0.035-in. guidewire positioned in the left ventricle.

Direct Aortic Approach

A direct aortic approach was used with either a median hemisternotomy or right thoracotomy between the first and second ribs. The 18F sheath was advanced into the aorta over a stiff 0.035-in. guidewire positioned in the left ventricle. The technical details of the subclavian and direct aortic implantation approaches have been previously published.¹¹

Procedural Details

The size of the selected bioprosthesis was determined from the pre-enrollment computed tomographic angiogram. Aspirin, 81 to 325 mg, was recommended before the procedure. After general anesthesia was induced, anticoagulation with intravenous heparin or bivalirudin was given to achieve an activated clotting time of ≥ 250 seconds. Through an 18F sheath, aortic valvuloplasty was performed with rapid ventricular pacing. The self-expanding THV was then advanced across the aortic valve. Contrast injections were performed through a pigtail catheter

positioned at the base of 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 echocardiography, aortography, and hemodynamic measurements. Dual antiplatelet therapy with aspirin, 81 mg daily, and clopidogrel, 75 mg daily, were recommended for 3 months after the procedure. In the event that warfarin was indicated for other reasons, aspirin, ≥ 81 mg daily, was also recommended.

Analysis Populations

The intended treatment population included all patients accepted by the Screening Committee and who were then enrolled or treated through an alternative access in the study by the clinical sites in the Alternative Access Arm. A detailed assessment of the patient baseline comorbidities was performed using the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (STS-PROM),¹² logistic EuroSCORE,¹² and Charlson comorbidity index.¹³ Frailty markers included a 5-m gait speed test¹⁴ and grip strength testing.¹⁵ Disability was assessed using Katz Activities of Daily Living¹⁶ and a mini-mental status examination for dementia. The intended treatment population included all patients accepted by the Screening Committee and who were then enrolled or treated through an alternative access in the study in the Alternative Access Arm.

Study Endpoints

The primary endpoint was the rate of all-cause mortality or major stroke at 12 months after the procedure in the attempted implant population. Major and minor stroke were defined using the Valve Academic Research Consortium-1 criteria.¹⁷ The criteria for major adverse cardiovascular and cerebral events included all-cause death, myocardial infarction, all stroke events, and reintervention to alter, adjust, or replace a previously implanted valve. Symptom status was assessed using the New York Heart Association (NYHA) classification system. Serial echocardiograms were collected at screening, after the procedure (within 24–48 hours), at hospital discharge, and 1, 6, and 12 months after THV implantation and were interpreted by a Central Laboratory (Mayo Echocardiography Core Laboratory, Rochester, Minn). Prosthetic valve dysfunction and paravalvular regurgitation were determined using Valve Academic Research Consortium-1 criteria.¹⁷

Statistical Analysis

The study had 1 primary objective—to assess the combined all-cause mortality or major stroke rate at 12 months after treatment with the self-expanding THV. Because the outcomes of patients unsuitable for surgery who had prohibitive iliofemoral anatomy had not been previously reported, no objective performance goal was included. The categorical variables were compared using Fisher's exact test or the chi-square test, as appropriate. Continuous variables are presented as the mean $\pm$ standard deviation and were compared using the Student *t* test. Kaplan-Meier estimates were used to construct the survival curves using all available follow-up data for the time-to-event analysis. All testing used a 2-sided α level of 0.05. All statistical analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

From February 2011 to August 2012, 150 patients with prohibitive iliofemoral anatomy were enrolled at 41 centers in the United States and treated with the CoreValve THV (Figure 1). After enrollment completion of the CoreValve Extreme Risk US Pivotal Trial, an additional 339 patients were treated at 45 clinical sites in the Continued Access Study and had ≥ 30 days of follow-up data available for analysis.

FIGURE 1. Study flow.

Patient Demographics

The demographics and anatomic contraindications to SAVR for patients in the Pivotal Study and Continued Access Study are reported in Table 1. The patients in the Pivotal Study were elderly (age, 81.3 ± 7.4 years), commonly women (54.7%), and severely symptomatic (NYHA class III or IV, 92.0%). The mean Society for Thoracic Surgeons Predicted Risk of Mortality was $10.7\% \pm 5.7\%$ and exceeded 15% in 17.3% of the patients. A history of atrial fibrillation was present in 48.3% of patients. No significant differences were found in the standard demographics between the patients enrolled in the Alternative Access Arms of the Pivotal Trial and the Continued Access Study.

Using Society of Thoracic Surgeons criteria, severe lung disease was present in 39.3% of the patients, and home oxygen therapy was used in 44.0% of the patients (Table 2). Of the patients, 68.0% had severe comorbidities when categorized using the Charlson comorbidity index. The average 5-m gait speed was >6 seconds for 81.7% of patients, and the grip strength was less than the age- and sex-matched threshold for 75.0% of the patients. Objective

