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Clinical Outcomes and Revascularization Strategies in Patients With Low-Flow, Low-Gradient Severe Aortic Valve Stenosis According to the Assigned Treatment Modality

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ABSTRACT

OBJECTIVES This study compared clinical outcomes and revascularization strategies among patients presenting with low ejection fraction, low-gradient (LEF-LG) severe aortic stenosis (AS) according to the assigned treatment modality.

BACKGROUND The optimal treatment modality for patients with LEF-LG severe AS and concomitant coronary artery disease (CAD) requiring revascularization is unknown.

METHODS Of 1,551 patients, 204 with LEF-LG severe AS (aortic valve area <1.0 cm^2, ejection fraction <50%, and mean gradient <40 mm Hg) were allocated to medical therapy (MT) (n = 44), surgical aortic valve replacement (SAVR) (n = 52), or transcatheter aortic valve replacement (TAVR) (n = 108). CAD complexity was assessed using the SYNTAX score (SS) in 187 of 204 patients (92%). The primary endpoint was mortality at 1 year.

RESULTS LEF-LG severe AS patients undergoing SAVR were more likely to undergo complete revascularization (17 of 52, 35%) compared with TAVR (8 of 108, 8%) and MT (0 of 44, 0%) patients ($p < 0.001$). Compared with MT, both SAVR (adjusted hazard ratio [adj HR]: 0.16; 95% confidence interval [CI]: 0.07 to 0.38; $p < 0.001$) and TAVR (adj HR: 0.30; 95% CI: 0.18 to 0.52; $p < 0.001$) improved survival at 1 year. In TAVR and SAVR patients, CAD severity was associated with higher rates of cardiovascular death (no CAD: 12.2% vs. low SS [0 to 22], 15.3% vs. high SS [>22], 31.5%; $p = 0.037$) at 1 year. Compared with no CAD/complete revascularization, TAVR and SAVR patients undergoing incomplete revascularization had significantly higher 1-year cardiovascular death rates (adj HR: 2.80; 95% CI: 1.07 to 7.36; $p = 0.037$).

CONCLUSIONS Among LEF-LG severe AS patients, SAVR and TAVR improved survival compared with MT. CAD severity was associated with worse outcomes and incomplete revascularization predicted 1-year cardiovascular mortality among TAVR and SAVR patients. (J Am Coll Cardiol Intv 2015;8:704–17) © 2015 by the American College of Cardiology Foundation.

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Patients presenting with low ejection fraction heart failure and severe aortic stenosis (AS) typically exhibit a low mean gradient on hemodynamic evaluation despite the presence of a tight aortic valve orifice (1–5). Patients with this condition, low ejection fraction, low-gradient (LEF-LG) severe AS, present a management challenge because previous studies have shown LEF-LG severe AS patients undergoing conventional surgical aortic valve replacement (SAVR) to have a high perioperative mortality rate (range 6% to 33%), particularly in the absence of flow reserve, but an abysmal outcome when managed conservatively (2–4,6–13).

Transcatheter aortic valve replacement (TAVR) is a novel, less invasive alternative for the treatment of high-risk or inoperable patients presenting with severe AS (14,15). Because most patients presenting with low ejection fraction heart failure and severe AS are deemed high risk, TAVR may be an attractive option for these patients (5,16,17). A recent post-hoc analysis of the PARTNER (Placement of Aortic Transcatheter Valves) trial underscored the dismal outcome of patients with LEF-LG severe AS assigned to conservative management but also revealed for the first time that LEF-LG severe AS patients undergoing TAVR and SAVR had similar mortality rates at 2 years (18). However, this study was limited by the fact that the PARTNER trial systematically excluded all patients with coronary artery disease (CAD) requiring revascularization and a left ventricular ejection fraction (LVEF) <20% and no echocardiographic follow-up was reported (18). However, LEF-LG severe AS patients undergoing conventional aortic valve replacement in the "real world" typically have a high prevalence of concomitant CAD (66% to 69%) (4,6). Furthermore, little is known about revascularization strategies in LEF-LG severe AS patients, particularly among those undergoing TAVR. The primary aim of the present study was to describe "real-world" clinical outcomes of LEF-LG severe AS patients according to the assigned treatment modality (i.e., medical therapy [MT], SAVR, or TAVR). The secondary aim was to quantify CAD severity among LEF-LG severe AS patients using the SYNTAX score (SS) (19) and to describe the revascularization strategies and the completeness of revascularization among patients with left ventricular (LV) systolic dysfunction and low-gradient severe AS a function of the assigned treatment modality.

ABBREVIATIONS AND ACRONYMS

adj HR = adjusted hazard ratio
AS = aortic stenosis
AVA = aortic valve area
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence interval
LEF-LG = low ejection fraction, low gradient
LV = left ventricular
LVEF = left ventricular ejection fraction
MT = medical therapy
PCI = percutaneous coronary intervention
SAVR = surgical aortic valve replacement
SS = SYNTAX score
TAVR = transcatheter aortic valve replacement

METHODS

PATIENT POPULATION. The present study included patients meeting inclusion criteria who underwent TAVR, SAVR, or MT between January 2005 and December 2012 at Bern University Hospital, Bern, Switzerland. Inclusion criteria were as follows: 1) LVEF <50%; 2) mean gradient ≤40 mm Hg; 3) aortic valve area (AVA) <1 cm^2; 4) native aortic valve; and 5) age 70 years or older. Exclusion criteria consisted of patients undergoing a concomitant valve procedure (e.g., mitral valve replacement or repair) or aortic surgery (e.g., aortic root enlargement, Bentall procedure), previous valve replacement or repair, redo sternotomy in SAVR patients, patients presenting with unstable acute coronary syndromes, and patients undergoing emergency procedures. Patients undergoing concomitant revascularization procedures (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) were included.

MULTIDISCIPLINARY EVALUATION FOR HIGH-RISK PATIENTS AND ASSIGNMENT TO TREATMENT MODALITY. Since the beginning of the TAVR program at our institution in August 2007, all patients with severe AS at increased surgical risk underwent a multidisciplinary assessment according to a standardized protocol during a short hospitalization, as previously described (20). Between January 2005 and July 2007, the only treatment options for patients presenting with symptomatic severe AS at our institution were MT and conventional SAVR. The evaluation included both a noninvasive (transthoracic and transesophageal echocardiography, computed tomography angiography) and invasive (left and right heart catheterization, aortography) assessment. Risk algorithms (logistic EuroSCORE and Society of Thoracic Surgeons score) were used as an aid for patient selection and treatment allocation. Since August 2007, the selection of the most appropriate treatment strategy for high-risk patients was based on a consensus decision by

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the Heart Team. Treatment allocation was based on anatomic and technical considerations, estimated periprocedural risk, and patient preference.

The present analysis included all patients with LEF-LG severe AS meeting inclusion criteria undergoing SAVR between January 2005 and December 2012 and those assigned to MT or TAVR between August 2007 and December 2012. MT comprised treatment of comorbidities according to best clinical practice. In patients with severe CAD and symptomatic angina, PCI was performed as indicated. Balloon aortic valvuloplasty was not offered as part of the medical treatment strategy or as a bridge to SAVR. In some cases, treatment allocation was reconsidered and discussed with the Heart Team. Consequently, some patients originally assigned to undergo MT were crossed over to either TAVR or SAVR at a later stage.

SAVR was performed as previously described in detail (20). TAVR was performed with either the CoreValve (Medtronic, Minneapolis, Minnesota) or the SAPIEN valve (Edwards Lifesciences, Irvine, California) via transfemoral, transapical, or a transsubclavian access using standard techniques (20).

Coronary revascularization was performed if indicated on the basis of coronary angiography findings. In patients undergoing SAVR, revascularization was performed using arterial or venous conduits. In patients undergoing TAVR, revascularization by PCI was performed in proximal coronary segments with a diameter stenosis ≥70% either as a staged or concomitant procedure.

ANGIOGRAPHIC ANALYSIS. All coronary angiographic analyses for calculation of the baseline SS (all patients with available angiograms; n = 187 of 204 [92%]) and residual SS (MT and TAVR patients only; n = 145 of 204 [71%]) were performed at the Core Angiographic Laboratory of the Department of Cardiology at Bern University Hospital, Bern, Switzerland, as previously described (21). Briefly, all available baseline coronary angiograms of patients were reviewed by 2 experienced invasive cardiologists trained in the assessment of SS and blinded to clinical outcomes (22). For patients with CAD, baseline SS (i.e., SS before any PCI) was calculated by the consensus of the 2 readers using the SS algorithm (available at www.syntaxscore.com) (19). In case of disagreement, the opinion of a third reviewer was obtained, and a final consensus decision was reached. The SS of patients without CAD was deemed to be 0. For patients with a previous CABG, the CABG SS was used (23). For MT and TAVR patients undergoing PCI, the extent and complexity of untreated CAD were determined by assessing the residual SS (24). Complete revascularization was defined as treatment of any lesion with a stenosis diameter more than 50% in vessels ≥1.5 mm as estimated on the diagnostic angiogram as previously described (25).

