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Stratification of Outcomes After Transcatheter Aortic Valve Replacement According to Surgical Inoperability for Technical Versus Clinical Reasons

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Objectives The goal of this study was to examine the impact of reasons for surgical inoperability on outcomes in patients undergoing transcatheter aortic valve replacement (TAVR).

Background Patients with severe aortic stenosis may be deemed inoperable due to technical or clinical reasons. The relative impact of each designation on early and late outcomes after TAVR is unclear.

Methods Patients were studied from the inoperable arm (cohort B) of the randomized PARTNER (Placement of Aortic Transcatheter Valve) trial and the nonrandomized continued access registry. Patients were classified according to whether they were classified as technically inoperable (TI) or clinically inoperable (CLI). Reasons for TI included porcelain aorta, previous mediastinal radiation, chest wall deformity, and potential for injury to previous bypass graft on sternal re-entry. Reasons for CLI were systemic factors that were deemed to make survival unlikely.

Results Of the 369 patients, 23.0% were considered inoperable for technical reasons alone; the remaining were judged to be CLI. For TI, the most common cause was a porcelain aorta (42%); for CLI, it was multiple comorbidities (48%) and frailty (31%). Quality of life and 2-year mortality were significantly better among TI patients compared with CLI patients (mortality 23.3% vs. 43.8%; $p < 0.001$). Nonetheless, TAVR led to substantial survival benefits compared with standard therapy in both inoperable cohorts.

Conclusions Patients undergoing TAVR based solely on TI have better survival and quality of life improvements than those who are inoperable due to clinical comorbidities. Both TI and CLI TAVR have significant survival benefit in the context of standard therapy. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894) (J Am Coll Cardiol 2014;63:901–11) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AS = aortic stenosis
BMI = body mass index
CI = confidence interval
CLI = clinically inoperable
COPD = chronic obstructive pulmonary disease
HR = hazard ratio
NYHA = New York Heart Association
QOL = quality of life
SAVR = surgical aortic valve replacement
SF-12 = Medical Outcomes Study Short-Form 12-item Health Survey
ST = standard therapy
STS = Society of Thoracic Surgeons
TI = technically inoperable

The U.S. PARTNER (Placement of Aortic Transcatheter Valve) trial (cohort B) was a randomized trial of patients with severe aortic stenosis (AS) who could not have surgery (1,2). The trial demonstrated a significant survival benefit with transcatheter aortic valve replacement (TAVR). However, the mortality at 1 and 2 years, although substantially lower than the standard therapy (ST) arm, remained high (at 30.7% and 43.3%, respectively), reflecting the substantial burden of comorbidities present in this cohort.

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Patients can be deemed inoperable for surgical aortic valve replacement (SAVR) based on clinical comorbidities, frailty, or specific technical contraindications such as porcelain aorta, mediastinal radiation, chest deformities, or the presence of coronary bypass grafts attached to the chest wall. A substantial variability in late survival of inoperable patients was observed according to surgical risk factors in the 2-year analysis of the randomized PARTNER cohort B (2). Clinical outcomes may differ according to the reason for inoperability. We sought to analyze outcomes of inoperable patients enrolled in the PARTNER cohort B randomized study and accompanying continued access registry according to factors that influenced the decision of inoperability.

Methods

Study design and patients. PARTNER 1B was a multicenter, randomized study among patients with severe AS (aortic valve area <0.8 cm^2), with cardiac symptoms (New York Heart Association [NYHA] class II or higher) who were considered inoperable, either for clinical or technical reasons. An as-treated analysis was performed, including both patients randomized to and treated with TAVR in the PARTNER 1B trial and patients subsequently treated in the continued access registry. The PARTNER multicenter continued access registry was a U.S. Food and Drug Administration–approved registry that continued after completion of the randomized trial and had a single arm of treatment (TAVR). Patients enrolled in this part of the study had the same entry criteria as for the randomized trial. The entry criteria were stringent, requiring attestation by 2 cardiac surgeons and an interventional cardiologist regarding surgical inoperability, defined as a $\geq$50% probability of either death or serious irreversible morbidity after conventional SAVR. Moreover, this classification of inoperability required approval by a central steering committee after a Web-based presentation by a cardiac surgeon on a weekly conference call as to the specific reasons for the declaration of inoperability. This inoperability was further subclassified as technical or clinical through a retrospective review of individual patient data. Patients were classified as technically inoperable (TI) if they had anatomic factors that make the procedural steps of SAVR either technically impossible or dangerous.

Those patients who were considered to be inoperable either for clinical reasons or due to a combination of clinical and technical reasons were defined as clinically inoperable (CLI). The Society of Thoracic Surgeons (STS) risk score was used as a measure of clinical risk and comorbidities, stratifying groups according to STS categories (<5%, 5% to 14.9%, and $\geq$15%), broadly defining clinical risk for surgery as low, intermediate to high, and very high, respectively (2). Both technical reasons (porcelain aorta, previous bypass graft beneath the sternum, and chest wall deformity) and some clinical factors (frailty) for inoperability are not captured by the STS risk algorithm. The logistic euroSCORE (European System for Cardiac Operative Risk Evaluation) was also calculated as a measure of clinical risk for surgery, although specific cut-offs were not defined for categorical groups.

Procedure. The Edwards Sapien heart valve system (Edwards Lifesciences Corporation, Irvine, California) used in this study comprised a balloon-expandable, stainless steel stent frame housing a tri-leaflet bovine pericardial valve. The system was mounted on a deflectable delivery catheter and inserted via the common femoral artery under aseptic conditions as described previously (1).

