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Original Investigation

Evaluation of Flow After Transcatheter Aortic Valve Replacement in Patients With Low-Flow Aortic Stenosis
A Secondary Analysis of the PARTNER Randomized Clinical Trial

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IMPORTANCE Low-flow (LF) severe aortic stenosis (AS) is an independent predictor of mortality in patients undergoing aortic valve replacement (AVR). Little is known about improvement in flow after AVR and its effects on survival.

OBJECTIVE To determine whether higher flow (left-ventricular stroke volume index [LVSVI]) after transcatheter AVR (TAVR) would indicate better clinical outcomes in this at-risk population.

DESIGN, SETTING, AND PARTICIPANTS A substudy analysis of data from the Placement of Aortic Transcatheter Valves (PARTNER) randomized clinical trial and continued-access registry was conducted. A total of 984 participants with evaluable echocardiograms and baseline LF AS (LVSVI ≤35 mL/m^2) were included. The trial was conducted at 26 sites in the United States and Canada. Patients were stratified after TAVR into tertiles by discharge LVSVI status (severe low flow [SLF], moderate low flow [MLF], and normal flow [(NF]). The present study was conducted from May 11, 2007, to January 9, 2012, with data analysis performed from April 25, 2014, to January 21, 2016.

MAIN OUTCOMES AND MEASURES The primary end point was all-cause mortality at 1 year.

RESULTS Baseline characteristics of 984 patients with LF AS included mean (SD) age, 84 (7) years; 582 (59.1%) men; mean Society of Thoracic Surgeons (STS) score, 11.4% (4.0%); and mean LVSVI, 27.6 (5.0) mL/m^2. The discharge LVSVI values by group were SLF, 23.1 (3.5) mL/m^2; MLF, 31.7 (2.2) mL/m^2; and NF, 43.1 (7.0). All-cause mortality at 1 year was SLF, 26.5%; MLF, 20.1%; and NF, 19.6% (P = .045). Mean LVSVI normalized by 6 months in the MLF (35.9 [9.3] mL/m^2) and NF (38.8 [11.1] mL/m^2) groups, but remained low in the SLF group at 6 months and 1 year (31.4 [8.4] and 33.0 [8.3] mL/m^2], respectively) (P < .001 for all groups). Reported as multivariate hazard ratio, mortality at 1 year was higher in the SLF group compared with the other groups (1.61; 95% CI, 1.17-2.23; P = .004). In addition to SLF, sex (1.59; 95% CI, 1.18-2.13; P = .002), presence of atrial fibrillation (1.41; 95% CI, 1.06-1.87; P = .02), STS score (1.03; 95% CI, 1.01-1.06; P = .02), presence of moderate or severe mitral regurgitation at discharge (1.65; 95% CI, 1.21-2.26; P = .001), pre-TAVR mean transvalvular gradient (0.98; 95% CI, 0.97-0.99; P = .004), and effective orifice area index (1.87; 95% CI, 1.09-3.19; P = .02) were independent predictors of 1-year mortality.

CONCLUSIONS AND RELEVANCE Severe LF at discharge is associated with an increased risk of mortality following TAVR in patients with severe AS and preexisting LF. The identification of remedial causes of persistent LF after TAVR may represent an opportunity to improve the outcome of these patients.

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Invited Commentary

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Low-flow (LF) aortic stenosis (AS) is present in 5% to 10% of patients with severe AS and is a predictor of mortality for patients undergoing surgical and transcatheter aortic valve replacement (SAVR and TAVR) or medical treatment.[1-3] Patients with LF AS can be categorized into 2 subtypes: classic LF AS (ejection fraction <50%) and paradoxical LF AS (ejection fraction ≥50%).[4-6]

Transcatheter aortic valve replacement is an attractive option for patients with both types of LF AS because it is less invasive than SAVR and does not require cardiopulmonary bypass.[7,8] The American Heart Association/American College of Cardiology 2014 valvular guidelines[6] currently recommend a class IIa indication for SAVR in patients with LF AS and that those at high risk for SAVR can be considered for TAVR. Recent studies[2,9-13] have demonstrated that patients with low ejection fraction LF AS have better recovery of ejection fraction and improved functional status with TAVR compared with those who undergo SAVR. To better understand the potential benefit of TAVR in LF AS, we examined the post-TAVR hemodynamics of a large population of patients in the Placement of Aortic Transcatheter Valves (PARTNER) study.[14] We sought to characterize the effects of TAVR on blood flow and hypothesized that a higher postprocedural left ventricular stroke volume index (LVSVI) achieved by hospital discharge would be associated with improved clinical outcomes in patients undergoing TAVR.