DATA COLLECTION. Patients were included in the present registry at the time of SAVR or TAVR; for patients receiving MT, the date of hospitalization for multimodality evaluation was used as the inclusion date. Follow-up was performed by means of standardized telephone interviews or clinic visits. Medical records, discharge summaries, and documentation of hospitalization were systematically collected from referring hospitals and general practitioners. Patient and procedure characteristics as well as follow-up data were entered into a dedicated database held at the Clinical Trials Unit in Bern, Switzerland.

DEFINITIONS. Definitions used in the present analysis have been previously reported (20). All events were adjudicated by a clinical events committee comprising interventional cardiologists and cardiac surgeons. Cardiovascular death was defined as death secondary to a proximate cardiac cause and was assumed when the cause of death was unknown. Myocardial infarction was defined as an increase in at least 1 value of a cardiac biomarker above the 99th percentile of the upper reference limit more than 72 h after intervention in combination with evidence of myocardial ischemia determined by one of the following: electrocardiographic changes indicative of new ischemia, new pathological Q waves in at least 2 contiguous leads, or imaging evidence of a new loss of viable myocardium or new wall motion abnormality. Major stroke was documented in case of a rapid onset of focal or global neurological deficit of ≥24-h duration, requiring therapeutic intervention, or documentation of a new intracranial defect using magnetic resonance imaging or computed tomography. Transient ischemic attack as determined as a neurological deficit with complete remission within 24 h of onset. Major adverse cerebrocardiovascular events comprised all-cause mortality, myocardial infarction, and major stroke.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD if their distribution is approximately normal and as median/range otherwise. The means were compared using analysis of variance, and the differences in medians were evaluated with the Mann-Whitney or Kruskal-Wallis test. Categorical data are expressed as frequency (percent) and were compared using the chi-square and Fisher exact tests. Survival was estimated using

the Kaplan-Meier method, and differences in estimates were compared by means of the log-rank test. All time-to-event analyses were based on the initial treatment allocation, in analogy to the intention-to-treat principle unless otherwise specified. The at-risk time span was derived from the date of intervention on one side and the last available date of a patient on the other side, determined either by the date of death or the last follow-up or information coming from referring hospitals and practitioners. Univariate and multivariate Cox proportional hazard models were used to derive crude and adjusted survival estimates and to assess the association of baseline characteristics with clinical outcomes. Adjusted hazard ratios (adj HRs) and 95% confidence intervals (CIs) were derived from Cox regression analyses, adjusting for the following baseline variables: hypercholesterolemia, peripheral vascular disease, previous cardiac surgery, atrial fibrillation, and the logistic EuroSCORE, after multiple imputations of missing values using chained equations (20 datasets produced). Life expectancy after conversion to either SAVR or TAVR was predicted using Poisson regression. All p values and 95% CIs are 2-sided, and all analyses were performed using STATA version 13 (StataCorp, College Station, Texas).

RESULTS

BASELINE CHARACTERISTICS. Patient characteristics are shown in Table 1, and patient flow is shown in Figure 1. A total of 1,551 patients were screened for inclusion in the present study during the inclusion period: 606 consecutive patients undergoing TAVR (August 2007 to December 2012), 835 patients 70 years of age and older without previous sternotomy undergoing SAVR (with or without CABG but without concomitant valvular intervention; January 2005 to December 2012), and 110 patients assigned to MT (August 2007 to December 2012). Of these, 204 patients with LEF-LG severe AS met inclusion criteria for the present analysis (108 TAVR, 52 SAVR, and 44 MT). The reasons for allocation of LEF-LG severe AS patients to MT were comorbidities with a poor prognosis (38.6%), excessive peri-interventional risk (13.6%), anatomic reasons (11.4%), and patient preference (36.4%). Patients allocated to SAVR were significantly younger and were at lower risk compared with patients allocated to TAVR and MT. MT patients had higher rates of renal failure, atrial fibrillation, previous CABG, and a trend toward more complex CAD as assessed using the SS compared with SAVR and TAVR patients. TAVR patients had higher rates of previous PCI and were more symptomatic compared with MT and SAVR patients.

ECHOCARDIOGRAPHIC AND INVASIVE HEMODYNAMIC CHARACTERISTICS. Echocardiographic and invasive hemodynamic characteristics at baseline are shown in Tables 2 and 3, respectively. Compared with SAVR patients, both MT and TAVR patients had significantly worse LV and right ventricular systolic function, a higher prevalence of moderate to severe mitral and tricuspid regurgitation, lower invasive mean gradients, lower stroke volumes and cardiac outputs, and higher pulmonary artery systolic pressures measured both echocardiographically and invasively. There were no significant differences in other hemodynamic parameters. Dobutamine stress echocardiography was performed in 48 of 204 patients (24%). Flow reserve was present in 40%, 100%, and 73% of MT, SAVR, and TAVR patients undergoing dobutamine stress echocardiography, respectively.

PROCEDURAL CHARACTERISTICS. Procedural characteristics are shown in Table 4. Three LEF-LG severe AS patients originally allocated to MT were crossed over to TAVR and 1 transapical TAVR patient was emergently crossed over to SAVR and subsequently died. TAVR was performed using conscious sedation in the majority of patients (60%). The Medtronic CoreValve was used in most TAVR patients. SAVR patients received either a stented (n = 48) or stentless (n = 4) bioprostheses. The most frequently implanted stented bioprosthesis was the Perimount Magna Ease bioprosthesis (n = 38) (Edwards Lifesciences), whereas the most frequently implanted stentless bioprosthesis was the Sorin Freedom SOLO (n = 3) (Sorin Group, Milan, Italy). Patients undergoing SAVR had a significantly longer length of hospital stay compared with MT and TAVR patients (MT vs. SAVR vs. TAVR: 4.9 ± 5.6 days vs. 11.9 ± 4.6 days vs. 8.5 ± 4.1 days; $p < 0.001$). Revascularization was performed in 69% of patients selected for SAVR by means of CABG, 36% of patients undergoing TAVR by means of either staged (21%) or concomitant (15%) PCI, and 16% of MT patients by PCI. Complete revascularization was achieved in 17 of 52 SAVR patients (35%), 8 of 108 TAVR patients (8%), and 0 of 44 of MT patients (0%) ($p < 0.001$). SAVR patients were more likely to undergo additional concomitant interventions, with occlusion of the left atrial appendage being the most frequent structural intervention performed (Table 4).

CLINICAL OUTCOMES ACCORDING TO TREATMENT MODALITY. All comparisons among the 3 treatment arms are descriptive. One-year follow-up was complete for 100% patients allocated to MT, 99% of patients assigned to TAVR (1 TA patient withdrew consent after 113 days), and 92% of patients assigned

TABLE 1 Baseline Characteristics

	MT (n = 44)	SAVR (n = 52)	TAVR (n = 108)	p Value
Age, yrs	82.7 ± 4.7	78.4 ± 4.1	82.5 ± 4.4	<0.001
Female	18 (41)	19 (37)	45 (42)	0.82
Height, cm	166.9 ± 8.2	167.1 ± 8.9	165.3 ± 8.0	0.35
Weight, kg	68.2 ± 11.2	74.0 ± 15.3	69.6 ± 14.4	0.09
Body mass index, kg/m^2	24.6 ± 3.2	26.4 ± 4.6	25.4 ± 4.8	0.13
Body surface area, m^2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.15
Cardiac risk factors				
Diabetes mellitus	13 (30)	17 (33)	35 (32)	0.93
Hypercholesterolemia	25 (57)	32 (62)	72 (67)	0.50
Hypertension	31 (70)	43 (83)	87 (81)	0.29
Current smoker	5 (11%)	23 (44%)	12 (11%)	<0.001
Medical history				
Previous stroke	9 (20)	7 (13)	9 (8)	0.11
Peripheral vascular disease	11 (25)	6 (12)	29 (27)	0.09
Chronic obstructive pulmonary disease	10 (23)	7 (13)	17 (16)	0.45
Renal failure (GFR <50 ml/min/1.73 m^2)	31 (74)	20 (38)	36 (33)	<0.001
Previous permanent pacemaker	5 (11)	9 (17)	13 (12)	0.60
Coronary artery disease				
SYNTAX score*	22.3 ± 19.3	14.0 ± 14.1	16.1 ± 15.5	0.06
Coronary artery disease	32 (73)	40 (77)	80 (74)	0.89
Previous MI	15 (34)	13 (25)	27 (25)	0.49
Previous CABG	15 (34)	0 (0)	27 (25)	<0.001
Previous PCI	9 (20)	4 (8)	42 (39)	<0.001
Baseline cardiac rhythm				
Atrial fibrillation	22 (50)	17 (33)	30 (28)	0.04
Symptoms				
NYHA functional class III/IV	29 (66)	35 (67)	85 (82)	0.05
CCS angina status III/IV	7 (16)	13 (25)	16 (15)	0.27
Risk assessment				
Logistic EuroSCORE, %	41.2 ± 16.0	18.7 ± 13.0	34.5 ± 15.3	<0.001
STS score, %	11.2 ± 7.3	4.9 ± 2.9	7.9 ± 4.9	<0.001
STS score, %	9.8 (5.9–15.8)	4.2 (3.2–5.5)	6.6 (4.6–9.9)	<0.001
Medications				
Aspirin	21 (48)	40 (77)	72 (67)	0.01
Clopidogrel	8 (18)	2 (4)	29 (27)	0.00
Oral anticoagulation	18 (41)	11 (21)	34 (31)	0.11