Analysis according to technical inoperability and clinical risk. Baseline and procedural characteristics as well as clinical endpoints were studied according to both the dichotomy of technical versus clinical inoperability and the aforementioned STS score trichotomy. Thirty-day clinical outcomes and late outcomes beyond 1 year were studied. The key endpoints for this analysis were all-cause mortality, cardiovascular mortality, stroke, and repeat hospitalization. Repeat hospitalization was defined as rehospitalization for symptoms

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Table 1 Baseline Variables According to Inoperable Category and STS Score

	Technically Inoperable (n = 85)	Clinically Inoperable (n = 284)	p Value	STS <5% (n = 74)	STS ≥5%/<15% (n = 222)	STS ≥15% (n = 73)	p Value
Age (yrs)	73.4 ± 10.0 (84)	83.6 ± 8.6 (284)	<0.0001	71.0 ± 10.4 (74)	82.5 ± 7.8 (221)	88.4 ± 5.6 (73)	<0.0001
Male	57.6 (49/85)	47.5 (135/284)	0.1	58.1 (43/74)	49.1 (109/222)	43.8 (32/73)	0.21
BMI (kg/m^2)	28.6 ± 6.6 (85)	26.6 ± 7.2 (284)	0.005	29.9 ± 6.5 (74)	26.8 ± 7.4 (222)	25.0 ± 6.1 (73)	<0.0001
STS score	5.4 ± 2.9 (85)	12.0 ± 5.8 (284)	<0.0001	3.3 ± 1.1 (74)	9.8 ± 2.6 (222)	19.7 ± 4.1 (73)	<0.0001
Logistic euroSCORE	14.5 ± 12.0 (84)	26.9 ± 17.2 (279)	<0.0001	9.4 ± 8.5 (73)	24.5 ± 14.2 (218)	37.6 ± 19.1 (72)	<0.0001
Diabetes	28.2 (24/85)	35.9 (102/284)	0.19	27.0 (20/74)	32.4 (72/222)	46.6 (34/73)	0.03
Hypertension	81.2 (69/85)	86.9 (246/283)	0.19	75.7 (56/74)	87.8 (194/221)	89.0 (65/73)	0.02
NYHA class III and IV	84.7 (72/85)	96.5 (274/284)	<0.0001	86.5 (64/74)	94.6 (210/222)	98.6 (72/73)	0.007
Previous PCI	40.0 (34/85)	27.1 (77/284)	0.02	33.8 (25/74)	29.3 (65/222)	28.8 (21/73)	0.74
Previous CABG	37.6 (32/85)	31.4 (89/283)	0.29	20.3 (15/74)	35.7 (79/221)	37.0 (27/73)	0.03
CVD	21.4 (18/84)	26.0 (72/277)	0.4	23.3 (17/73)	24.4 (53/217)	28.2 (20/71)	0.77
PVD	15.7 (13/83)	28.9 (81/280)	0.02	10.8 (8/74)	28.1 (61/217)	34.7 (25/72)	0.002
PHT	34.2 (26/76)	41.2 (96/233)	0.28	28.8 (19/66)	41.0 (77/188)	47.3 (26/55)	0.09
Renal disease*	9.4 (8/85)	19.7 (56/284)	0.03	5.4 (4/74)	13.1 (29/222)	42.5 (31/73)	<0.0001
Malignant tumors	43.5 (37/85)	26.4 (74/280)	0.003	44.6 (33/74)	25.1 (55/219)	31.9 (23/72)	0.007
Liver disease	1.2 (1/85)	4.9 (14/283)	0.21	6.8 (5/74)	3.6 (8/222)	2.8 (2/72)	0.41
COPD	25.9 (22/85)	50.4 (143/284)	<0.0001	37.8 (28/74)	45.5 (101/222)	49.3 (36/73)	0.35
Anemia	43.5 (37/85)	71.0 (201/283)	<0.0001	51.4 (38/74)	62.9 (139/221)	83.6 (61/73)	0.0002

Values are mean ± SD (n) or % (n/N). *Creatinine ≥2 mg/dl.

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; euroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PHT = pulmonary hypertension; PVD = peripheral vascular disease; STS = Society of Thoracic Surgeons.

of AS and/or complications of the valve procedure. These endpoints for TI and CLI patients were placed in context through a comparison with patients recruited in the PARTNER 1B study receiving ST by using an as-treated analysis.

Quality of life assessment. Health status, which includes symptoms, functional status, and quality of life (QOL), was evaluated with standardized written questionnaires pre-procedure and at 1, 6, and 12 months post-procedure (3). Follow-up questionnaires were administered during in-person visits to the enrolling centers or by mail. Disease-specific health status was assessed from the patient's perspective by using the Kansas City Cardiomyopathy Questionnaire (4), and generic health status was evaluated with the Medical Outcomes Study Short-Form 12-Item Health Survey (SF-12) (5). Other details of the QOL analyses performed have been described previously (3).

Statistical analysis. Categorical variables, presented as frequencies with their respective percentages, were compared by using the Fisher exact test. Continuous variables, presented as mean ± SD, were compared by using the Student *t* test. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data with the use of Kaplan-Meier estimates and were compared by using the log-rank test. Patients were censored according to the time of their last known follow-up. A 2-sided alpha level of 0.05 was used for superiority testing. Given the as-treated analysis, the start date for TAVR patients was the date of the procedure; for ST patients, it was the date of randomization.

A multivariable analysis for 2-year mortality in the TAVR patients was performed by using a Cox regression model with forward stepwise analysis. The multivariable analysis incorporated baseline clinical variables related to 2-year mortality with a significance level of $p \leq 0.1$; this included randomized study versus continued access, age, body mass index (BMI), chronic obstructive pulmonary disease (COPD), major arrhythmia, NYHA class III and IV, angina, anemia, peripheral vascular disease, porcelain aorta, aortic valve mean gradient at baseline, TI, and STS risk score (as a continuous variable). QOL analyses, comparing the TI and CLI TAVR groups, were performed by using an analysis of covariance to adjust for baseline differences between groups. All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Table 2 Comparison of Baseline QOL Scores According to Inoperability Category

	Raw Mean Value		
	Technical	Clinical	p Value
KCCQ			
Summary	45.18 ± 20.99	35.12 ± 19.85	<0.001
Physical limitations	49.86 ± 24.71	30.55 ± 24.04	<0.001
Total symptoms	56.92 ± 21.34	47.35 ± 22.09	<0.001
Self-efficacy	81.85 ± 19.73	76.78 ± 22.43	0.064
QOL	35.61 ± 19.46	33.18 ± 21.29	0.35
Social limitation	38.59 ± 30.51	28.15 ± 26.32	0.003
SF-12			
Physical	30.60 ± 8.01	28.57 ± 7.16	0.033
Mental	48.46 ± 10.32	44.44 ± 11.77	0.006

Values are mean ± SD.
KCCQ = Kansas City Cardiomyopathy Questionnaire; QOL = quality of life; SF-12 = Medical Outcomes Study Short-Form 12-Item Health Survey.