TABLE 1. Patient baseline demographics

Demographic data	Pivotal (n = 150)	Continued access (n = 339)	P value
Age (y)	81.3 ± 7.4	81.8 ± 8.2	.50
Female sex	82 (54.7)	170 (50.1)	.38
NYHA classification			.23
Class II	12 (8.0)	42 (12.4)	
Class III	98 (65.3)	224 (66.1)	
Class IV	40 (26.7)	73 (21.5)	
STS-PROM (%)	10.7 ± 5.7	10.1 ± 5.6	.23
STS-PROM level			.25
<10%	75 (50.0)	195 (57.5)	
10%-15%	49 (32.7)	88 (26.0)	
>15%	26 (17.3)	56 (16.5)	
Logistic EuroSCORE (%)	22.9 ± 15.9	24.2 ± 17.2	.45
Diabetes mellitus	51 (34.0)	134 (39.5)	.27
CKD class 4/5	21 (14.1)	48 (14.4)	1.00
History of hypertension	137 (91.3)	308 (90.9)	1.00
PVD	92 (61.3)	213 (68.1)	.15
Previous stroke	21 (14.1)	48 (14.2)	1.00
Previous TIA	16 (10.7)	34 (10.1)	.87
Cardiac risk factors			
Coronary artery disease	120 (80.0)	277 (81.7)	.71
Previous CABG	61 (40.7)	118 (34.8)	.22
Previous PCI	48 (32.0)	138 (40.7)	.07
Previous balloon valvuloplasty	34 (22.7)	68 (20.1)	.55
Previous pacemaker/defibrillator	38 (25.3)	66 (19.5)	.15
Previous myocardial infarction	49 (32.7)	104 (30.7)	.67
Previous atrial fibrillation/atrial flutter	72 (48.3)	154 (45.8)	.62
Unfavorable anatomy			
Aorta calcification			.67
Severe	25 (16.8)	61 (18.0)	
Porcelain	12 (8.1)	21 (6.2)	
Chest wall deformity	3 (2.0)	7 (2.1)	1.00
Hostile mediastinum	13 (8.7)	23 (6.8)	.46

Data presented as mean ± standard deviation or n (%). Denominator was 489, unless otherwise indicated. *NYHA*, New York Heart Association; *STS-PROM*, Society of Thoracic Surgeons Predicted Risk of Mortality; *CKD*, chronic kidney disease; *PVD*, peripheral vascular disease; *TIA*, transient ischemic attack; *CABG*, coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation.

measures of disability before the procedure were common (Table 2). The rates of STS severe lung disease ($P < .05$), home oxygen use ($P = .04$), and disability using the Katz Activities of Daily Living ($P = .02$) were less for the patients enrolled in the Continued Access Study than for those enrolled in the Pivotal Trial.

Subclavian Approach

A total of 70 patients (46.7%) underwent THV implantation using the subclavian approach. The mean total procedure time was 67.3 ± 52.6 minutes (median, 54.0). The distribution of CoreValve valve sizes was 23 mm in 0.0%, 26 mm in 42.0%, 29 mm in 53.6%, and 31 mm in 4.3%. During the procedure, packed red blood cells were

TABLE 2. Comorbidities and frailty

Assessment	Pivotal (n = 150)	Continued access (n = 339)	P value
Comorbidities			
STS chronic lung disease			<.05
None	42 (28.0)	125 (36.9)	
Mild	27 (18.0)	59 (17.4)	
Moderate	22 (14.7)	62 (18.3)	
Severe	59 (39.3)	93 (27.4)	
Home oxygen use	66 (44.0)	116 (34.2)	.04
FEV1 < 1000 mL	51 (34.0)	93 (27.4)	.12
DLCO < 50%	60 (40.0)	Not performed	
Liver cirrhosis	1 (0.7)	6 (1.8)	.68
Connective tissue disease	3 (2.0)	14 (4.1)	.29
Immunosuppressive therapy	28 (18.7)	70 (20.6)	.71
Charlson comorbidity index	5.7 ± 2.2	5.6 ± 2.3	.96
None (score 0)	0 (0.0)	0 (0.0)	.27
Mild (score 1, 2)	9 (6.0)	13 (3.8)	
Moderate (score 3, 4)	39 (26.0)	108 (32.0)	
Severe (score 5)	102 (68.0)	217 (64.2)	
Frailty			
Anemia with transfusion	36 (24.7)	83 (25.5)	.91
BMI < 21 kg/m ²	22 (14.7)	55 (16.2)	.79
Albumin < 3.3 g/dL	25 (17.1)	65 (19.5)	.61
Unplanned weight loss	21 (14.0)	44 (13.0)	.77
Fall within past 6 mo	30 (20.0)	63 (18.6)	.71
5-m Gait speed >6 s	98 (81.7)	257 (89.2)	.05
Grip strength less than threshold	111 (75.0)	247 (74.4)	.91
Disabilities			
Living in assisted living facility	24 (16.0)	38 (11.2)	.14
ADLs			
Deficit ≥1 ADLs	42 (28.0)	61 (18.0)	.02
Deficit ≥2 ADLs	29 (19.3)	39 (11.5)	.02
Deficit ≥3 ADLs	15 (10.0)	27 (8.0)	.49
Dementia according to MMSE score			
None (≥25)	110 (73.8)	250 (74.0)	.49
Mild (21-24)	29 (19.5)	74 (21.9)	
Moderate (10-20)	10 (6.7)	13 (3.8)	
Severe (<10)	0 (0.0)	1 (0.3)	

STS, Society of Thoracic Surgeons; FEV1, forced expiratory volume in 1 second; DLCO, diffusion capacity of lung carbon monoxide; BMI, body mass index; ADLs, activities of daily living; MMSE, mini-mental state examination.

administered to 11.4% of the patients, and 1.4% received a transfusion of packed red blood cells of ≥ 4 U. Postimplantation balloon valvuloplasty was performed in 13.0% of the patients. No events of device migration or embolization occurred. None of the patients required emergency conversion to surgery because of coronary obstruction. None of the patients underwent a concomitant percutaneous coronary intervention. Two valves were implanted in 2.9% of the patients.