Values are mean ± SD with p values from analyses of variance or n (%) with p values from chi-square tests. STS score was left-skewed, and therefore also median (25% to 75% interquartile range) with Kruskal-Wallis and Mann-Whitney *U* tests is reported. *Sample sizes for SYNTAX score: 33, 48, 106; renal failure, n = 2 missing for medical therapy; chronic obstructive pulmonary disease, n = 1 missing for transcatheter aortic valve replacement; atrial fibrillation; n = 2 missing for transcatheter aortic valve replacement.

CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; GFR = glomerular filtration rate; MI = myocardial infarction; MT = medical therapy; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

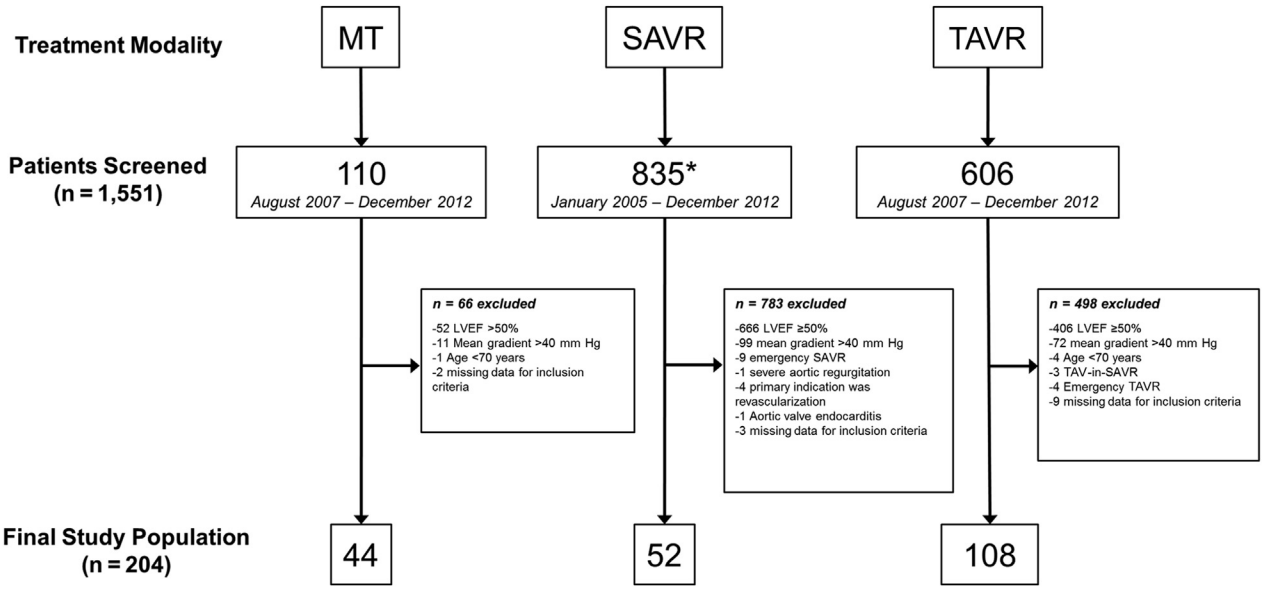
to SAVR. The median duration of clinical follow-up was 365 days (interquartile range: 240 to 365 days, i.e., longer follow-ups censored at 1 year). Unadjusted and adjusted event rates at 30 days and 1 year are provided in Tables 5 and 6, respectively. Compared with MT patients, patients undergoing both TAVR and SAVR had similar 30-day survival rates after adjustment for baseline comorbidities (MT vs. SAVR, adj HR: 0.64; 95% CI: 0.16 to 2.61; p = 0.54; MT vs. TAVR, adj HR: 0.36; 95% CI: 0.13 to 1.04; p = 0.058). No significant differences in all-cause mortality were observed between SAVR and TAVR patients at 30 days (adj HR: 0.69; 95% CI: 0.14 to 3.35; p = 0.65). Patients assigned to TAVR had significantly higher rates of bleeding and vascular complications and permanent pacemaker implantation, and patients assigned to SAVR had significantly higher rates of acute renal failure. Two SAVR patients required a periprocedural redo sternotomy for management of pericardial tamponade.

Survival curves showing all-cause death and cardiovascular death at 1 year according to treatment modality are shown in Figure 2. At 1 year, both SAVR and TAVR significantly improved survival compared with MT among patients presenting with LEF-LG severe AS (MT vs. SAVR, unadjusted HR: 0.16; 95% CI: 0.07 to 0.38; p < 0.001; MT vs. TAVR, HR: 0.30; 95% CI: 0.18 to 0.52; p < 0.001). Mortality was predominantly driven by cardiovascular death in all groups. After adjustment for univariate predictors of 1-year mortality (peripheral vascular disease, atrial fibrillation, and logistic EuroSCORE), both SAVR and TAVR improved survival compared with MT (MT vs. SAVR, adj HR: 0.37; 95% CI: 0.15 to 0.93; p = 0.034; MT vs. TAV, adj HR: 0.43; 95% CI: 0.24 to 0.79; p = 0.006) (Table 6). No significant differences in adjusted overall mortality (adj HR: 1.28; 95% CI: 0.51 to 3.22; p = 0.60) or cardiovascular death (adj HR: 1.49; 95% CI: 0.52 to 4.23; p = 0.46) rates were observed in patients undergoing SAVR and TAVR at 1 year.

CLINICAL OUTCOMES ACCORDING TO BASELINE CAD SEVERITY AND COMPLETENESS OF REVASCULARIZATION (SAVR AND TAVR PATIENTS ONLY). In total, 187 of 204 patients (91.7%) had a baseline angiogram available for evaluation, and CAD was confirmed to be present in 138 of 187 LEF-LG severe AS patients (73.8%). Survival curves showing all-cause mortality and cardiovascular death according to baseline SS in patients undergoing TAVR and SAVR only (i.e., MT patients excluded) at 1 year are shown in Figure 3. Compared with no CAD, LEF-LG severe AS patients with a high SS (>22) had significantly higher rates of cardiovascular death (12.2% vs. 31.5%; adj HR: 3.29; 95% CI: 1.08 to 10.05; p = 0.037) and a trend toward higher rates of overall mortality (16.8% vs. 33.7%; adj HR: 2.59; 95% CI: 0.95 to 7.03; p = 0.062) at 1 year. Compared with no CAD, no significant differences in cardiovascular death (p = 0.86) or all-cause death (p = 0.98) were observed among patients with a low to intermediate SS (0 to 22) at 1 year (Online Tables 1 to 3).

Survival curves showing all-cause death and cardiovascular death rates according to completeness of

FIGURE 1 Patient Flow



The 835 SAVR patients were all 70 years or older without a previous sternotomy undergoing SAVR (with or without coronary artery bypass grafting) without a concomitant valvular intervention between January 2005 and December 2012. LVEF = left ventricular ejection fraction; MT = medical therapy; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

revascularization by either CABG or PCI in patients undergoing SAVR and TAVR only (i.e., MT patients were excluded) are shown in Figure 4. Compared with no CAD/complete revascularization, LEF-LG severe AS patients undergoing incomplete revascularization had significantly higher rates of overall (13.6% vs. 29.2%; HR: 2.30; 95% CI: 1.07 to 4.92; p = 0.032) and cardiac mortality (9.1% vs. 27.0%; HR: 3.15; 95% CI: 1.28 to 7.74; p = 0.012) at 1 year. After adjustment, incomplete revascularization remained an independent predictor of cardiovascular mortality (adj HR: 2.80; 95% CI: 1.07 to 7.36; p = 0.037) at 1 year (Online Tables 4 and 5).