Results

Patients and baseline characteristics. A total of 369 patients were treated with TAVR, including 175 from the randomized study and 194 from the continued access registry. Among these, 85 patients (23.0%) were not operated on for technical reasons alone and 284 (77.0%) were CLI; 34 of the

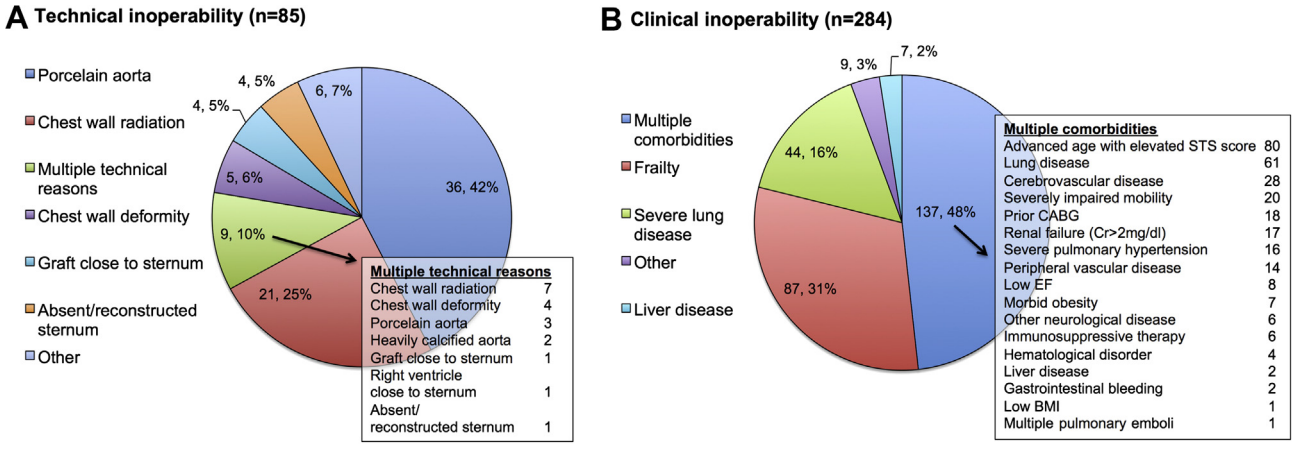

Figure 1 Technical and Clinical Causes of Inoperability

The underlying reasons are shown in pie chart format for **(A)** technical inoperability and **(B)** clinical inoperability. Those with multiple technical or clinical reasons have a hierarchical breakdown represented (inset box for A and B, respectively). BMI = body mass index; CABG = coronary artery bypass grafting; Cr = creatinine; EF = ejection fraction; STS = Society of Thoracic Surgeons.

Table 3 Periprocedural Variables According to Inoperable Category and STS Score

	Technically Inoperable (n = 85)	Clinically Inoperable (n = 284)	p Value	STS <5% (n = 74)	STS ≥5%/<15% (n = 222)	STS ≥15% (n = 73)	p Value
Device success	75.9 (63/83)	78.1 (214/274)	0.67	80.8 (59/73)	75.8 (163/215)	79.7 (55/69)	0.6
Procedure success	70.6 (60/85)	69.4 (197/284)	0.83	74.3 (55/74)	69.4 (154/222)	65.8 (48/73)	0.52
Valve size							
23 mm	48.8 (40/82)	58.5 (162/277)	0.12	43.7 (31/71)	58.8 (127/216)	61.1 (44/72)	0.054
26 mm	51.2 (42/82)	41.5 (115/277)		56.3 (40/71)	41.2 (89/216)	38.9 (28/72)	
Hemodynamic support (CPB or IABP)	1.2 (1/85)	3.2 (9/284)	0.46	0.0 (0/74)	3.2 (7/222)	4.1 (3/73)	0.25
Conversion to open heart surgery	1.2 (1/85)	1.1 (3/284)	>0.9	1.4 (1/74)	1.4 (3/222)	0.0 (0/73)	0.61
Volume of contrast media	144 ± 101 (82)	131 ± 79 (275)	0.31	134 ± 90 (72)	130 ± 75 (214)	143 ± 104 (71)	0.88
Total procedure time (skin-to-skin) (min)	130 ± 72 (85)	140 ± 78 (283)	0.28	124 ± 71 (74)	142 ± 82 (221)	139 ± 66 (73)	0.08
Days in hospital postprocedure	5.3 ± 2.2 (68)	5.9 ± 2.0 (189)	0.04	5.2 ± 2.0 (56)	5.9 ± 2.1 (158)	5.7 ± 1.9 (43)	0.04

Values are % (n/N) or mean ± SD (n).
CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; other abbreviation as in Table 1.

latter were inoperable for a combination of clinical and technical reasons. A total of 181 patients received ST.

When stratified according to STS score, 74 (20.0%), 222 (60.2%), and 73 (19.8%) had STS scores <5%, 5% to 14.9%, and ≥15%, respectively. For CLI, 32 (11.3%), 179 (63.0%), and 73 (25.7%) had STS scores <5%, 5% to 14.9%, and ≥15%. In the TI group, 42 (49.4%) and 43 (50.6%) had STS scores <5% and 5% to 14.9%, respectively; no TI patients had STS scores ≥15%.

A total of 366 patients (99.2%) completed clinical follow-up to 1 year and 347 (94.0%) to 2 years. Patients not operated on for technical reasons alone, compared with patients not operated on for other (clinical) reasons, were younger, were less likely to be in NYHA class III or IV, and had lower STS scores and logistic euroSCORE findings (Table 1). They were more likely to have higher BMI values and a history of previous malignancy and previous percutaneous coronary intervention and less likely to have peripheral vascular disease, chronic kidney disease, COPD, and anemia. The excess of malignancy in the TI versus the CLI group (43.5% vs. 26.4%) was commensurate with the 25% of TI patients who were inoperable for a "hostile chest" related to previous chest wall radiation. TI patients had better QOL scores at baseline than CLI patients (Table 2). Considering the entire TAVR cohort, patients with lower STS risk scores were younger, had higher BMI values, and were less likely to be diabetic, hypertensive, and in NYHA class III or IV (Table 1). They had less peripheral vascular disease, previous coronary artery bypass grafting, renal disease, and anemia.