Direct Aortic Approach

Of the 150 patients, 80 (53.3%) underwent THV implantation using the direct aortic approach. The mean

TABLE 3. Clinical outcomes at 12 months in the Alternative Access Pivotal Study*

Outcome	Pivotal (n = 150)
Death from any cause or major stroke	59 (39.4)
Death	
From any cause	54 (36.0)
Cardiovascular	42 (28.8)
Stroke	18 (13.0)
Major	13 (9.1)
Minor	6 (4.7)
TIA	3 (2.3)
MACCE	62 (41.4)
Myocardial infarction	3 (2.1)
Periprocedural	2 (1.3)
Spontaneous	1 (0.7)
Reintervention	1 (1.0)
Major or life-threatening bleeding	96 (65.1)
Life-threatening or disabling	43 (29.4)
Major	60 (41.9)
Major vascular complications	14 (9.5)
Acute kidney injury	21 (14.2)
Permanent pacemaker placement†	30 (21.5)
Cardiogenic shock	9 (6.0)
Cardiac perforation	2 (1.3)
Device migration	0 (0.0)
Device embolization	0 (0.0)

Data presented as n (%). TIA, Transient ischemic attack; MACCE, major adverse cardiovascular and cerebrovascular events. *All percentages are Kaplan-Meier estimates at the specific point and thus do not equal the number of patients divided by the total number in the study group. †Patients with pacemaker or implantable cardioverter defibrillator at baseline included.

total procedure time was 54.6 ± 39.9 minutes (median, 40.5). The distribution of the CoreValve valve sizes was 23 mm in 11.4%, 26 mm in 40.5%, 29 mm in 45.6%, and 31 mm in 2.5%. During the procedure, packed red blood cells were administered to 35.0% of the patients, and 3.8% received a transfusion of packed red blood cells of ≥4 U. Postimplantation balloon valvuloplasty was performed in 13.9% of the patients. No episodes of device migration or embolization occurred, and no patient required implantation of >1 prosthesis. None of the patients developed coronary obstruction requiring emergency surgical bypass surgery. None of the patients underwent a concomitant percutaneous coronary intervention. None of the patients had 2 valves implanted.

Clinical Outcomes

By 30 days, the primary endpoint of death or major stroke had occurred in 23 patients (15.3%). Of the 23 patients, 17 (11.3%) had died and 11 (7.5%) had experienced major stroke (some patients experienced both). The clinical outcomes at 30 days in the Pivotal and Continued Access Studies are listed in Tables E3 and E4. The rates were slightly lower in the Continued Access Study, with death or major stroke in 40 patients (11.9%;

FIGURE 2. Changes in mean aortic valve gradient (blue) and mean effective orifice area (red) during the study period at each follow-up point.

32 [9.5%] died and 10 [3.0%] experienced major stroke; Table E3).

In the attempted implant population, the primary endpoint of the rate of all-cause mortality or major stroke at 12 months was 39.4%, with an upper 95% confidence interval of 47.2% (Figure E2; Table 3). The rate of all-cause mortality at 12 months was 36.0% and the rate of major stroke at 12 months was 9.1%. Permanent pacemaker implantation was required in 24 patients (16.4%) by 30 days and 30 patients (21.5%) by 1 year.

The NYHA class mean had improved significantly from baseline to the 12-month follow-up point ($\Delta -1.4 \pm 0.8$; $P < .0001$). At baseline, most patients (91.9%) were in NYHA class III or IV, and at each subsequent follow-up visit, most patients were in NYHA class I or II (Figure E3).

The echocardiographic data showed a baseline aortic valve area of $0.72 \pm 0.27 \text{ cm}^2$ and mean aortic valve gradient of $49.5 \pm 17.0 \text{ mm Hg}$. After CoreValve TAVR, the effective aortic valve area was $1.82 \pm 0.64 \text{ cm}^2$ at 1 month and $1.85 \pm 0.51 \text{ cm}^2$ at 12 months. The mean aortic valve gradient was $9.7 \pm 5.8 \text{ mm Hg}$ at 1 month and $9.5 \pm 5.7 \text{ mm Hg}$ at 12 months (Figure 2). The degree of paravalvular regurgitation decreased during the follow-up period, with no regurgitation present in 33.6% of patients immediately after TAVR and 47.6% at 1 year. Moderate to severe paravalvular leak was present in 7.0% at discharge and 2.4% at 1 year (Figure E4). Paired analysis showed that 85.7% of patients with moderate or severe paravalvular leak at discharge had improved by 12 months.

DISCUSSION

We studied alternative access approaches to TAVR using the CoreValve prosthesis to treat severe aortic stenosis in a cohort of patients who had not been studied previously. The patients had been deemed by a local interdisciplinary heart team and a national screening committee to be at extreme risk if undergoing conventional surgery. These decisions were determined using traditional surgical risk

assessment tools,¹⁸ such as the STS-PROM¹² or the logistic EuroSCORE,¹⁹ and also included subjective assessments that incorporated factors beyond those included in the STS-PROM and EuroSCORE predictive models. Unlike previous populations, the patients in present study (23.5%; 150 of the 639 “attempted patients” in the Pivotal Trial) also had peripheral vascular disease severe enough to prohibit placement of an 18F femoral sheath. We found that alternative access TAVR with the CoreValve prosthesis in this “no option” population was associated with an acceptable rate of death or major stroke at 12 months (39.4%). Implantation of this self-expanding aortic bioprosthesis also provided sustained improvement in the aortic valve effective orifice area, a reduction in the mean aortic valve gradient with low rates of aortic insufficiency, and an overall improvement in the NYHA functional class.