Key Points

Question What are the effects on outcome and time course of changes in flow after transcatheter aortic valve replacement (TAVR) in patients with low-flow aortic stenosis?

Findings In this secondary analysis of 984 patients in the PARTNER randomized clinical trial with low-flow severe aortic stenosis undergoing TAVR, flow improved in approximately two-thirds of patients by 6 months. Severe low flow at discharge was independently associated with an increased risk of 1-year mortality.

Meaning The identification of remedial causes of persistent low flow after TAVR may represent an opportunity to improve the outcome of these patients.

Methods

The PARTNER trial was a multicenter, randomized clinical trial comparing TAVR with SAVR in high-risk patients (cohort A) and standard therapy in patients who were not considered to be suitable candidates for surgery (ie, inoperable, cohort B).[7,8] All patients had symptoms (New York Heart Association [NYHA] classes II-IV) and severe AS. The present study was a post hoc analysis performed on patients included in the PARTNER trial and continuing access registry.

The study was approved by the institutional review boards of the participating sites, and all patients provided written informed consent. The database for the study is maintained at the Cardiovascular Research Foundation, and independent statistical analyses can be requested by investigators. The present study (conducted from May 11, 2007, to January 9, 2012) performed by the investigators used deidentified data.

Inclusion criteria for this trial included a site-measured echocardiographic aortic valve area of less than 0.8 cm^2 (or indexed aortic valve area <0.5 cm^2/m^2) and either a mean transvalvular gradient of 40 mm Hg or more or a peak aortic jet velocity of 4.0 m/s (64 mm Hg) or more on resting or dobutamine stress echocardiogram. Important exclusion criteria included substantial coronary artery disease requiring revascularization, ejection fraction less than 20%, or severe (4+) aortic regurgitation or mitral regurgitation. Patients received a balloon-expandable bovine pericardial heart valve system (Sapien; Edwards Lifesciences Corp). The primary end point for the study (both cohorts) was all-cause mortality at 1 year, but follow-up has continued, allowing subsequent analyses with adjudicated events.[15,16] All echocardiograms were analyzed by an independent core laboratory.[17] After enrollment concluded in the randomized clinical trial in August 2009, but before commercial approval of the transcatheter heart valve, sites were able to enroll patients in a continuing access registry (March 16, 2009, to January 9, 2012), which used the same inclusion/exclusion criteria, core laboratory assessments, and clinical events committee adjudication process.

In the present analysis, all patients who received a TAVR with evaluable echocardiograms and LF AS (LVSVI ≤35 mL/m^2) formed the study population. These patients were subsequently classified into 3 groups by tertiles of discharge LVSVI: severe low flow (SLF), moderate low flow (MLF), and normal flow (NF). Patients were also divided into groups of either classic (ejection fraction <50%) or paradoxical (ejection fraction ≥50%) LF AS and were then separated into tertiles by discharge LVSVI for separate analysis.

Echocardiographic Measurements

All baseline and follow-up echocardiograms were interpreted by an independent core laboratory housed at the Duke Clinical Research Institute. Study workflow, reproducibility testing, image acquisition and analysis, and quality assurance data have been published.[18] All chamber variables were measured in standard views according to the recommendations of the American Society of Echocardiography.[19] Left ventricular volumes and ejection fraction were measured using the biplane Simpson volumetric method[19] combining apical 4-chamber and 2-chamber views when possible; if image quality was inadequate, ejection fraction was estimated visually in 5 percentage point increments. Stroke volume and cardiac output were calculated by Doppler using the velocity time integral of the distal LV outflow tract and its diameter in midsystole of the aortic annulus in the parasternal long axis view at baseline.[17,19] After implant, both Doppler and outflow tract measurements were obtained just below the edge of the valve stent.

Statistical Analysis

All continuous variables are summarized as mean (SD) or medians and quartiles. The Kruskal-Wallis test for medians and analysis of variance for means were used to compare the groups. Categorical variables are described as number (percentage) and compared using a χ^2 test or Fisher exact test, as appropriate.