Underlying reasons for technical and clinical inoperability. Site-reported underlying technical causes for inoperability included porcelain aorta, defined as near or complete circumferential calcification of the ascending aorta and/or aortic arch precluding safe cross-clamping or cannulation of the aorta or requiring circulatory arrest with ascending aorta/arch replacement. Other reasons included chest wall radiation, chest wall deformity, bypass grafts close to the sternum creating a potentially hostile re-entry, an absent or reconstructed sternum (Fig. 1), and other causes, including mediastinal adhesions (1 after 3 previous cardiac surgeries and 2 on aborted SAVR), a right ventricle adherent to the sternum, a case with recurrent fungal mediastinitis requiring multiple sternotomies after previous cardiac surgery, a case with a previous pneumonectomy and severely distorted mediastinal/thoracic anatomy, or a combination of the aforementioned factors ("multiple technical reasons" [further detailed in Fig. 1]). Underlying clinical causes of inoperability were multiple comorbidities, frailty, severe lung disease, and others (including poor left and right ventricular function, neurological disease, and pulmonary hypertension).

Clinical outcomes. The duration of postprocedure hospital stay was marginally shorter in TI patients versus CLI patients undergoing TAVR (5.34 ± 2.18 days vs. 5.86 ± 1.97 days; p = 0.04). There were no other significant

Table 4 30-Day Outcomes (Kaplan-Meier Analysis) According to Inoperability Category and STS Score

	Technically Inoperable (n = 85)	Clinically Inoperable (n = 284)	p Value	STS <5% (n = 74)	STS ≥5%/<15% (n = 222)	STS ≥15% (n = 73)	p Value Across Groups
Death							
From any cause	4.7% (4)	8.8% (25)	0.22	4.1% (3)	7.2% (16)	13.7% (10)	0.076
From cardiovascular cause	3.6% (3)	7.8% (22)	0.18	1.4% (1)	7.2% (16)	11.0% (8)	0.063
Repeat hospitalization	6.0% (5)	8.3% (22)	0.54	4.1% (3)	7.1% (15)	13.9% (9)	0.096
Death from any cause or repeat hospitalization	10.6% (9)	16.5% (47)	0.19	8.1% (6)	14.0% (31)	26.0% (19)	0.0066
Stroke or TIA	3.6% (3)	4.7% (13)	0.66	5.4% (4)	3.7% (8)	5.6% (4)	0.69
TIA	0.0% (0)	0.4% (1)	0.58	0.0% (0)	0.5% (1)	0.0% (0)	0.72
Stroke	3.6% (3)	4.3% (12)	0.76	5.4% (4)	3.3% (7)	5.6% (4)	0.54
Major	3.6% (3)	3.2% (9)	0.89	5.4% (4)	2.3% (5)	4.2% (3)	0.38
Minor	0.0% (0)	1.1% (3)	0.34	0.0% (0)	0.9% (2)	1.4% (1)	0.63
Myocardial infarction	0.0% (0)	0.7% (2)	0.44	0.0% (0)	0.5% (1)	1.4% (1)	0.50
Hemorrhagic event	13.0% (11)	20.2% (57)	0.13	15.0% (11)	18.5% (41)	22.3% (16)	0.53
Major bleeding	10.6% (9)	14.9% (42)	0.32	13.6% (10)	13.1% (29)	16.9% (12)	0.78
Minor bleeding	2.4% (2)	6.0% (17)	0.18	1.4% (1)	5.9% (13)	6.9% (5)	0.24
Vascular complications	17.6% (15)	25.5% (72)	0.14	14.9% (11)	25.8% (57)	26.2% (19)	0.14
Major	5.9% (5)	9.5% (27)	0.3	6.8% (5)	9.0% (20)	9.6% (7)	0.80
Permanent pacemaker	5.9% (5)	3.3% (9)	0.26	8.2% (6)	3.2% (7)	1.4% (1)	0.083
Renal failure (dialysis required)	1.2% (1)	2.9% (8)	0.37	0.0% (0)	1.9% (4)	7.2% (5)	0.013

Values are % (n).
TIA = transient ischemic attack; other abbreviation as in Table 1.

differences in periprocedural (Table 3) or 30-day (Table 4) outcomes in the TI versus CLI cohorts. Differences in outcomes emerged as early trends with statistical significance later, with lower all-cause mortality at both 1 year (14.1% vs. 32.0%; p = 0.002) and 2 years (23.1% vs. 43.8%; p = 0.001) in the TI group versus the CLI group (Fig. 2). At 2 years, the mortality (67.4%) and cardiac mortality (44.1%) in the ST arm was significantly greater than both TI (p < 0.0001) and CLI (p < 0.0001) patients. Similarly, repeat hospitalization was 70.0% for ST patients versus 20.3% and 29.0% for TI and CLI TAVR patients, respectively (p < 0.0001 for each comparison). Although there was a numerically higher rate of stroke at 2 years' postprocedure in the CLI TAVR patients (8.5%), there was no difference in TI TAVR patients (4.8%) versus ST patients (5.4%) (p = NS for the 3 groups). Of the CLI patients, 34 also had technical reasons for inoperability. These patients had a 2-year mortality (43.8%) similar to those who were inoperable for clinical reasons alone (43.3%) (p = NS). However, these patients with a combination of clinical and additional technical reasons for inoperability had more emergent conversion to open heart surgery during the TAVR procedure (5.9% vs. 0.4%; p = 0.003), late stroke or transient ischemic attack (22.2% vs. 8.9%; p = 0.048), and myocardial infarction (6.7% vs. 0.4%; p = 0.0043) than those who were inoperable for clinical reasons alone.

After clinical risk stratification of TAVR patients according to the STS score (Table 4), patients with lower STS scores were more likely to develop renal failure at 30 days (p = 0.0129). However, there was no difference in the incidence of 30-day stroke rates (5.4% with STS scores <5%; 3.3% with STS scores 5% to 14.9%, and 5.6% with STS scores ≥15%; p = 0.54 across groups). For later (2-year) outcomes, both all-cause and cardiovascular mortality were significantly lower in the group with STS scores <5% (Fig. 3).