Mortality and Major Stroke

Within the present trial, no prespecified performance goal was identified, because no suitable standard was available to allow estimation of event rates in either treated or untreated patients. However, peripheral vascular disease has been shown in multiple studies to be an independent predictor of mortality in multiple studies of general populations, patients treated medically, and those undergoing surgery, with risk ratios as high as 4.1.²⁰ Thus, mortality in the Extreme Risk Pivotal Trial Alternative Access Arm might be expected to exceed the rates among patients undergoing femoral access TAVR. Within the PARTNER B trial, nonfemoral access was not allowed in patients who had been deemed inoperable. Transapical TAVR was permitted only in patients in the PARTNER A trial who were operable but with high surgical risk. Within the latter trial, the mortality rate 1 year after transapical TAVR was greater than that reported after transfemoral TAVR (29.0% vs 22.2%).² The 30-day mortality rate of 11.3% in our study was greater than the 5.0% reported in PARTNER Cohort B¹ or the 8.4% reported in the CoreValve Extreme Risk Trial Iliofemoral Arm⁴ (both of which required femoral access) but was comparable to the 30-day mortality rate of 10.6% in the PARTNER A high-risk transapical group²¹ and the 30-day mortality rate of 12.6% in inoperable patients who were treated with the alternative access and the SAPIEN valve (Lifesciences) in the Transcatheter Valve Therapy Registry.²² As expected, the rate of major stroke at 1 year of 9.1% was similar to the 7.8% rate reported in PARTNER Cohort B and comparable to the 10.8% reported in the PARTNER Cohort A transapical group.²¹ Taken in aggregate, these findings suggest strongly that the relatively high event rates were in large part likely to be a consequence of the advanced degree of illness in this patient group.

Aortic Regurgitation

The results of our study have demonstrated a relatively low rate of moderate or severe paravalvular aortic valve regurgitation (2.4%) 1 year after CoreValve THV placement. This rate was lower than those previously reported and most likely attributable to precise valve sizing according to the computed tomography assessment of the aortic annular diameter,^{23,24} more precise placement of the bioprosthesis within the aortic annulus using access routes shorter than those for the femoral approach, and the use of postdilatation when significant paravalvular regurgitation was noted during the procedure. The prevalence of moderate aortic regurgitation in our patients decreased during the follow-up period, suggesting ongoing remodeling of the annular–bioprosthesis interface with the self-expanding device.

Conduction System Disturbances

Conduction system disturbances can occur after CoreValve TAVR owing to the mechanical trauma applied by the inflow portion of the valve frame to the membranous septum in the region of the atrioventricular conduction system and left bundle branch.^{25,26} Accordingly, the need for a permanent pacemaker placement after CoreValve THV implantation has been reported to range from 25.8% to 33.0%.^{27,28} Although placement of a permanent pacemaker does not seem to affect late mortality,²⁹ we used “best practices” to reduce the occurrence of conduction disturbances during TAVR, including smaller predilatation balloons, valve sizing using computed tomography guidance, and higher positioning of the CoreValve THV, with avoidance of the conduction system.³⁰ In the present study, the rate of permanent pacemaker implantation was 16.4% at 30 days.

Subclavian Versus Direct Aortic Access

Subclavian access resulted in lower 30-day all-cause mortality rate than the direct aortic access (8.6% vs 13.7%) but a greater major stroke rate (8.6% vs 6.5%, respectively). The conduct of the trial in patients not suitable for femoral access was to move to subclavian access next and then direct aortic access, if subclavian access, was not considered feasible. Direct aortic access requires a more invasive approach than subclavian, and because it is the last approach to consider, these patients might also represent a different risk group.

Continued Access

We included data from patients enrolled in the Continued Access Study, who had been enrolled between the point of enrollment completion in the Pivotal Study and Food and Drug Administration approval of the CoreValve THV and who had ≥ 30 days of follow-up data to analyze. The

traditional patient characteristics were similar to those observed in the Pivotal Trial, but the patients treated in the Continued Access Study had lower rates of disabilities (Table 2). Coupled with a procedural learning curve, this might have contributed to the lower rates of 30-day mortality (9.5%) and major stroke (3.0%). In the nonrandomized continued access portion of the PARTNER A trial, similar observations included improvement in the transapical TAVR outcomes as site experience increased.²¹

Study Limitations

Although the present study is the first to describe the outcomes of a new technique in a hitherto unexplored population, it had several limitations. First, because of ethical concerns surrounding the futility of medical treatment for patients with symptomatic severe aortic stenosis, the study was performed without a medically managed control group. The novelty of the present population also made it impossible to determine a virtual event rate for a control group, which would have been required to establish a performance standard, such as was done in the CoreValve Extreme Risk US Pivotal Trial Iliofemoral Arm. Thus, although we consider it a reasonable assumption that treatment of these patients using noniliofemoral access is superior to medical therapy alone, the statement cannot be made with absolute certainty. However, some reassurance can be found in the observation by the PARTNER Cohort A investigators that in a lower risk group of patients, the 1-year outcomes after transapical TAVR were not different than those after surgical AVR. A second limitation was that the number of patients enrolled in the present study was inadequate to permit a reliable comparison between the subclavian and direct aortic approaches to TAVR.