Table 1. Clinical Characteristics of Patients Undergoing TAVR[a]

Characteristic	SLF (n = 328)	MLF (n = 328)	NF (n = 328)	Overall *P* Value	*P* Value[b]		
					SLF vs MLF	SLF vs NF	MLF vs NF
Age, mean (SD)	84 (8)	84 (7)	85 (7)	.01	.51	.005	.03
Male sex, No. (%)	182 (55.5)	202 (61.6)	198 (60.4)	.24	.11	.21	.75
BMI, mean (SD)	26.98 (6.11)	27.25 (6.13)	26.35 (6.47)	.17	.59	.19	.07
STS score, mean (SD)[c]	11.70 (4.70)	11.22 (3.70)	11.32 (3.49)	.26	.12	.22	.76
Diabetes, No. (%)	132 (40.2)	134 (40.9)	111 (33.9)	.13	.87	.10	.07
NYHA class IV, No. (%)	158 (48.2)	159 (48.5)	144 (43.9)	.42	.94	.27	.24
Coronary artery disease, No. (%)	272 (82.9)	256 (78.0)	253 (77.4)	.16	.11	.07	.83
Prior cardiac events, No. (%)							
CABG	156 (47.6)	149 (45.4)	148 (45.3)	.80	.58	.55	.97
Stroke or TIA	88 (27.5)	78 (24.1)	82 (25.6)	.62	.33	.59	.67
Pacemaker	85 (25.9)	79 (24.2)	88 (26.9)	.72	.60	.77	.42
Peripheral arterial disease, No. (%)	134 (41.9)	142 (43.6)	126 (39.0)	.49	.67	.46	.24
Concomitant disease, No. (%)							
Renal	59 (18.0)	51 (15.6)	54 (16.6)	.71	.41	.63	.74
Liver	6 (1.8)	6 (1.8)	3 (0.9)	.54	.99	.31	.32
COPD	156 (47.6)	157 (47.9)	127 (38.6)	.03	.94	.02	.02
6-min Walk test, mean (SD), m	146 (96)	169 (105)	157 (94)	.07	.18	.87	.24
Death, No. (%)							
In-hospital	9 (2.7)	6 (1.8)	3 (0.9)	.22	.43	.08	.31
30 d	12 (3.7)	8 (2.4)	5 (1.5)	.22	.36	.09	.41
1 y	85 (26.5)	65 (20.1)	63 (19.6)	.045	.055	.02	.74

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MLF, moderate low flow; NF, normal flow; NYHA, New York Heart Association; SLF, severe low flow; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack.

[a] Minor discrepancies between the number of patients shown and the percentage of the total study population are the result of missing data.

[b] *P* values were not corrected for multiple pairwise comparisons.

[c] Score indicates the probability of mortality at 30 days by measuring patient risk at the time of surgery on a scale from 0% to 100%. An STS score of less than 4% is generally considered low risk; 4% to 8%, intermediate risk; and higher than 8%, high risk.

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 with the use of the log-rank test. We performed univariate and multivariate Cox regression models to determine univariate and multivariate predictors of 1-year all-cause mortality.

A separate analysis using a linear regression model was done to assess indicators of an increase in LVSVI after TAVR. The response variable was the difference in LVSVI between baseline and discharge. The following variables were included in the regression model: age, sex, ejection fraction, mean transvalvular gradient, NYHA class, moderate or severe mitral regurgitation on discharge echo, moderate or severe aortic regurgitation on discharge echo, aortic valve area index on discharge echocardiogram, and Society of Thoracic Surgeons (STS) score. This score indicates the probability of mortality at 30 days by measuring patient risk at the time of surgery on a scale from 0% to 100%; an STS score of less than 4% is generally considered low risk; 4% to 8%, intermediate risk; and higher than 8%, high risk.

We performed statistical analyses using SAS, version 9.4 (SAS Institute Inc). $P < .05$ was considered statistically significant. Data analysis for the present study was conducted from April 25, 2014, to January 21, 2016.

Results

Baseline Characteristics

A total of 984 patients with LF AS who underwent TAVR in the PARTNER randomized clinical trial or were within the continuing access registry were included in this study. The mean (SD) age was 84 (7) years, 582 (59.1%) were male, and the mean (SD) STS score was 11.4% (4.0%); data are reported by group in **Table 1**. There were no significant differences between the NF, MLF, and SLF groups in the following comorbidities: coronary artery disease, prior coronary artery bypass grafting, diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure (all NYHA classes), prior cerebrovascular disease, chronic kidney disease, and liver disease.