ECHOCARDIOGRAPHIC OUTCOMES. Echocardiographic characteristics are shown in Table 7. No significant differences in indexed AVAs were observed between TAVR and SAVR groups at discharge (SAVR vs. TAVR: 1.03 ± 0.22 vs. 1.05 ± 0.37 $cm^2 \cdot m^{-2}$) or 1 year (0.94 ± 0.27 vs. 1.00 ± 0.27 $cm^2 \cdot m^{-2}$; p = 0.49) follow-up. However, compared with SAVR, TAVR patients had significantly lower mean gradients at both discharge (9.49 ± 3.40 vs. 7.20 ± 2.94 mm Hg; p = 0.001) and 1-year follow-up (11.52 ± 3.58 vs. 8.06 ± 2.92 mm Hg; p < 0.001). No significant differences in rates of patient prosthetic mismatch (indexed AVA ≤0.85 $cm^2 \cdot m^{-2}$) were observed between the SAVR and TAVR groups at either discharge (p = 0.32) or 1-year (p = 0.10) follow-up. Compared with SAVR patients, those undergoing TAVR had a significantly higher incidence of moderate to severe paravalvular aortic regurgitation at both discharge (1% vs. 17%; p < 0.001) and 1 year (0% vs. 15%; p = 0.001) follow-up. LVEF recovery up to 1 year in LEF-LG severe AS patients undergoing TAVR and SAVR is shown in Figure 5. Compared with SAVR patients, TAVR patients exhibited better early improvement in LVEF on discharge echocardiography (ΔLVEF in SAVR vs. TAVR: −0.2 ± 15.3% vs. 4.7 ± 10.3%; p = 0.041). However, both SAVR and TAVR patients had similar LVEF improvement at 1-year follow-up (ΔLVEF in SAVR vs. TAVR: 7.8 ± 16.2% vs. 10.0 ± 12.2%; p = 0.54).

DISCUSSION

The main findings of the present study were as follows: First, both TAVR and SAVR improved survival compared with MT in LEF-LG severe AS patients at 1-year follow-up. No significant differences in mortality rates were observed between TAVR and SAVR patients at either 30 days or 1 year even though SAVR patients were at considerably lower risk and had a more favorable hemodynamic profile at baseline compared with TAVR and MT patients. Second, LEF-LG severe AS was associated with a high

TABLE 2 Echocardiographic Characteristics

	MT (n = 44)	SAVR (n = 52)	TAVR (n = 108)	p Value
Aortic stenosis severity				
Aortic valve area, cm^2	0.70 ± 0.22	0.73 ± 0.23	0.74 ± 0.21	0.56
Indexed aortic valve area, $cm^2 \cdot m^{-2}$	0.40 ± 0.13	0.41 ± 0.12	0.42 ± 0.12	0.51
Aortic maximal velocity, cm/s	2.97 ± 0.48	3.32 ± 0.60	3.24 ± 0.61	0.05
Mean gradient, mm Hg	25.25 ± 9.37	29.26 ± 9.54	28.57 ± 10.29	0.11
Peak gradient, mm Hg	40.66 ± 14.40	48.34 ± 15.89	46.55 ± 15.98	0.05
LV geometry and 2D measurements				
Interventricular septum in diastole, mm	12.75 ± 2.82	16.24 ± 9.62	12.86 ± 3.15	0.014
Posterior wall thickness in diastole, mm	12.76 ± 5.86	11.40 ± 2.46	12.56 ± 7.00	0.60
LV end-systolic diameter, mm	46.23 ± 10.90	43.10 ± 8.01	43.93 ± 10.81	0.46
LV end-diastolic diameter, mm	54.93 ± 9.64	54.15 ± 10.02	55.22 ± 10.56	0.86
Relative wall thickness	0.51 ± 0.32	0.48 ± 0.32	0.51 ± 0.39	0.94
LV mass index, g/m^2	173.52 ± 60.22	164.09 ± 46.25	159.77 ± 36.20	0.38
Geometry				0.87
Normal	1 (3)	2 (11)	3 (5)	0.54
Concentric hypertrophy	12 (41)	7 (39)	25 (45)	0.90
Eccentric hypertrophy	12 (41)	8 (44)	24 (43)	0.98
Concentric remodeling	4 (14)	1 (6)	4 (7)	0.51
LV systolic function				
LV ejection fraction, %	29.64 ± 9.33	38.90 ± 11.95	34.52 ± 11.38	<0.001
LV ejection fraction ≤30%	35 (79.5)	16 (30.8)	59 (54.6)	<0.001
LV ejection fraction ≤20%	13 (29.5)	6 (11.5)	19 (17.6)	0.07
LV diastolic function				
E/A ratio	2.09 ± 0.86	1.47 ± 0.82	1.93 ± 1.08	0.21
Deceleration time, ms	147.30 ± 38.46	173.95 ± 60.95	173.35 ± 65.79	0.46
Isovolumic relaxation time, ms	77.33 ± 17.86	92.50 ± 23.54	80.73 ± 34.38	0.62
Left atrial diameter, mm	50.58 ± 9.45	45.43 ± 8.42	49.09 ± 6.01	0.029
RV systolic function				
TAPSE, mm	12.74 ± 5.29	16.50 ± 4.70	14.33 ± 4.52	0.07
DTI S′, cm/s	8.54 ± 2.32	12.23 ± 2.79	9.53 ± 2.97	<0.001
Associated valvular abnormality				
Aortic regurgitation				0.32
None	15 (37)	16 (36)	27 (27)	
Mild	24 (59)	26 (59)	63 (64)	
Moderate	2 (5)	1 (2)	9 (9)	
Severe	0 (0)	1 (2)	0 (0)	
Mitral regurgitation				0.036
None	4 (10)	5 (10)	2 (2)	
Mild	16 (39)	30 (60)	49 (45)	
Moderate	19 (46)	15 (30)	54 (50)	
Severe	2 (5)	0 (0)	3 (3)	
Tricuspid regurgitation				0.03
None	4 (10)	5 (11)	10 (11)	
Mild	21 (53)	35 (76)	51 (55)	
Moderate	9 (23)	6 (13)	27 (29)	
Severe	6 (15)	0 (0)	5 (5)	
Right-sided hemodynamics				
RV/RA gradient, mm Hg	43.04 ± 16.27	35.89 ± 11.11	41.94 ± 11.98	0.043
PA systolic pressure, mm Hg	52.88 ± 17.70	45.49 ± 11.93	52.03 ± 13.87	0.049

Vales are mean ± SD with p values from analyses of variance or n (%) with p values from chi-square tests.

2D = 2-dimensional; DTI S′ = pulsed Doppler peak velocity at the annulus; LV = left ventricular; PA = pulmonary artery; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

TABLE 3 Invasive Hemodynamic Characteristics

	MT (n = 44)	SAVR (n = 52)	TAVR (n = 108)	p Value
Aortic stenosis severity				
Aortic valve area, cm^2	0.60 ± 0.21	0.59 ± 0.20	0.68 ± 0.30	0.16
Indexed aortic valve area, $cm^2 \cdot m^{-2}$	0.34 ± 0.10	0.32 ± 0.12	0.38 ± 0.18	0.20
Peak-to-peak gradient, mm Hg	31.60 ± 16.39	32.06 ± 20.09	31.42 ± 21.37	0.99
Mean gradient, mm Hg	23.50 ± 10.67	29.81 ± 7.29	25.96 ± 8.55	0.013
Systemic vascular load				
Systolic arterial pressure, mm Hg	116.97 ± 23.50	129.00 ± 23.61	125.76 ± 25.48	0.12
Diastolic arterial pressure, mm Hg	64.68 ± 13.77	68.33 ± 15.46	66.59 ± 14.50	0.59
Mean arterial pressure, mm Hg	87.16 ± 16.50	92.11 ± 16.00	90.75 ± 16.47	0.44
Systemic vascular resistance, mm Hg·min·l^{-1}	2,036.07 ± 702.33	1,888.29 ± 493.85	2,105.45 ± 726.18	0.34
Systemic arterial compliance, ml·mm Hg^{-1}	0.46 ± 0.24	0.48 ± 0.16	0.46 ± 0.25	0.95
LV global afterload				
Valvuloarterial impedance, mm Hg·$ml^{-1} \cdot m^2$	6.94 ± 2.37	6.75 ± 2.16	6.99 ± 2.51	0.91
LV systolic function				
Angiographic ejection fraction, %	29.17 ± 9.08	36.08 ± 8.62	32.43 ± 8.50	0.007
LV end-systolic pressure, mm Hg	149.21 ± 27.83	162.00 ± 26.00	156.42 ± 24.87	0.15
LV end-diastolic pressure, mm Hg	21.93 ± 7.86	24.35 ± 24.45	21.94 ± 7.70	0.66
Stroke volume, ml	38.67 ± 12.31	49.22 ± 20.20	43.50 ± 14.05	0.029
Stroke volume index, ml/m^2	21.79 ± 5.66	26.03 ± 9.77	24.47 ± 7.31	0.09
Cardiac output, l/min	3.11 ± 0.69	3.77 ± 1.17	3.38 ± 1.01	0.023
Cardiac index, l/(min·m^2)	1.75 ± 0.30	2.05 ± 0.60	1.90 ± 0.50	0.049
Heart rate (beats/min)	83.39 ± 14.60	82.64 ± 16.96	79.94 ± 16.36	0.51
Right-sided hemodynamics				
PA systolic pressure, mm Hg	59.32 ± 15.92	50.63 ± 16.15	58.01 ± 14.51	0.031
Mean PA pressure, mm Hg	38.32 ± 10.11	33.71 ± 11.54	38.41 ± 10.00	0.07
Pulmonary hypertension	27 (87)	26 (74)	71 (87)	0.22