CONCLUSIONS

The results of the present study have demonstrated that noniliofemoral alternative access for TAVR with the CoreValve prosthesis is technically feasible and associated with acceptable rates of death or major stroke, low rates of moderate or severe aortic insufficiency, and marked improvements in symptomatic status in patients with severe aortic stenosis who are at prohibitive risk of surgical AVR.

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Discussion

Dr Friedrich M. Mohr (Leipzig, Germany). Dr Reardon, thank you very much for this excellent presentation and also for providing the report in advance, which only had the 150 patients in writing compared with 338 patients right now in your talk, which is, of course, something I could not review in advance.

I will focus on the 150 patients in your report. In this analysis, you report the early and 1-year outcome of 150 patients with severe aortic stenosis and aortoiliac and femoral stenosis. All patients were treated using the transcatheter CoreValve system for aortic valve replacement through an alternative route, which was, in 70 times, the subclavian artery, or in 80 times, the direct aortic approach.

All patients could be treated successfully. In some of the patients, 2 valves were implanted. Perhaps you can expand on that, whether it was 1 patient who received 2, a valve-in-valve, or 2 patients. A number of 2.9 did not make any sense to me. This is question 1.

By 30 days, the primary endpoint of death and major stroke had occurred in 23 or 15% of the patients. You further reported that death occurred in 17 patients or 11.3%, and major stroke in 11 or 17.5%. If you sum the data, 11 and 17, this does not equal 23. This somehow does not fit together. So, I have a mathematical problem.

The reported stroke rates seem to be greater compared with those from other studies, such as the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry identified major access complications associated with high 30-day mortality and/or the German Aortic Valve Registry reporting on transapical access implanting other alternative valves compared with the CoreValve. Can you comment on that?

Finally, I congratulate you on the reported results in this high-risk population. Although, a control group is lacking, the published data from the past 10 years has proved the benefit of TAVR versus medical treatment. It would be interesting to randomly compare all alternative routes, including the transapical approach.

Dr Reardon. Thank you, Dr Mohr.

As far as the question about the SOURCE registry and GARY, of course, these are registries with self-reported data. In the CoreValve trial, we already knew that the Food and Drug Administration was keenly interested in stroke; thus, every patient in the CoreValve Pivotal Trial had a National Institutes of Health stroke scale assessment before treatment and a National Institutes of Health stroke scale assessment immediately after treatment. If any changes at all were found, the patient underwent a neurologic evaluation and imaging studies.

Thus, we actually studied the data a lot more than registries have tended to or that the PARTNER trial did because the study of the data was all retrospective. So, it was not surprising if we had a greater incidence of strokes, because if you look harder, you tend to find more.

Additionally, transapical access was not allowed in the nonoperable extreme risk patients in the PARTNER B trial, and most of the patients in the registries you mentioned were high- to intermediate-risk patients. These were not high-risk patients as you stated but extreme risk patients comparable to those in the PARTNER B trial.

I believe the 339 additional patients in the continued access group were included in the report, and I apologize for any confusion. The number of patients who required the use of 2 valves was 2.9% and included those with a valve-in-valve and those who had had the first valve removed and a second valve placed, ending with only 1 valve in place but 2 valves used.

The question about death or major stroke at 30 days occurring in 23 patients, death as an isolated event in 17 and major stroke as an isolated event in 11 does add up, because some patients experienced both major stroke and death. They were therefore counted individually in each the death and major stroke isolated categories but only once in the death or major stroke group, because this is an "or" statement.

Dr Mohr. Okay.

Dr Reardon. However, there are some differences, and, again, I think, 1 of the differences, when you try to compare our study to registries such as SOURCE or GARY or the France II or UK, is that this was really a single-arm longitudinal study that demands data input. It requires outside monitoring. It requires outside clinical events review. It demands outside core laboratories, and it fits all the criteria of a very strict Food and Drug Administration trial. So it does make it a unique way of looking at this.

Dr Mohr. Thank you.

FIGURE E1. 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.

FIGURE E3. New York Heart Association (NYHA) classification during the study period. Symptom status according to New York Heart Association class is shown at baseline and 30 days, 6 months, and 12 months for patients undergoing attempted transcatheter aortic valve replacement.

FIGURE E2. Cumulative event curve for all-cause mortality or major stroke. Event rates were calculated using the Kaplan-Meier method. Brackets indicate 95% confidence intervals.

FIGURE E4. Changes in paravalvular regurgitation during the study period. The percentage of patients by degree of paravalvular aortic regurgitation is shown at each follow-up interval. TAVR, Transcatheter aortic valve replacement.