Functional outcomes and QOL. Clinical reasons for inoperability was associated with increased baseline hazard for severe symptomatic heart failure (NYHA class III and IV) compared with technical reasons (1.14 [95% confidence interval (CI): 1.04 to 1.25]; p < 0.0001]). The hazard for persistent severe symptomatic heart failure increased to 1.48 (95% CI: 1.06 to 2.08; p = 0.01) at discharge, 1.86 (95% CI: 1.12 to 3.09; p = 0.01) at 30 days, 2.49 (95% CI: 1.01 to 6.13; p = 0.03) at 6 months, and 2.32 (95% CI: 1.10 to 4.89; p = 0.02) at 1 year. At 1 year, persistent severe symptomatic heart failure was present in 24.6% of patients with clinical reasons for inoperability and 10.6% of patients with technical reasons alone (Fig. 4). Even after adjusting for baseline, follow-up QOL scores on both the Kansas City Cardiomyopathy Questionnaire and the SF-12 were higher among the TI group compared with the CLI group (Table 5). QOL measures, adjusted relative to baseline, showed a significantly greater improvement in TI patients versus CLI patients. The differences were seen across all measures but were most sustained in the physical measures of QOL.

Independent predictors of late mortality. In the multivariable model for 2-year mortality (Table 6), higher STS score (hazard ratio [HR]: 1.03 [95% CI: 1.00 to 1.06]; p = 0.0466) was a significant independent predictor of all-cause mortality, as was clinical inoperability (HR: 1.85 [95% CI: 1.12 to 3.12]; p = 0.0166). Conversely stated,

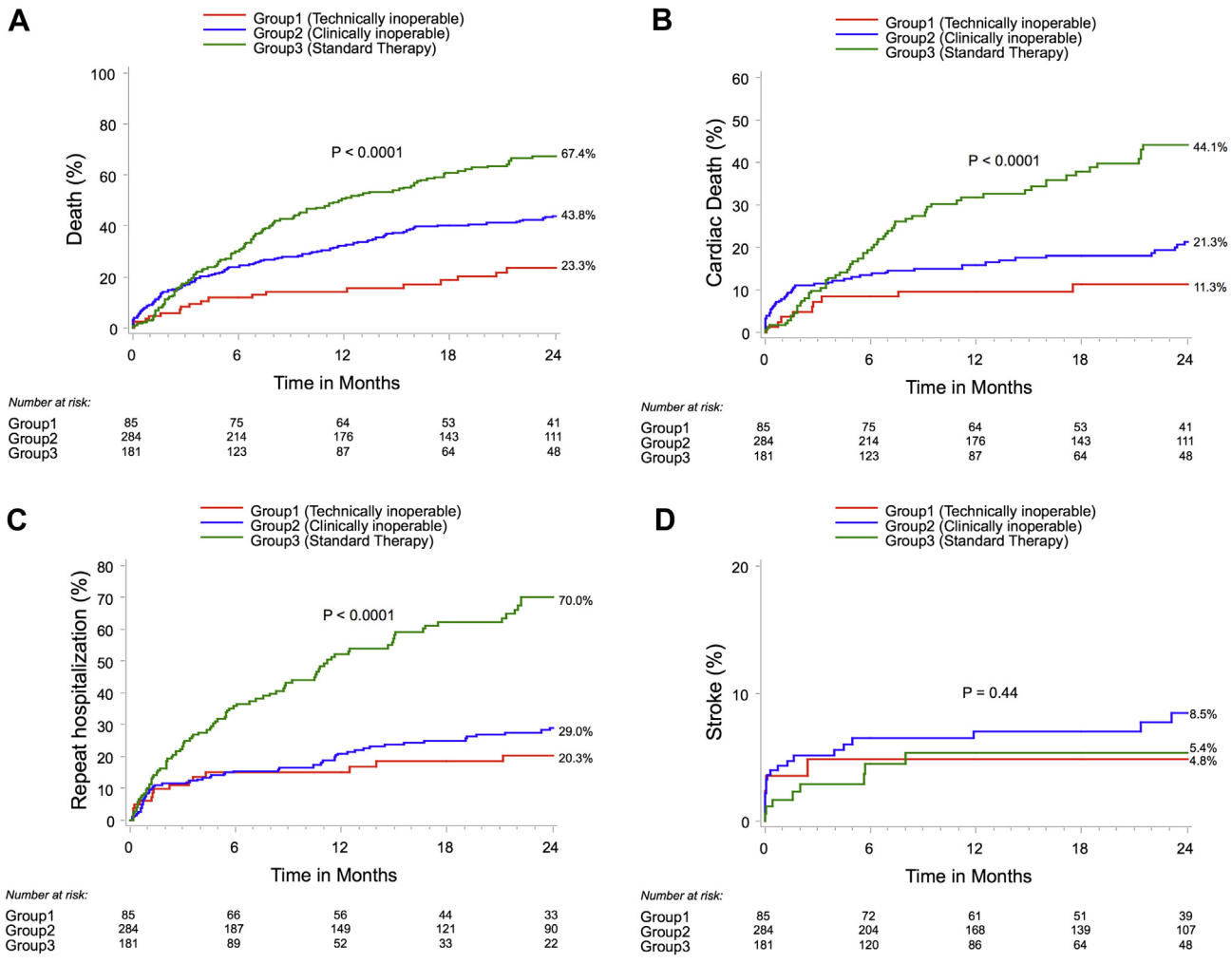

Figure 2 **Key Endpoints According to Technical Versus Clinical Inoperability in the Context of Standard Therapy**

Kaplan-Meier curves are shown with **(A)** death, **(B)** cardiac death, **(C)** repeat hospitalization, and **(D)** stroke.

technical inoperability was independently protective (HR: 0.54 [95% CI: 0.32 to 0.89]; p = 0.0166). Because the STS score was generally low in TI patients, the STS score had prognostic relevance primarily in the CLI patients (Table 7), in whom greatest survival was seen in those with the lower STS scores. TI patients with low and intermediate STS scores had similar survival.

Discussion

The present study produced several salient findings. First, there was a significant heterogeneity in the reasons for inoperability in patients with severe AS undergoing TAVR. In the TI group, the most common reason was porcelain aorta followed by "hostile chest," predominantly associated with previous radiation exposure. In the CLI group, multiple comorbidities, frailty, and lung disease were common. Second, although these factors had only a small influence on early outcomes, they had a significant bearing on 2-year outcomes. In the subset deemed inoperable solely based on technical reasons (approximately one-quarter of all inoperable patients), 2-year outcomes after TAVR were excellent, with mortality one-half that of CLI patients (23.3% vs. 43.8%; p < 0.0001). Third, although the CLI group had worse clinical outcomes overall, there was significant heterogeneity with 2-year mortality increasing progressively with increasing STS score, a risk score based on early mortality after conventional surgery (Table 7). These outcomes were still better than those receiving ST (43.8% vs. 67.4% at 2 years; p < 0.001). Finally, there were also substantial differences in QOL according to type of inoperability, with more substantial improvements in those with technical rather than clinical reasons for inoperability.