Vales are mean ± SD with p values from analyses of variance or n (%) with p values from chi-square tests.
Abbreviations as in Tables 1 and 2.

prevalence of concomitant CAD (74%) of at least moderate complexity in the present analysis. We found that a higher degree of CAD complexity (SS >22) was an independent predictor of cardiovascular death at 1 year in LEF-LG severe AS patients undergoing TAVR and SAVR. Therefore, revascularization strategies are an important consideration in the overall management of patients presenting with LEF-LG severe AS. LEF-LG severe AS patients undergoing SAVR were almost twice as likely to undergo revascularization and more than 4 times as likely to be completely revascularized compared with LEF-LG severe AS patients undergoing TAVR despite having a similar degree of CAD complexity at baseline. Furthermore, incomplete revascularization was an independent predictor of 1-year cardiovascular mortality in LEF-LG severe AS patients with CAD undergoing TAVR and SAVR. Therefore, LEF-LG severe AS patients with concomitant CAD of high complexity should be considered for SAVR and CABG if the risk profile permits. Complete revascularization should be considered in inoperable LEF-LG severe AS patients with concomitant CAD of high complexity. Third, LVEF improved to a similar extent in both SAVR and TAVR patients at 1-year follow-up. However, the timing of LVEF improvement differed in both groups, with TAVR patients experiencing an early improvement in LVEF before discharge and those undergoing SAVR experiencing most LVEF improvement after discharge. Finally, we observed patients undergoing TAVR to have significantly lower post-procedural mean gradients compared with SAVR patients, although no differences in post-procedural AVAs were observed in the TAVR and SAVR groups.

LOW EJECTION FRACTION, LOW-GRADIENT SEVERE AS AND SAVR. The first description of LEF-LG severe AS and its association with a high perioperative mortality during SAVR was made by Carabello et al. (1) in 1980. Several subsequent reports confirmed this association (2–4,6–9,12,13). In a pivotal study in 1995, deFilippi et al. (3) first described the use of echocardiographic dobutamine stress testing to distinguish between true severe and pseudosevere AS and noted that in the absence of flow reserve (i.e., <20% stroke volume increase with dobutamine infusion), the

TABLE 4 Procedural Characteristics

	MT (n = 44)	SAVR (n = 52)	TAVR (n = 108)	p Value
Crossover to TAVR	3* (7)	0 (0)	NA	
Crossover to SAVR	0 (0)	NA	1 (1)	
General anesthesia	NA	52 (100)	43 (40)	<0.001
Procedure duration, min	NA	190.21 ± 47.73	67.58 ± 38.86	<0.001
Aortic valve intervention				
Balloon pre-dilation	NA	0 (0)	99 (92)	<0.001
Medtronic CoreValve	NA	0 (0)	63 (58)	<0.001
Edwards SAPIEN valve	NA	0 (0)	43 (40)	<0.001
Symetis valve	NA	0 (0)	2 (2)	1.00
Surgical bioprosthesis	NA	52 (100)	1 (1)	<0.001
Stentless	NA	4 (8)	0 (0)	0.01
Revascularization	7 (16)	36 (69)	39 (36)	<0.001
Vessel treated				
Left anterior descending artery	6 (14)	30 (58)	26 (24)	<0.001
Left circumflex artery	3 (7)	24 (46)	7 (7)	<0.001
Right coronary artery	1 (2)	24 (46)	12 (11)	<0.001
Saphenous vein graft	0 (0)	0 (0)	3 (3)	0.255
Complete revascularization	0 (0)	17 (35)	8 (8)	<0.001
Residual SYNTAX score†	20.02 ± 18.59	NA	12.76 ± 14.26	0.019
Percutaneous coronary intervention	7 (16)	1 (2)	39 (36)	<0.001
Concomitant	6 (14)	0 (0)	16 (15)	0.014
Staged	1 (2)	1 (2)	23 (21)	<0.001
Coronary artery bypass graft	0 (0)	36 (69)	0 (0)	<0.001
Other concomitant interventions	0 (0)	10 (19)	1 (1)	<0.001
Carotid endarterectomy	NA	1 (10)	0 (0)	
Coronary endarterectomy	NA	2 (20)	0 (0)	
Left atrial appendage occlusion	NA	4 (40)	0 (0)	
Patent foramen ovale closure	NA	1 (10)	1 (100)	
Pulmonary vein ablation	NA	1 (10)	0 (0)	
Subvalvular myectomy	NA	1 (10)	0 (0)	
Hospital length of stay, days	4.93 ± 5.55	11.94 ± 4.57	8.48 ± 4.13	<0.001

Values are mean ± SD with p values from analyses of variance or unpaired Student *t* tests or n (%) with p values using the Fisher exact or chi-square test. *Three patients assigned to medical therapy after heart team discussion subsequently crossed over to TAVR at 833 days (29-mm Medtronic CoreValve), at 25 days (26-mm Edwards SAPIEN XT valve), and at 493 days (29-mm Medtronic CoreValve) after initial medical therapy allocation. †Residual SYNTAX score has not been validated in post-CABG patients.

NA = not available; other abbreviations as in Table 1.

distinction between true severe and pseudosevere AS could not be made. Monin et al. (8,9) subsequently demonstrated that perioperative risk is markedly increased in LEF-LG severe AS patients without flow reserve. The same group, however, subsequently demonstrated that in LEF-LG severe AS patients surviving SAVR, LVEF recovery was independent of whether flow reserve was present at baseline, suggesting that SAVR should not be contraindicated in the absence of flow reserve alone (10). Tribouilloy et al. (13) demonstrated in 42 propensity score–matched patients that LEF-LG severe AS patients without flow reserve undergoing SAVR had improved 5-year mortality rates compared with similar patients undergoing medical management. Although the perioperative mortality rate was high (22%), the investigators concluded that SAVR should not be withheld from LEF-LG severe AS patients on the basis of a lack of flow reserve alone (13).

SAVR VERSUS TAVR IN PATIENTS WITH SEVERE AS AND LOW LVEF. To date, there are only a few studies comparing TAVR and SAVR treatment modalities in patients presenting with severe AS and LV systolic dysfunction (26,27). Furthermore, there is an ongoing controversy regarding the impact of TAVR versus SAVR on LV functional recovery in patients presenting with severe AS and LV systolic dysfunction (26,27). Clavel et al. (26) found that TAVR was associated with better LVEF recovery compared with SAVR at 1-year follow-up. Conversely, Elmariah et al. (27) found no differences in the rate or degree of LV functional recovery between TAVR and SAVR in patients with severe AS and an LVEF <50% at baseline. Both SAVR and TAVR resulted in a similar LVEF improvement at 1-year follow-up in this post-hoc analysis of the PARTNER trial (27). The reasons for this discrepancy may relate to the fact that concomitant CABG was not performed in SAVR patients enrolled in the PARTNER trial, whereas it was performed in 60% of patients in the Clavel et al. study (26,27). The presence of nonrevascularized CAD at the initiation of surgery in addition to prolonged cardiopulmonary bypass with concomitant CABG were hypothesized to have impeded LVEF recovery in the SAVR patients in the latter study (26). Both studies, however, included patients with low LVEF and high gradients and therefore differ from the present study. Patients with a low LVEF and high-gradient severe AS have been shown to have better LVEF recovery and clinical outcomes compared with those presenting with a low LVEF and low gradient (5). The present study compared LVEF recovery exclusively between low-ejection-fraction, low-gradient severe AS patients undergoing either TAVR or SAVR. We observed that LVEF recovery was similar in TAVR and SAVR patients at 1 year despite the fact that 69% of SAVR patients underwent concomitant CABG. However, LVEF recovery occurred earlier among patients undergoing TAVR. These findings suggest that LVEF recovery in LEF-LG severe AS patients undergoing SAVR may be somewhat delayed due to surgical insults related to, for example, cardioplegia, ischemia reperfusion, apoptosis, and inflammation, but that there then appears to be a "late catch-up" phenomenon.