ACD

TABLE E1. Participating investigational sites and personnel

Center	Location
Banner Good Samaritan	Phoenix, Ariz
Baylor Heart and Vascular Hospital	Dallas, Tex
Beth Israel Deaconess Medical Center	Boston, Mass
Cardiovascular Institute of the South	Houma, La
Detroit Medical Center Cardiovascular Institute	Detroit, Mich
Duke University Medical Center	Durham, NC
El Camino Hospital	Mountain View, Calif
Fletcher Allen Health Care	Burlington, Vt
Geisinger Medical Center	Danville, Pa
Hartford Hospital	Hartford, Conn
Inova Fairfax Hospital, Inova Heart and Vascular Institute	Falls Church, Va
Iowa Heart Center	Des Moines, Iowa
Kaiser Permanente Los Angeles Medical Center	Los Angeles, Calif
Lenox Hill Hospital	New York, NY
Loyola University Medical Center	Maywood, Ill
Morristown Memorial Hospital	Morristown, NJ
Mount Sinai Medical Center	Miami Beach, Fla
New York University/Langone Medical Center	New York, NY
North Shore University Hospital	Manhasset, NY
Piedmont Heart Institute	Atlanta, Ga
Pinnacle Health	Harrisburg, Pa
Providence Sacred Heart Medical Center	Spokane, Wash
Riverside Methodist Hospital/Ohio Health Research Institute	Columbus, Ohio
Saint Joseph's Hospital of Atlanta	Atlanta, Ga
Spectrum Health Hospitals	Grand Rapids, Mich
St Francis Hospital	Roslyn, NY
St John Hospital and Medical Center	Detroit, Mich
St Luke's Medical Center, Aurora Health Center	Milwaukee, Wis
St Vincent Heart Center of Indiana	Indianapolis, Ind
Texas Heart Institute, St Luke's Episcopal Hospital/Baylor College of Medicine	Houston, Tex
Houston-Methodist-DeBakey Heart and Vascular Center/Methodist Hospital	Houston, Tex
Johns Hopkins University Hospital	Baltimore, Md
Mount Sinai Medical Center	New York, NY
Ohio State University Medical Center, The Richard M. Ross Heart Hospital	Columbus, Ohio
University Hospitals/Case Medical Center	Cleveland, Ohio
University of Kansas Hospital	Kansas City, Kan
University of Miami Health System	Miami, Fla
University of Michigan Health System	Ann Arbor, Mich
University of Pittsburgh Medical Center	Pittsburgh, Pa
University of Southern California, University Hospital	Los Angeles, Calif
Veterans Affairs Palo Alto Health Care System	Palo Alto, Calif
Vanderbilt University Medical Center	Nashville, Tenn
Wake Forest University Baptist Medical Center	Winston-Salem, NC
Washington Hospital Center, Georgetown Hospital	Washington, DC
Yale New Haven Hospital, Yale University School of Medicine	New Haven, Conn

TABLE E2. CoreValve US Pivotal Study organization

Steering committee	<p>Jeffrey Popma (co-chair), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Mass; Thomas Armitage (co-chair), Structural Heart, Medtronic, Inc, Mounds View, Minn</p> <p>Cardiac surgeons: David Adams, Mount Sinai Medical Center, New York, NY; John Byrne, Vanderbilt University School of Medicine, Nashville, Tenn; Joseph Coselli, Texas Heart Institute, Houston, Tex; Tom Gleason, University of Pittsburgh Medical Center, Pittsburgh, Pa; G. Michael Deeb, University of Michigan, Ann Arbor, Mich; Michael Reardon, Houston-Methodist-DeBakey Heart and Vascular Center, Houston, Tex</p> <p>Interventional cardiologists: William Anderson, University of Pittsburgh Medical Center, Pittsburgh, Pa; James Hermiller, St Vincent Heart Center of Indiana, Indianapolis, Ind; Steven Yakubov, Riverside Methodist Hospital/Ohio Health Research Institute, Columbus, Ohio; Maurice Buchbinder, Veterans Affairs Palo Alto Health Care System, San Diego, Calif</p> <p>Consultants: Patrick Serruys, Thoraxcenter, Erasmus University, Rotterdam, The Netherlands; Blasé Carabello, Baylor College of Medicine, Houston, Tex</p>
Screening committee	<p>Cardiac surgeons: David H. Adams, Mount Sinai Medical Center, New York, NY; John Byrne, Vanderbilt University, Nashville, Tenn; Thomas G. Gleason, University of Pittsburgh Medical Center, Pittsburgh, Pa; G. Michael Deeb, University of Michigan, Ann Arbor, Mich; Michael Reardon, Houston-Methodist-DeBakey Heart and Vascular Center, Houston, Tex (chair); John Conte, Johns Hopkins Medical Center, Baltimore, Md</p> <p>Interventional cardiologists: Steven Yakubov, Riverside Methodist Hospital/Ohio Health Research Institute, Columbus, Ohio; Jeffrey J. Popma, Beth Israel Deaconess Medical Center, Boston, Mass</p>
Site monitoring	Global Clinical Operations, Medtronic, Inc, Mounds View, Minn
Electronic database	Oracle Clinical, Oracle Corporation, Redwood Shores, Calif
Data management	Global Clinical Operations, Medtronic, Inc, Mounds View, Minn
Biostatistics	Structural Heart, Medtronic, Inc, Mounds View, Minn; Harvard Clinical Research Institute, Boston, Mass
Data safety monitoring board	<p>David Faxon (chair, IC), Brigham and Women's Hospital, Boston, Mass; William Holman (CS), Birmingham, Ala; John Orav (biostatistics), Brigham and Women's Hospital, Boston, Mass; Scott E. Kasner (neurologist), Hospital of the University of Pennsylvania; John J. Lopex (IC), Loyola University, Maywood, Ill</p>
Safety officer	Tom Vassiliades, Jr, Office of Medical Affairs, Structural Heart, Medtronic, Inc, Mounds View, Minn
Clinical events committee	<p>Cardiac or vascular surgeons (CS): Ed Gravereaux, Brigham and Women's Hospital, Boston, Mass; Roberto Rodriguez, Caritas St Elizabeth Medical Center, Brighton, Mass; Sanjay Samy, Guthrie Clinic, Sayre, Pa</p> <p>Interventional cardiologists (IC): Cliff Berger, Boston Medical Center, Boston, Mass; Donald Cutlip, Beth Israel Deaconess Medical Center, Boston, Mass; Carey Kimmelstiel, New England Medical Center, Boston, Mass; Sergio Waxman, Lahey Medical Center, Burlington, Mass</p> <p>Neurologists: John Dashe, New England Medical Center, Boston, Mass; David Thaler, Lahey Medical Center, Burlington, Mass</p> <p>Heart failure specialist: David DeNofrio, New England Medical Center, Boston, Mass</p>
Echocardiography core laboratory	Jae K. Oh, Mayo Echocardiography Core Laboratory, Rochester, Minn
ECG core laboratory	Peter Zimetbaum, Harvard Clinical Research Institute, Boston, Mass
Economic and quality of life core laboratory	David Cohen, Mid-America Medical Center, Kansas City, Mo; Matthew Reynolds, Harvard Clinical Research Institute, Boston, Mass
Global proctors	<p>Raoul Bonan, Montreal, Quebec, Canada; Stephen Brecker, St George's Hospital, London, UK; Haim Danenberg, Hadassah Hebrew University, Jerusalem, Israel; Eberhard Grube, Heart Center Siegburg, Germany; Anders Jonsson, Karolinska, Stockholm, Sweden; Iassen Michev, New York, NY; Jean-Claude Laborde, Clinique Pasteur, Toulouse, France</p>