Procedure

The procedural characteristics of the LF AS patients undergoing TAVR by group are presented in the eTable in the Supplement. There was a significantly lower percentage of transfemoral cases in the SLF group compared with the MLF and NF groups. There was no significant difference in valve size used or procedural time among the 3 groups. Hospital length of stay was longer in patients with SLF.

Table 2. Echocardiographic Characteristics of Patients Undergoing TAVR

Characteristic	Mean (SD)			*P* Value for All	*P* Value[a]		
	SLF (n = 328)	MLF (n = 328)	NF (n = 328)		SLF vs MLF	SLF vs NF	MLF vs NF
Baseline Echocardiogram							
Ejection fraction, %	47 (14)	49 (13)	48 (14)	.10	.03	.25	.32
Left ventricular							
Stroke volume, mL	47.8 (11.2)	52.4 (10.9)	52.3 (10.1)	.005	.02	.001	.36
Stroke volume index, mL/m^2	25.9 (5.3)	28.2 (4.6)	28.8 (4.3)	<.001	<.001	<.001	.07
End diastolic dimension, cm	4.58 (0.76)	4.63 (0.74)	4.61 (0.82)	.72	.43	.60	.79
End systolic dimension, cm	3.54 (0.94)	3.51 (0.93)	3.49 (0.96)	.84	.75	.86	.78
Mass, g	246 (74)	254 (76)	262 (75)	.03	.18	.008	.20
Mean transvalvular gradient, mm Hg	38.90 (13.07)	41.21 (13.13)	42.18 (13.24)	.005	.02	.001	.35
Aortic valve							
Area, cm^2	0.56 (0.15)	0.57 (0.15)	0.57 (0.16)	.47	.25	.35	.83
Area index, cm^2/m^2	0.30 (0.08)	0.31 (0.07)	0.31 (0.08)	.18	.42	.07	.31
Moderate or severe regurgitation, %							
Mitral	30	24	28	.26	.08	.59	.22
Aortic	11	8	9	.34	.14	.27	.69
Discharge Echocardiogram							
Ejection fraction, %	49 (13)	52 (12)	52 (12)	<.001	.004	<.001	.29
Left ventricular							
Stroke volume, mL	43.1 (8.5)	59.4 (8.5)	78.1 (14.5)	<.001	.001	<.001	.79
Stroke volume index, mL/m^2	23.1 (3.5)	31.7 (2.2)	43.1 (7.0)	<.001	<.001	<.001	<.001
End diastolic dimension, cm	4.57 (0.77	4.64 (0.78)	4.67 (0.81)	.27	.24	.12	.70
End systolic dimension, cm	3.41 (0.87)	3.42 (0.90)	3.37 (0.92)	.81	.95	.60	.55
Mass, g	239 (74)	250 (74)	256 (71)	.01			
Mean transvalvular gradient, mm Hg	8.8 (3.9)	10.1 (4.7)	11.5 (4.7)	<.001	<.001	<.001	<.001
Aortic valve							
Area, cm^2	1.30 (0.34)	1.59 (0.40)	1.89 (0.50)	<.001	<.001	<.001	<.001
Area indexed, cm^2/m^2	0.70 (0.18)	0.86 (0.21)	1.04 (0.28)	<.001	<.001	<.001	<.001
Moderate or severe regurgitation, %							
Mitral	20.1	18.4	18	.78	.58	.51	.92
Aortic	8.6	9.8	16.2	.005	.61	.003	.92

Abbreviations: MLF, moderate low flow; NF, normal flow; SLF, severe low flow; TAVR, transcatheter aortic valve replacement.

[a] *P* values were not corrected for multiple pairwise comparisons.