SAVR VERSUS TAVR IN PATIENTS WITH LOW EJECTION FRACTION, LOW-GRADIENT SEVERE AS. Herrmann et al. (18), in a post-hoc analysis of the PARTNER trial, were the first and only group to date to compare

TABLE 5 Unadjusted Clinical Outcomes at 30 Days and 1 Year

	Treatment Modality			SAVR vs. MT		TAVR vs. MT		
	MT (n = 44)	SAVR (n = 52)	TAVR (n = 108)	HR or RR (95% CI)	p Value	HR or RR (95% CI)	p Value	Overall p Value
30-day follow-up								
All-cause death	11 (25.0)	3 (5.8)	6 (5.6)	0.21 (0.06–0.76)	0.017	0.21 (0.08–0.56)	0.002	0.002
Cardiovascular death	10 (23.2)	3 (5.8)	6 (5.6)	0.23 (0.06–0.84)	0.026	0.23 (0.08–0.62)	0.004	0.006
Cerebrovascular events	0 (0.0)	2 (3.8)	6 (5.6)	4.24 (0.21–86.02)	0.50	5.33 (0.31–92.62)	0.18	0.39
Major stroke	0 (0.0)	1 (1.9)	3 (2.8)	2.54 (0.11–60.81)	1.00	2.87 (0.15–54.43)	0.56	0.81
Minor stroke	0 (0.0)	0 (0.0)	1 (0.9)			1.23 (0.05–29.62)	1.00	1.00
Transient ischemic attack	0 (0.0)	1 (1.9)	2 (1.9)	2.54 (0.11–60.81)	1.00	2.05 (0.10–41.85)	1.00	1.00
Myocardial infarction	0 (0.0)	2 (3.8)	1 (0.9)	4.24 (0.21–86.02)	0.50	1.23 (0.05–29.62)	1.00	0.28
All-cause death, major stroke, or MI	11 (25.0)	5 (9.6)	8 (7.4)	0.37 (0.13–1.07)	0.07	0.29 (0.11–0.71)	0.007	0.017
Bleeding	1 (2.3)	5 (9.7)	39 (36.1)	4.21 (0.49–36.03)	0.19	17.79 (2.44–129.57)	0.004	<0.001
Life-threatening	0 (0.0)	2 (3.8)	14 (13.0)	4.24 (0.21–86.02)	0.50	11.89 (0.72–195.04)	0.011	0.009
Major	1 (2.3)	3 (5.9)	14 (13.1)	2.46 (0.26–23.69)	0.44	5.90 (0.78–44.88)	0.09	0.11
Minor	0 (0.0)	0 (0.0)	14 (13.1)			11.89 (0.72–195.04)	0.011	0.001
Acute renal failure	5 (11.6)	17 (32.7)	17 (16.2)	3.07 (1.13–8.32)	0.028	1.49 (0.55–4.03)	0.44	0.031
Vascular complications	0 (0.0)	2 (3.8)	19 (17.7)	4.24 (0.21–86.02)	0.50	16.00 (0.99–259.29)	0.002	0.001
Major	0 (0.0)	2 (3.8)	8 (7.5)	4.24 (0.21–86.02)	0.50	6.97 (0.41–118.20)	0.11	0.15
Minor	0 (0.0)	0 (0.0)	11 (10.2)			9.43 (0.57–156.61)	0.034	0.005
Repeat unplanned intervention	1 (2.3)	2 (3.8)	1 (0.9)	1.71 (0.15–18.83)	0.66	0.41 (0.03–6.57)	0.53	0.51
Permanent pacemaker implantation	1 (2.3)	1 (2.0)	27 (25.6)	0.80 (0.05–12.85)	0.88	11.98 (1.63–88.19)	0.015	0.002
1-year follow-up								
All-cause death	26 (59.2)	7 (13.9)	27 (25.1)	0.16 (0.07–0.38)	<0.001	0.30 (0.18–0.52)	<0.001	<0.001
Cardiovascular death	25 (58.2)	5 (9.6)	24 (22.6)	0.12 (0.05–0.32)	<0.001	0.29 (0.16–0.50)	<0.001	<0.001
Cerebrovascular events	0 (0.0)	2 (3.8)	7 (6.6)	4.24 (0.21–86.02)	0.50	6.15 (0.36–105.41)	0.19	0.25
Major stroke	0 (0.0)	1 (1.9)	4 (3.8)	2.54 (0.11–60.81)	1.0	3.69 (0.20–67.12)	0.32	0.61
Minor stroke	0 (0.0)	0 (0.0)	1 (0.9)			1.23 (0.05–29.62)	1.0	1.00
Transient ischemic attack	0 (0.0)	1 (1.9)	2 (1.9)	2.54 (0.11–60.81)	1.0	2.05 (0.10–41.85)	1.0	1.00
MI	0 (0.0)	3 (6.1)	1 (0.9)	5.93 (0.31–111.74)	0.25	1.23 (0.05–29.62)	1.0	0.10
All cause death, major stroke, or MI	26 (59.2)	9 (17.5)	30 (27.9)	0.23 (0.11–0.48)	<0.001	0.36 (0.21–0.60)	<0.001	<0.001

Values are number of events (incidence rates from life tables %). HR (95% CI) from Cox regressions. In case of zero events, continuity corrected RR (95% CI) and Fisher exact test p values are reported.

CI = confidence interval; HR = hazard ratio; RR = relative risk.

clinical outcomes of patients with low ejection fraction (<50%), low-gradient (<40 mm Hg) severe AS (AVA <0.8 cm^2 or indexed AVA <0.5 $cm^2 \cdot m^{-2}$) according to treatment modality. The investigators found that TAVR improved 2-year survival compared with MT (PARTNER B cohort) and revealed for the first time that LEF-LG severe AS patients undergoing TAVR and SAVR had similar clinical outcomes at 2

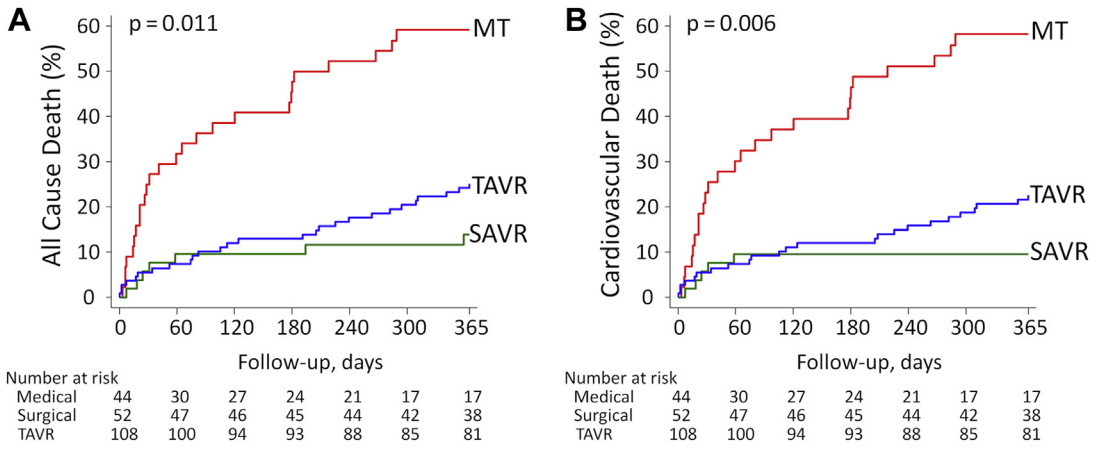
TABLE 6 Adjusted Clinical Outcomes at 30 Days and 1 Year