ECG, Electrocardiography; IC, interventional cardiologist; CS, cardiac or vascular surgeon.

TABLE E3. Clinical outcomes at 30 days*

Outcome	Pivotal (n = 150)	Continued access (n = 339)	P value
Death from any cause or major stroke	23 (15.3)	40 (11.9)	.28
Death			
From any cause	17 (11.3)	32 (9.5)	.55
Cardiovascular	17 (11.3)	32 (9.5)	.55
Stroke	13 (8.8)	18 (5.4)	.16
Major	11 (7.5)	10 (3.0)	.03
Minor	3 (2.1)	8 (2.4)	.79
TIA	2 (1.4)	1 (0.3)	.18
MACCE	26 (17.3)	52 (15.4)	.60
Myocardial infarction	3 (2.1)	4 (1.2)	.48
Periprocedural	2 (1.3)	4 (1.2)	.89
Spontaneous	1 (0.7)	0 (0.0)	.13
Reintervention	0 (0.0)	2 (0.6)	.35
Major or life-threatening bleeding	87 (58.3)	184 (54.4)	.51
Life-threatening or disabling	36 (24.2)	80 (23.7)	.95
Major	55 (37.1)	110 (32.7)	.37
Major vascular complications	13 (8.7)	14 (4.2)	.04
Permanent pacemaker placement†	24 (16.4)	60 (18.2)	.64
Acute kidney injury	21 (14.2)	48 (14.5)	.89
Cardiogenic shock	9 (6.0)	21 (6.2)	.93
Cardiac perforation	2 (1.3)	7 (2.1)	.58

TIA, Transient ischemic attack; MACCE, major adverse cardiovascular and cerebrovascular events. *All percentages presented as Kaplan-Meier estimates at the specific point and thus do not equal the number of patients divided by the total number in the study group. †Patients with pacemaker or implantable cardioverter defibrillator at baseline were included.

TABLE E4. Clinical outcomes at 30 days*

Outcome	Subclavian			Direct aortic		
	Pivotal (n = 70)	Continued access (n = 76)	P value	Pivotal (n = 80)	Continued access (n = 260)	P value
Death from any cause or major stroke	10 (14.3)	5 (6.8)	.13	13 (16.2)	34 (13.1)	.5
Death						
From any cause	6 (8.6)	3 (4.2)	.25	11 (13.7)	28 (10.8)	.5
Cardiovascular	6 (8.6)	3 (4.2)	.25	11 (13.7)	28 (10.8)	.5
Stroke	6 (8.6)	6 (7.9)	.85	7 (9.1)	12 (4.7)	.17
Major	6 (8.6)	3 (3.9)	.24	5 (6.5)	7 (2.7)	.14
Minor	1 (1.5)	3 (3.9)	.36	2 (2.5)	5 (2.0)	.76
TIA	1 (1.5)	0 (0.0)	.29	1 (1.3)	1 (0.4)	.38
MACCE	10 (14.3)	9 (12.1)	.67	16 (20.0)	42 (16.2)	.45
Myocardial infarction	1 (1.4)	1 (1.3)	.95	2 (2.6)	3 (1.2)	.38
Periprocedural	1 (1.4)	1 (1.3)	.95	1 (1.2)	3 (1.2)	.94
Spontaneous	0 (0.0)	0 (0.0)	NA	1 (1.4)	0 (0.0)	.07
Reintervention	0 (0.0)	1 (1.3)	.34	0 (0.0)	1 (0.4)	.58
Major or life-threatening bleeding	31 (44.6)	23 (30.3)	.09	56 (70.3)	161 (62.1)	.20
Life-threatening or disabling	7 (10.2)	8 (10.5)	.91	29 (36.4)	72 (27.8)	.15
Major	27 (39.2)	15 (19.8)	.01	28 (35.3)	95 (36.9)	.82
Major vascular complications	10 (14.3)	6 (7.9)	.22	3 (3.8)	8 (3.1)	.78
Acute kidney injury	6 (8.7)	3 (3.9)	.25	15 (19.0)	45 (17.7)	.83
Permanent pacemaker placement†	8 (11.8)	18 (23.7)	.06	16 (20.6)	42 (16.7)	.42
Cardiogenic shock	3 (4.3)	2 (2.6)	.58	6 (7.5)	19 (7.3)	.95
Cardiac perforation	1 (1.4)	2 (2.6)	.61	1 (1.2)	5 (1.9)	.69
Device migration	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Device embolization	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA

Data presented as n (%). Three patients in the attempted implant cohort of Continued Access Study Alternative Access Arm had procedures aborted before attempting access through a subclavian or direct aortic route and their data were not included. *TIA*, Transient ischemic attack; *MACCE*, major adverse cardiovascular and cerebrovascular events; *NA*, not applicable. *All percentages presented as Kaplan-Meier estimates at the specific point and thus do not equal the number of patients divided by the total number in the study group. †Patients with a pacemaker or implantable cardioverter defibrillator at baseline were included.