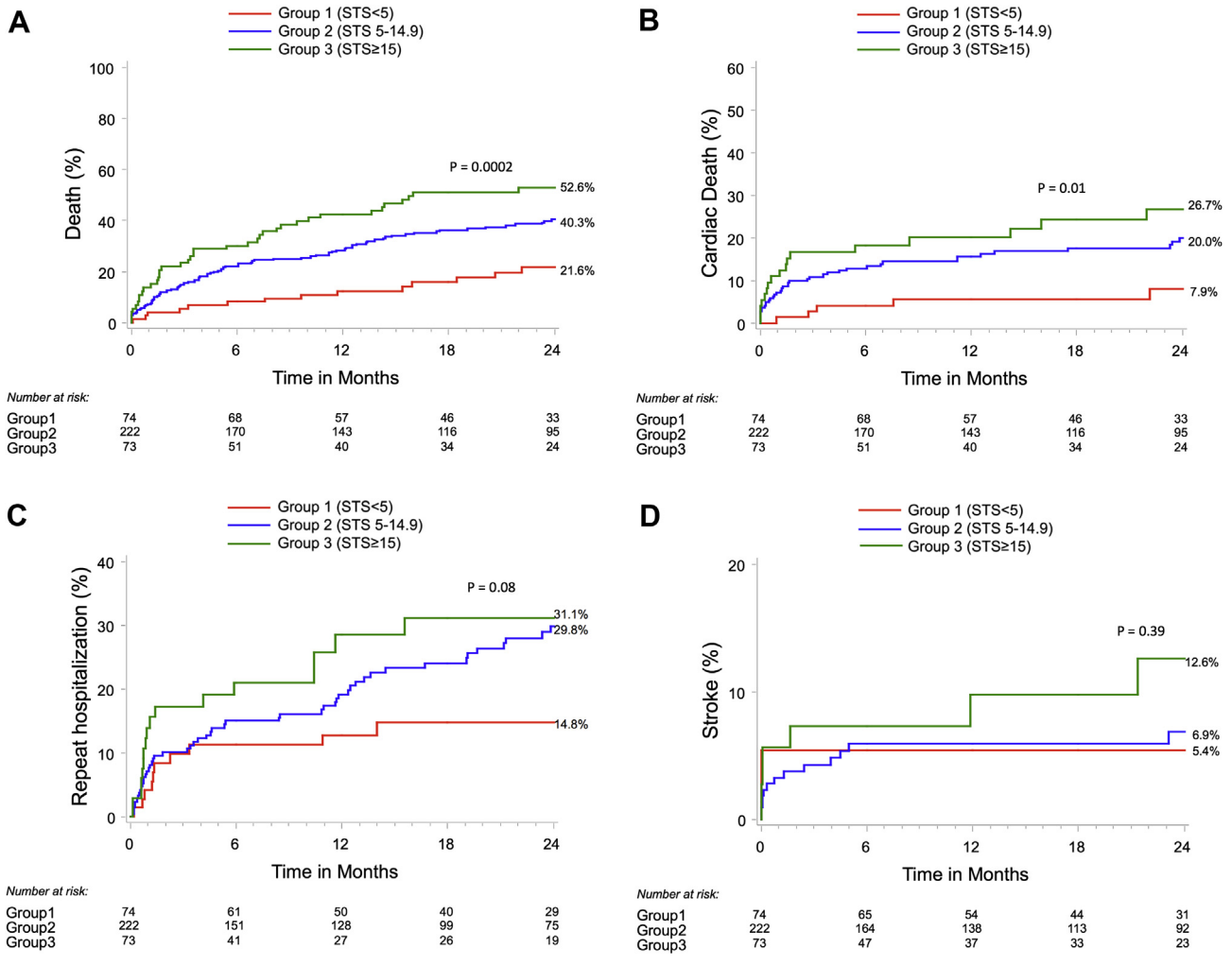

Figure 3 Key Endpoints According to STS Score Groups (Kaplan-Meier Curves)

Kaplan-Meier curves are shown with **(A)** death, **(B)** cardiac death, **(C)** repeat hospitalization, and **(D)** stroke. The STS risk score was used as a measure of clinical risk and comorbidities, stratifying groups according to STS categories: low, STS score <5%; intermediate to high, STS score 5% to 14.9%; and very high, STS score ≥15. Abbreviation as in Figure 1.

Technical inoperability in the context of surgical outcomes. TAVR has shown outcomes superior to ST in inoperable patients (1,2) and noninferiority to surgery in high-risk operable patients (6,7). Patients with technical reasons alone for inoperability frequently have a much lower clinical risk profile (on average, 10 years younger with [among other differences] one-half the frequency of renal failure and COPD) (Table 1). In the absence of clinical reasons of inoperability, they have better outcomes than the remainder of the inoperable population.

Our findings are similar to those of a Canadian registry (8), which reported that porcelain aorta, the most common cause of technical inoperability in the present series, is associated with similar procedural outcomes and better 2-year outcomes than those without porcelain aorta. Conversely, a German registry of self-expanding TAVR reported worse acute outcomes in patients with porcelain aorta (9). These patients, however, had more comorbidities in their porcelain aorta cohort. Thus, one may speculate that the TI cohort most likely had better clinical outcomes not due to the presence of technical reasons of inoperability but rather to the absence of clinical reasons for inoperability. Moreover, this German registry used access approaches other than the transfemoral approach. In the present series, although the TI group had the best clinical outcome data, cases from the CLI group whose inoperability was compounded with technical reasons did worse than TI patients but also worse compared with CLI patients who had no additional technical reasons for inoperability, most notably with more cerebrovascular events.