	Treatment Modality			SAVR vs. MT		TAVR vs. MT		
	MT (n = 44)	SAVR (n = 52)	TAVR (n = 108)	HR (95% CI)	p Value	HR (95% CI)	p Value	Overall p Value
30-day follow-up								
All-cause death	11 (25.0)	3 (5.8)	6 (5.6)	0.64 (0.16–2.61)	0.54	0.36 (0.13–1.04)	0.058	0.17
Cardiovascular death	10 (23.2)	3 (5.8)	6 (5.6)	0.72 (0.17–2.99)	0.65	0.39 (0.13–1.13)	0.08	0.22
All-cause death, major stroke, or MI	11 (25.0)	5 (9.6)	8 (7.4)	1.02 (0.31–3.35)	0.97	0.47 (0.18–1.21)	0.12	0.23
1-year follow-up								
All cause death	26 (59.2)	7 (13.9)	27 (25.1)	0.37 (0.15–0.93)	0.034	0.43 (0.24–0.79)	0.006	0.011
Cardiovascular death	25 (58.2)	5 (9.6)	24 (22.6)	0.30 (0.11–0.84)	0.023	0.41 (0.22–0.76)	0.004	0.006
All-cause death, major stroke, or MI	26 (59.2)	9 (17.5)	30 (27.9)	0.53 (0.23–1.22)	0.13	0.53 (0.30–0.93)	0.028	0.07

Values are number of events (incidence rates from life tables %). Adjusted HR (95% CI) from Cox regressions, adjusting for the following baseline variables: hypercholesterolemia, peripheral vascular disease, SYNTAX score, previous cardiac surgery, atrial fibrillation, and the logistic EuroSCORE after multiple imputations of missing values using chained equations (20 datasets produced).

Abbreviations as in Tables 1 and 5.

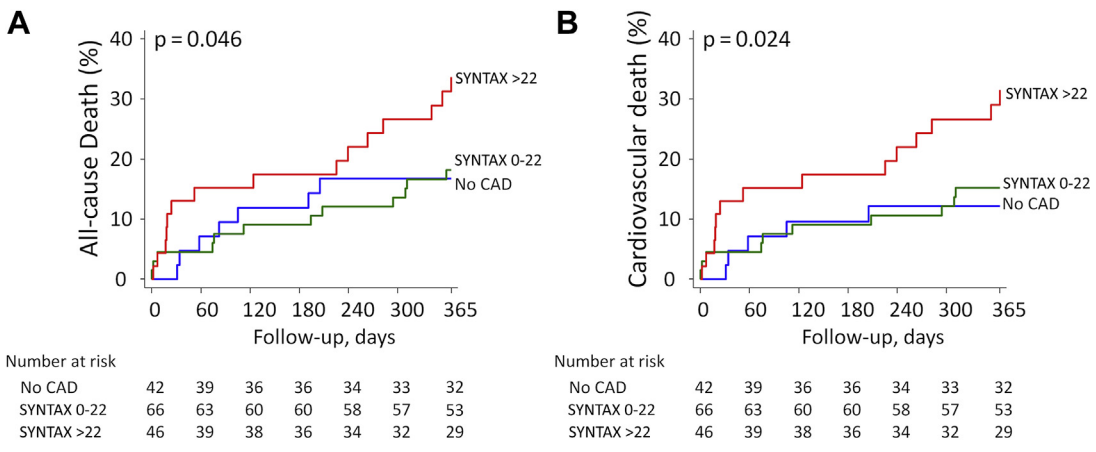
FIGURE 2 Kaplan-Meier Curves for Clinical Outcomes According to Assigned Treatment Modality



Kaplan-Meier analysis of death **(A)** and cardiovascular death **(B)** at 1 year according to the assigned treatment modality. Abbreviations as in Figure 1.

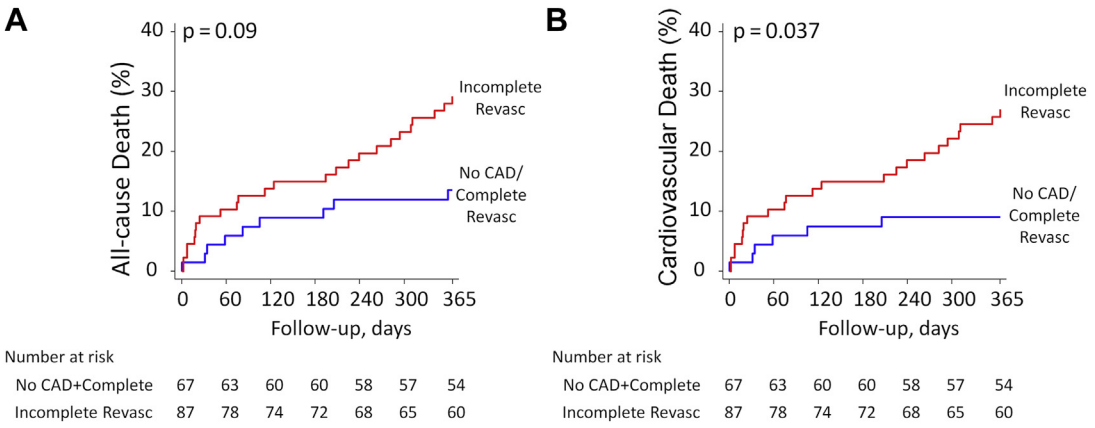
years (PARTNER A cohort) (18). However, this study was limited by the fact that the PARTNER trial systematically excluded all patients with CAD requiring revascularization and an LVEF <20%, and no follow-up echocardiography was reported (18). However, previous studies have shown that 66% to 69% of LEF-LG severe AS patients have concomitant CAD, and 60% to 62% of LEF-LG severe AS patients undergoing SAVR also undergo concomitant CABG (4,6). The present study provides "real-world" clinical outcomes of LEF-LG severe AS patients undergoing revascularization procedures according to the assigned treatment modality. We confirmed that LEF-LG severe AS patients undergoing MT have a dismal outcome and also observed that LEF-LG severe AS patients assigned to TAVR and SAVR had similar outcomes at 30 days and 1 year despite the fact that SAVR patients were at significantly lower operative risk at baseline. CAD was present in almost three-fourths of LEF-LG severe AS patients included in the present study. However, LEF-LG severe AS patients undergoing SAVR were more likely to undergo

FIGURE 3 Kaplan-Meier Curves for Clinical Outcomes Stratified by SYNTAX Score Among TAVR and SAVR Patients Only



Kaplan-Meier analysis of death **(A)** and cardiovascular death **(B)** at 1 year according to CAD severity as assessed using the SYNTAX score in patients with low-flow, low-gradient severe aortic stenosis undergoing either conventional SAVR or TAVR. Patients receiving MT were excluded from this analysis. CAD = coronary artery disease; other abbreviations as in Figure 1.

FIGURE 4 Kaplan-Meier Curves for Clinical Outcomes Stratified by Completeness of Revascularization Among TAVR and SAVR Patients Only



Kaplan-Meier analysis of death **(A)** and cardiovascular death **(B)** at 1 year according to the completeness of revascularization among patients with low-flow, low-gradient severe aortic stenosis undergoing either conventional SAVR or TAVR. Patients receiving MT were excluded from this analysis. Revasc = revascularization; other abbreviations as in Figures 1 and 3.

revascularization procedures compared with patients undergoing TAVR despite a similar degree of CAD complexity at baseline. In addition, a SS higher than 22 was an independent predictor of cardiovascular death at 1 year in LEF-LG severe AS patients undergoing either TAVR or SAVR. Furthermore, incomplete revascularization was an independent predictor of cardiovascular mortality in LEF-LG severe AS patients undergoing TAVR and SAVR. This suggests that revascularization strategies are an important component of the overall management of LEF-LG severe AS patients, particularly in patients with high CAD complexity. Recently, Stefanini et al. (21) found that in an unselected patient population with severe AS undergoing TAVR only, those with a residual SS higher than 14 had a worse clinical outcome at 1 year. Hence, complete revascularization should be the goal

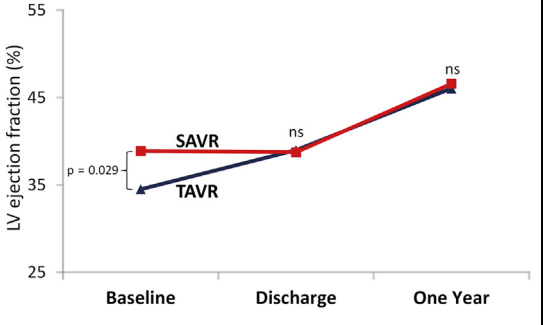
TABLE 7 Post-Procedural Changes in Echocardiographic Parameters