TABLE E5. Major clinical event definitions**Death***

All-cause death

All deaths from any cause after valve intervention (including all cardiovascular and noncardiovascular deaths)

Cardiovascular death

Any death from proximate cardiac cause (eg, MI, cardiac tamponade, worsening heart failure)

Unwitnessed death and death of unknown cause

All procedure-related deaths, including those related to a complication of the procedure or treatment of a complication of the procedure

Death caused by noncoronary vascular conditions (eg, cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease)

All deaths within 30 d of procedure

Noncardiovascular death

Any death not covered by the above definitions (eg, death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma)

Valve-related death

Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis

Death related to reintervention on the operated valve

Stroke*

Neurologic events were defined as

Rapid onset of a focal or global neurologic deficit with ≥ 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, Amaurosis fugax, or other neurologic signs or symptoms consistent with stroke

Duration of a focal or global neurologic deficit ≥ 24 h; OR <24 h, if therapeutic interventions were performed (eg, thrombolytic therapy or intracranial angioplasty); OR available neuroimaging studies documenting a new hemorrhage or infarct; OR the neurologic deficit resulted in death

No other readily identifiable nonstroke cause for the clinical presentations (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacologic influence)*

Confirmation of the diagnosis by ≥ 1 of the following:

Neurology or neurosurgical specialist

Neuroimaging procedure (MRI or CT or cerebral angiography)

Lumbar puncture (spinal fluid analysis diagnostic of intracranial hemorrhage)

Stroke definitions

Transient ischemia attack

A new focal neurologic deficit with rapid symptom resolution (usually 1-2 h) and always within 24 h

Neuroimaging without tissue injury

Stroke (diagnosed as above, preferably with positive neuroimaging findings)

Minor: modified Rankin < 2 at 30 and 90 d

Major: modified Rankin ≥ 2 at 30 and 90 d†

Myocardial infarction*Periprocedural MI (≤ 72 h after the index procedure)

New ischemic symptoms (eg, chest pain or shortness of breath) or new ischemic signs (eg, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes [elevation > 1 mm or depression > 1 mm in ≥ 2 contiguous leads], hemodynamic instability; or imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND

Elevated cardiac biomarker evidence (preferably creatinine kinase-MB) within 72 h after the index procedure, consisting of ≥ 2 postprocedure samples 6-8 h apart with a 20% increase in the second sample and a peak value > 10 times the 99th percentile URL or a peak value > 5 times the 99th percentile URL and with new pathologic Q waves in ≥ 2 contiguous leads

Spontaneous MI (> 72 h after the index procedure), including any of the following

Detection of increase and/or decrease in cardiac biomarkers (preferably troponin) with ≥ 1 value greater than the 99th percentile URL, together with evidence of myocardial ischemia with ≥ 1 of the following

ECG changes indicative of new ischemia (new ST-T changes or new LBBB)

New pathologic Q waves in ≥ 2 contiguous leads

Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or before the appearance of cardiac biomarkers in the blood

Pathologic findings of acute MI

(Continued)

TABLE E5. Continued

Bleeding events*
Life-threatening or disabling bleeding
Fatal bleeding OR
Bleeding in a critical area or organ (eg, intracranial, intraspinal, intraocular, or pericardial, necessitating pericardiocentesis, or intramuscular with compartment syndrome) OR
Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR
Overt source of bleeding with decrease in hemoglobin of ≥ 5 g/dL or whole blood or packed RBC transfusion of ≥ 4 U
Major bleeding
Overt bleeding associated with a decrease in hemoglobin level of ≥ 3.0 g/dL or requiring transfusion of 2 or 3 U of whole blood RBCs AND not meeting criteria for life-threatening or disabling bleeding
Major vascular complications*
Any thoracic aortic dissection
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to death, need for significant blood transfusions (≥ 4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (eg, hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment)
Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage
Device success*
Successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system
Correct position of the device in the proper anatomic location (placement in the annulus with no impedance on device function)
Intended performance of the prosthetic heart valve (aortic valve area ≥ 1.2 cm ² for 26-, 29-, and 31-mm valves or ≥ 0.9 cm ² for 23-mm valves) and mean aortic valve gradient < 20 mm Hg or peak velocity < 3 m/s without moderate or severe prosthetic valve aortic regurgitation
Only 1 valve implanted in the proper anatomic location

MI, Myocardial infarction; MRI, magnetic resonance imaging; CT, computed tomography; URL, upper reference limit; ECG, electrocardiographic; LBBB, left bundle branch block; RBC, red blood cell. *Adapted from Leon and colleagues.¹⁷ †Discrepancies between the modified Rankin score at 90 d were adjudicated by the Clinical Events Committee.