Echocardiographic Variables

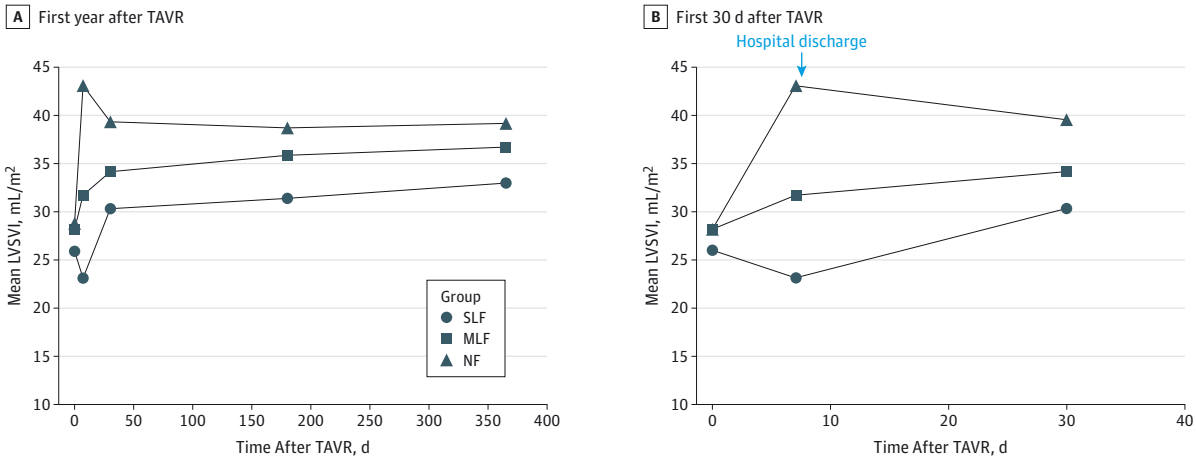
The mean LVSVI among all LF AS patients was 27.6 (5.0) mL/m^2. The baseline (pre-TAVR) LVSVI was lower in the SLF group (25.9 [5.3] mL/m^2) compared with the MLF and NF groups (28.2 [4.6] and 28.8 [4.3] mL/m^2, respectively) (**Table 2**). As per definition, there were significant differences in LVSVI at discharge among all 3 groups. At 30 days, 6 months, and 1 year, the disparity in LVSVI remained significantly different between the 3 groups (**Figure 1**). Mean LVSVI remained low in the SLF and MLF groups at 30 days, but normalized by 6 months in the MLF and NF groups (35.9 [9.3] mL/m^2 and 38.8 [11.1] mL/m^2) compared with the SLF group, which had LF at 6 months (31.4 [8.4] mL/m^2) and at 1 year (33.0 [8.3] mL/m^2; $P < .001$ for all groups) (Figure 1).

The SLF group had the lowest mean transvalvular gradient (39 [13] mm Hg) compared with MLF (41 [13]) and NF (42 [13]) patients ($P = .005$). There was no significant difference in baseline moderate to severe mitral or aortic regurgitation between groups. However, there was a significant difference ($P = .003$) in the incidence of moderate or severe aortic regurgitation after TAVR, with NF patients having the highest incidence (16.2%) compared with SLF (8.6%) and MLF (9.8%) patients.

Mortality Rates

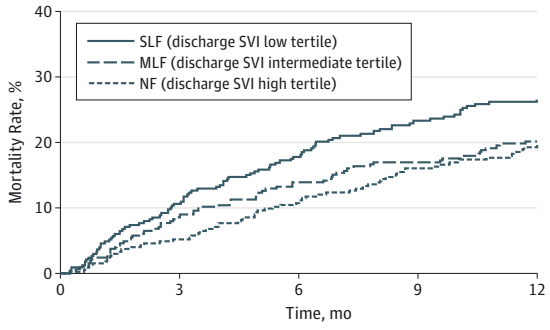
The 1-year all-cause mortality rate among LF AS patients undergoing TAVR was 22.1%. Patients with SLF had the highest mortality rate (26.5%), which was higher than that of the NF group (hazard ratio [HR], 1.45; 95% CI, 1.05-2.01; $P = .02$), the MLF group (HR, 1.37; 95% CI, 0.99-1.89; $P = .054$), and the combined MLF and NF groups (HR, 1.41; 95% CI, 1.07-1.86; $P = .01$). The mortality rates for the MLF and NF groups were 20.1% and 19.6%, respectively (**Figure 2**). Patients with SLF had the highest 1-year cardiovascular mortality rate at 11.4% compared with 7.9% and 6.0% for the MLF and NF groups, respectively. There was no significant difference in 1-year mortality rates between patients who did and those who did not have a 20% increase in LVSVI from baseline to discharge (eFigure 1 in the Supplement).

Figure 1. Mean Left-Ventricular Stroke Volume Index (LVSVI) by Echocardiogram for Patients With Low-Flow Aortic Stenosis Across 1 Year After Transcatheter Aortic Valve Replacement (TAVR)



MLF indicates moderate low flow; NF, normal flow; and SLF, severe low flow.