	SAVR (n = 52)	TAVR (n = 108)	p Value
AVA, cm^2			
Baseline	0.73 ± 0.23	0.74 ± 0.21	0.88
Discharge	1.89 ± 0.43	1.80 ± 0.60	0.62
1 year	1.68 ± 0.53	1.76 ± 0.49	0.66
Indexed AVA, $cm^2 \cdot m^{-2}$			
Baseline	0.41 ± 0.12	0.42 ± 0.12	0.57
Discharge	1.03 ± 0.22	1.05 ± 0.37	0.90
1 year	0.94 ± 0.27	1.00 ± 0.27	0.49
Mean gradient, mm Hg			
Baseline	29.3 ± 9.5	28.6 ± 10.3	0.69
Discharge	9.5 ± 3.4	7.2 ± 2.9	0.001
1 year	11.5 ± 3.6	8.1 ± 2.9	<0.001
Peak gradient, mm Hg			
Baseline	48.3 ± 15.9	46.6 ± 16.0	0.53
Discharge	16.9 ± 6.9	12.9 ± 4.9	0.002
1 year	21.0 ± 6.2	15.3 ± 5.6	0.001
LV ejection fraction, %			
Baseline	38.9 ± 12.0	34.5 ± 11.4	0.029
Discharge	38.8 ± 12.6	39.0 ± 12.4	0.92
1 year	46.6 ± 13.2	46.1 ± 12.8	0.88
PASP, mm Hg			
Baseline	45.5 ± 11.9	52.0 ± 13.9	0.016
Discharge	36.2 ± 10.9	46.9 ± 13.9	0.001
1 year	39.6 ± 15.3	42.0 ± 11.8	0.54

Values are mean ± SD.

AVA = aortic valve area; PASP = pulmonary artery systolic pressure; other abbreviations as in Tables 1 and 2.

FIGURE 5 Left Ventricular Ejection Fraction Recovery Over Time



Changes in LVEF over time in patients with low-flow, low-gradient severe aortic stenosis undergoing either conventional SAVR or TAVR. ns = nonsignificant; other abbreviations as in Figure 1.

among LEF-LG severe AS patients with concomitant CAD, and this target may be better achieved with SAVR and CABG in operable LEF-LG severe AS patients with concomitant CAD of high complexity.

STUDY LIMITATIONS. There are several limitations that need to be considered when interpreting the present study. First, this was a single-center, observational study, and therefore our results may contain unmeasured bias. Second, propensity score matching and inverse probability treated weighting were not performed due to the relatively low numbers of patients in each group, and the results should therefore be considered mainly descriptive. However, all clinical outcomes were adjusted for significant univariate predictors of the primary endpoint, and the number of LEF-LG severe AS patients compares favorably with that of the PARTNER substudy (18). Third, the residual SS after CABG has never been validated, and therefore we were unable to determine in the present study whether a certain threshold of residual CAD exists that may be associated with worse clinical outcomes at 1 year. Finally, dobutamine stress echocardiography was performed in only one-fourth of patients, and we were therefore unable to compare the impact of a lack of flow reserve on clinical outcomes according to treatment modality.

CONCLUSIONS

Both TAVR and SAVR improved survival compared with MT in LEF-LG severe AS patients, whereas clinical outcomes of TAVR and SAVR appeared similar among appropriately selected patients with LEF-LG severe AS at 1-year follow-up. Concomitant CAD is highly prevalent among LEF-LG severe AS patients and a baseline SS higher than 22 was an independent predictor of cardiovascular death at 1 year among LEF-LG severe AS patients undergoing either TAVR or SAVR. Furthermore, LEF-LG severe AS patients with concomitant CAD who underwent incomplete revascularization had worse outcomes at 1 year. Therefore, revascularization strategies are an important component of the overall management of LEF-LG severe AS patients undergoing either TAVR or SAVR.

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PERSPECTIVES

WHAT IS KNOWN: Patients with low ejection fraction, low-gradient (LEF-LG) severe aortic stenosis (AS) undergoing conventional surgical aortic valve replacement (SAVR) typically have a high prevalence of concomitant coronary artery disease (CAD) and a poor prognosis.

WHAT IS NEW: A higher SYNTAX score at baseline is associated with significantly higher rates of 1-year cardiovascular mortality among LEF-LG severe AS patients undergoing SAVR and TAVR. LEF-LG severe AS patients undergoing TAVR and SAVR with incomplete revascularization and concomitant CAD have significantly higher cardiovascular mortality rates at 1 year compared with similar patients with no CAD or complete revascularization.

WHAT IS NEXT: Further clinical trials are needed to develop an optimized interventional or surgical strategy for patients with symptomatic LEF-LG severe AS. Refined medical and electrophysiological post-interventional treatment strategies may help reduce the risk of cardiovascular mortality.

REFERENCES

1. Carabello BA, Green LH, Grossman W, Cohn LH, Koster JK, Collins JJ Jr. Hemodynamic determinants of prognosis of aortic valve replacement in critical aortic stenosis and advanced congestive heart failure. Circulation 1980;62:42–8.

2. Brogan WC 3rd, Grayburn PA, Lange RA, Hillis LD. Prognosis after valve replacement in patients with severe aortic stenosis and a low transvalvular pressure gradient. J Am Coll Cardiol 1993;21:1657–60.

3. deFilippi CR, Willett DL, Brickner ME, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. Am J Cardiol 1995;75:191–4.

4. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. Circulation 2000;101:1940–6.

5. O'Sullivan CJ, Stortecky S, Heg D, et al. Clinical outcomes of patients with low-flow, low-gradient, severe aortic stenosis and either preserved or reduced ejection fraction undergoing transcatheter aortic valve implantation. Eur Heart J 2013;34:3437–50.

6. Pereira JJ, Lauer MS, Bashir M, et al. Survival after aortic valve replacement for severe aortic stenosis with low transvalvular gradients and severe left ventricular dysfunction. J Am Coll Cardiol 2002;39:1356–63.

7. Blitz LR, Gorman M, Herrmann HC. Results of aortic valve replacement for aortic stenosis with relatively low transvalvular pressure gradients. Am J Cardiol 1998;81:358–62.

8. Monin JL, Quere JP, Monchi M, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation 2003;108:319–24.

9. Monin JL, Monchi M, Gest V, Duval-Moulin AM, Dubois-Rande JL, Gueret P. Aortic stenosis with severe left ventricular dysfunction and low transvalvular pressure gradients: risk stratification by low-dose dobutamine echocardiography. J Am Coll Cardiol 2001;37:2101–7.

10. Quere JP, Monin JL, Levy F, et al. Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. Circulation 2006;113:1738–44.

11. Clavel MA, Fuchs C, Burwash IG, et al. Predictors of outcomes in low-flow, low-gradient aortic stenosis: results of the multicenter TOPAS Study. Circulation 2008;118:S234–42.

12. Levy F, Laurent M, Monin JL, et al. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. J Am Coll Cardiol 2008;51:1466–72.

13. Tribouilloy C, Levy F, Rusinaru D, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol 2009;53:1865–73.

14. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–704.

15. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

16. Lauten A, Zahn R, Horack M, et al. Transcatheter aortic valve implantation in patients with low-flow, low-gradient aortic stenosis. J Am Coll Cardiol Intv 2012;5:552–9.

17. Le Ven F, Freeman M, Webb J, et al. Impact of low flow on the outcome of high-risk patients undergoing transcatheter aortic valve replacement. J Am Coll Cardiol 2013;62:782–8.

18. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. Circulation 2013;127:2316–26.

19. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.

20. Wenaweser P, Pilgrim T, Kadner A, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. J Am Coll Cardiol 2011;58:2151–62.

21. Stefanini GG, Stortecky S, Cao D, et al. Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation. Eur Heart J 2014;35:2530–40.

22. Genereux P, Palmerini T, Caixeta A, et al. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. Circ Cardiovasc Interv 2011;4:553–61.

23. Farooq V, Girasis C, Magro M, et al. The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy. EuroIntervention 2013;8:1277–85.

24. Genereux P, Palmerini T, Caixeta A, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: the residual SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score. J Am Coll Cardiol 2012;59:2165–74.

25. Farooq V, Serruys PW, Garcia-Garcia HM, et al. The negative impact of incomplete angiographic revascularization on clinical outcomes and its association with total occlusions: the SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial. J Am Coll Cardiol 2013;61:282–94.

26. Clavel MA, Webb JG, Rodes-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. Circulation 2010;122:1928–36.

27. Elmariah S, Palacios IF, McAndrew T, et al. Outcomes of transcatheter and surgical aortic valve replacement in high-risk patients with aortic stenosis and left ventricular dysfunction: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort A). Circ Cardiovasc Interv 2013;6:604–14.

KEY WORDS aortic stenosis, coronary artery disease, surgical aortic valve replacement, transcatheter aortic valve replacement

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