Clinical inoperability in the context of standard therapy. Overall, mortality (all-cause and cardiac) for CLI TAVR

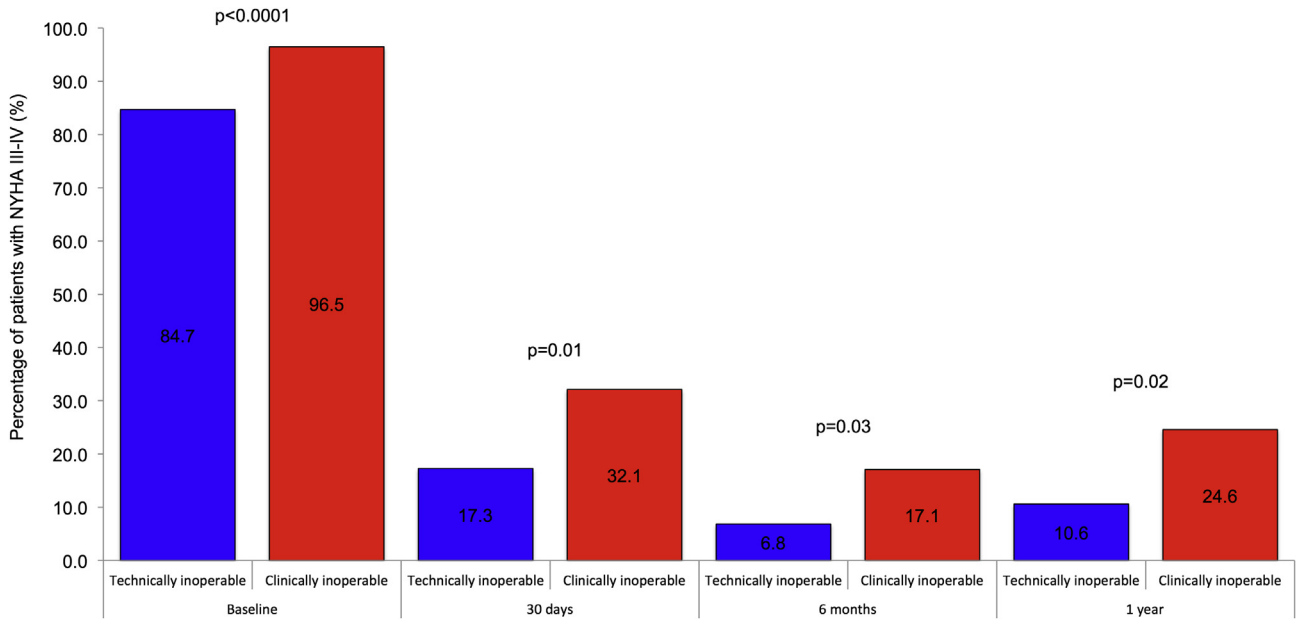

Figure 4 **Symptoms of Heart Failure According to Inoperability Criteria**

Changes in the frequency of persistent severe symptoms of heart failure (New York Heart Association [NYHA] III and IV) with time are shown according to technical or clinical reasons for inoperability.

patients was intermediate between those of the TI TAVR patients and patients receiving ST (Fig. 2). Repeat hospitalization after TAVR in the CLI group was significantly better than ST (70.0% vs. 29.0%; $p < 0.0001$). Among CLI patients undergoing TAVR, there are attenuated gains relative to TI patients, in that there was lower survival and a trend to higher stroke. Patients in the CLI group with an STS score ≥15% carried a high mortality (42.5% at 1 year and 52.6% at 2 years). This finding is in line with the previous stipulation that TAVR may have limited value in some patients; namely, those at the higher end of the surgical risk (2).

The STS score and further stratification of survival. Given considerable degrees of variation in the assessment of clinical criteria for inoperability, further stratification of this clinical risk is an important factor in decision making for treatment. An analysis of randomized patients in cohort B of the PARTNER trial demonstrated increasing 2-year mortality with increasing STS score (2). The present study corroborates these data in a larger cohort.

Although the comparison of SAVR with TAVR in intermediate and low clinical risk groups mandates randomized trial data, outcomes were observed in TI patients similar to those reported in surgery in patients of similarly low/intermediate clinical risk. The mean age of those inoperable for technical reasons alone was 73.4 ± 10.0 years, and the mean STS score was in the low to intermediate range (5.4 ± 2.9). In this population, the 30-day mortality was 4.7%, 1-year mortality was 14.1%, and 2-year mortality was 23.3%. Wendt et al. (10) reported mid-term data in patients undergoing SAVR; in an intermediate-risk group with an STS score of 6.5 ± 3.8, the 1-year mortality was 13.9% at 1 year and 19.2% at 2 years, comparable to that seen in the present study in TI patients. Arguably, the TI cohort data provide a preview of the impact of intermediate-level comorbidities on the outcomes of TAVR. The PARTNER II and SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trials are ongoing and should provide a definitive comparison of TAVR and surgery in intermediate surgical risk populations.

QOL and symptoms of heart failure. Taking the inoperable TAVR cohort as a whole, at 12 months, TAVR patients reported higher SF-12 physical and mental health scores compared with ST patients, with a difference of 5.7 and 6.4 points, respectively ($p < 0.0001$ for both comparisons) (3). There were clear differences in QOL improvement relative to baseline; there was a substantially better improvement in the SF-12 physical score in TI but no difference in the SF-12 mental score at 12 months after TAVR (Table 5). This disparity may be accounted for by the coexistence of respiratory disease and frailty (with associated symptoms of fatigue) prevalent in the CLI population. Similarly, despite an improvement in symptoms of heart failure in both TI and CLI patients, one-quarter of CLI patients had persistent substantial symptoms of heart failure (NYHA class III and IV) at follow-up versus one-tenth of TI patients.

Table 5 QOL at Follow-Up According to Reasons for Inoperability

	Adjusted Mean Value		Mean Difference	
	Technically Inoperable (n = 85)	Clinically Inoperable (n = 284)	(Technical – Clinical) 95% CI	p Value
KCCQ summary				
1 month	68.7 (63.3 to 74.2)	59.9 (56.8 to 63.1)	8.8 (2.4 to 15.2)	0.007
6 months	76.4 (71.3 to 81.4)	69.1 (66.0 to 72.2)	7.3 (1.3 to 13.3)	0.02
12 months	74.9 (69.0 to 80.9)	66.8 (63.0 to 70.7)	8.1 (0.9 to 15.2)	0.02
KCCQ physical limitations				
1 month	64.1 (57.7 to 70.6)	52.7 (48.6 to 56.7)	11.5 (3.7 to 19.2)	0.004
6 months	72.0 (65.2 to 78.8)	58.4 (54.2 to 62.7)	13.5 (5.3 to 21.7)	0.001
12 months	69.1 (62.6 to 75.7)	55.7 (51.1 to 60.4)	13.4 (5.1 to 21.7)	0.002
KCCQ total symptoms				
1 month	73.8 (68.8 to 78.8)	67.1 (64.2 to 70.1)	6.6 (0.8 to 12.5)	0.03
6 months	79.4 (74.5 to 84.4)	74.5 (71.5 to 77.5)	4.9 (−0.9 to 10.8)	0.10
12 months	78.0 (72.2 to 83.8)	72.3 (68.6 to 76.0)	5.7 (−1.3 to 12.6)	0.11
KCCQ self-efficacy				
1 month	87.9 (83.7 to 92.0)	84.3 (81.9 to 86.7)	3.6 (−1.2 to 8.4)	0.14
6 months	90.2 (86.4 to 94.0)	86.4 (84.1 to 88.7)	3.8 (−0.7 to 8.3)	0.095
12 months	85.2 (80.6 to 89.8)	85.3 (82.3 to 88.3)	−0.1 (−5.6 to 5.4)	0.98
KCCQ QOL				
1 month	73.0 (67.1 to 79.0)	62.7 (59.3 to 66.2)	10.3 (3.4 to 17.2)	0.003
6 months	81.2 (75.9 to 86.4)	74.1 (70.9 to 77.3)	7.1 (0.9 to 13.3)	0.02
12 months	78.6 (72.1 to 85.1)	72.7 (68.5 to 76.9)	5.9 (−1.9 to 13.7)	0.14
KCCQ social limitation				
1 month	64.9 (57.2 to 72.5)	52.4 (47.6 to 57.2)	12.4 (3.3 to 21.6)	0.008
6 months	76.7 (69.2 to 84.3)	66.0 (61.1 to 70.9)	10.7 (1.7 to 19.8)	0.02
12 months	73.6 (65.6 to 81.7)	61.4 (55.8 to 66.9)	12.2 (2.4 to 22.1)	0.02
SF-12 physical				
1 month	37.5 (35.3 to 39.7)	33.8 (32.5 to 35.0)	3.7 (1.1 to 6.3)	0.005
6 months	41.2 (38.9 to 43.5)	33.9 (32.5 to 35.4)	7.3 (4.5 to 10.0)	<.0001
12 months	39.7 (37.1 to 42.3)	34.7 (33.0 to 36.4)	5.0 (1.9 to 8.2)	0.002
SF-12 mental				
1 month	51.1 (48.4 to 53.8)	47.7 (46.1 to 49.3)	3.4 (0.2 to 6.5)	0.04
6 months	52.4 (49.9 to 55.0)	51.0 (49.5 to 52.6)	1.4 (−1.6 to 4.4)	0.36
12 months	52.8 (50.3 to 55.3)	52.3 (50.7 to 53.9)	0.5 (−2.5 to 3.4)	0.76

Comparison of mean scores over time from analysis of covariance, adjusting for baseline.
CI = confidence interval; other abbreviations as in Table 2.

Study limitations. This study relied on the judgment of the clinical team treating the patient for the underlying cause of inoperability. However, the labeling of inoperability required agreement by 2 cardiac surgeons and a joint case presentation, including demonstration of computed tomography images if a porcelain aorta was diagnosed. Reasons for inoperability were not studied in ST patients, limiting the validity of direct comparisons with TI/CLI TAVR subgroups separately. The ST group was from the PARTNER B randomized cohort alone, whereas the TAVR group included both randomized and continued access patients, introducing a potential bias in the TAVR group. However, to account for this possible bias, randomized versus nonrandomized status was introduced as a variable in the multivariable model for TAVR 2-year mortality and was not significant in the model. Frailty was not objectively defined or captured. Moreover, symptoms were analyzed by using a subjective scale. This was a retrospective analysis of subgroups that were not prespecified.

Table 6 Multivariable Cox Regression Model for 2-Year All-Cause Mortality

	Hazard Ratio (95% CI)	p Value
Technically inoperable*	0.54 (0.32–0.89)	0.017
STS risk score	1.03 (1.00–1.06)	0.047
BMI (kg/m^2)	0.95 (0.92–0.97)	0.0003
COPD	1.46 (1.04–2.06)	0.030

Multivariable predictors using stepwise Cox regression with entry/stay criteria of 0.1/0.1; variables included randomized study versus continued access, age, BMI, COPD, major arrhythmia, NYHA class III and IV, angina, anemia, PVD, porcelain aorta, aortic valve mean gradient at baseline, technical inoperability (i.e., not operated on for technical reasons alone), and STS risk score (as a continuous variable). *When conversely stated, clinical inoperability hazard ratio was 1.85 (95% CI: 1.12 to 3.12), p = 0.0166.
Abbreviations as in Table 1.

In this study of an early-generation, balloon-expandable TAVR device, vascular complications were frequently seen in close to 18% of the TI patients and >25% of the CLI patients. These rates are high, and the reduction in device profile with further device iterations is likely to contribute to

Table 7 The Interaction of Inoperability Category and STS Score on Mortality

	Technically Inoperable	Clinically Inoperable	p Value
30-day mortality			
STS <5%	4.8% (2)	3.1% (1)	0.73
STS ≥5%/<15%	4.7% (2)	7.8% (14)	0.47
STS ≥15%	–	13.7% (10)	NA
p value	0.99	0.16	
1-year mortality			
STS <5%	12.0% (5)	12.7% (4)	0.99
STS ≥5%/<15%	16.3% (7)	31.2% (55)	0.06
STS ≥15%	–	42.5% (31)	NA
p value	0.57	0.009	
2-year mortality			
STS <5%	22.4% (8)	20.5% (6)	0.82
STS ≥5%/<15%	24.4% (10)	44.2% (74)	0.03
STS ≥15%	–	52.6% (38)	NA
p value	0.73	0.008	

NA = not applicable; other abbreviation as in Table 1.

an ongoing improvement in TAVR outcomes. Similarly, the other prognostically important complication of paravalvular leak is likely to be attenuated by advances in device and procedural planning.

Conclusions

The identification of different risk subsets within the inoperable TAVR population is an important observation for patient selection for the procedure. Patients with severe calcific AS deemed inoperable for technical reasons alone have lower risk profiles and longer survival with greater improvements in QOL that make them excellent candidates for TAVR. In contrast, patients inoperable for clinical reasons are a heterogeneous group whose outcomes after TAVR seem reasonable compared with ST but inferior to those of TI patients.

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Key Words: inoperable ■ risk ■ TAVI ■ TAVR ■ transcatheter aortic valve.