Figure 2. One-Year Mortality Rates Among the Severe Low-Flow (SLF), Moderate Low-Flow (MLF), and Normal-Flow (NF) Groups After Transcatheter Aortic Valve Replacement



No. at risk					
SLF	328	291	263	239	210
MLF	328	298	277	264	226
NF	328	309	289	269	236

Log-rank analysis for overall survival, $P = .045$; SLF vs MLF, $P = .055$; SLF vs NF, $P = .02$; and MLF vs NF, $P = .74$. SVI indicates stroke volume index.

Classic and Paradoxical LF AS

There were 424 patients (43.1%) with classic LF AS and 559 patients (56.8%) with paradoxical LF AS (data missing on 1 patient). The time course of improvement in flow after TAVR was similar in the classic and paradoxical LF groups (eFigure 2 in the Supplement). Among patients with classic LF AS, there was not a significant difference in survival among the 3 groups (eFigure 3A in the Supplement), but higher survival was observed in patients whose flow normalized (NF) after TAVR. Among patients with paradoxical LF AS, those with SLF had the worst outcomes with a 1-year mortality rate of 24.7% (eFigure 3B in the Supplement).

Concomitant Valvular Heart Disease

Patients were analyzed separately by the presence or absence of moderate to severe mitral regurgitation at discharge (eFigure 4 and eFigure 5 in the Supplement). Similar nonsignificant trends in mortality with lower LVSVI were observed, but patients with moderate to severe mitral regurgitation had higher absolute mortality rates compared with those with trace to mild mitral regurgitation. Furthermore, within the persistent SLF and MLF groups, patients with moderate or severe mitral regurgitation at discharge had significantly higher mortality rates compared with patients in the same group who had no or trace mitral regurgitation. Since moderate or severe aortic regurgitation can elevate LVSVI, a separate sensitivity analysis was performed on patients with mild or less aortic regurgitation at discharge. Patients in the SLF range (mean LVSVI, 23.0 [3.5]) still had a significantly higher mortality rate compared with patients with MLF (mean LVSVI, 31.5 [2.2] and NF (mean LVSVI, 42.4 [6.2]) (eFigure 6 in the Supplement).

Univariate and Multivariate Analysis

In univariate and multivariate analysis, independent indicators of 1-year mortality were SLF group, sex, presence of atrial fibrillation, STS score, pre-TAVR mean gradient, effective orifice area index, and presence of moderate to severe mitral regurgitation at discharge (**Table 3**). Age, ejection fraction, transapical access, moderate or severe post-TAVR aortic regurgitation, and presence of classic vs paradoxical LF AS were not indicators of adjusted 1-year mortality (Table 3).

A separate analysis was done to assess indicators of an increase in LVSVI after TAVR. A lower baseline ejection fraction was an indicator of a decrease in LVSVI ($P < .001$), and a higher mean transvalvular gradient ($P = .006$) or moderate to severe aortic regurgitation ($P = .004$) on discharge echocardiogram were indicative of an increase in LVSVI.

Discussion

There are 5 major findings from this study. First, in patients with LF AS who underwent TAVR, those with severe LF (<28 mL/m^2)

Table 3. Clinical Indicators of 1-Year Mortality After TAVR

	Univariate Analysis		Multivariate Analysis	
Indicator	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.01 (0.99-1.03)	.20	ND	
Male sex	1.50 (1.12-2.00)	.006	1.59 (1.18-2.13)	.002
Atrial fibrillation	1.43 (1.08-1.90)	.01	1.41 (1.06-1.87)	.02
COPD	1.21 (0.92-1.58)	.18	ND	
Transapical access	1.21 (0.92-1.59)	.17	ND	
Ejection fraction	0.99 (0.98-1.00)	.09	ND	
STS score[a]	1.03 (1.00-1.05)	.03	1.03 (1.01-1.06)	.02
Discharge SLF vs MLF and NF combined	1.41 (1.07-1.86)	.01	1.61 (1.17-2.23)	.004
Paradoxical vs classic LF AS	0.77 (0.59-1.01)	.06	ND	
Mean transvalvular gradient	0.98 (0.97-0.99)	<.001	0.98 (0.97-0.99)	.004
Moderate or severe mitral regurgitation at discharge	1.43 (1.07-1.90)	.01	1.65 (1.21-2.26)	.001
Moderate or severe aortic regurgitation at discharge	0.93 (0.57-1.50)	.75	ND	
Effective orifice area index	1.50 (0.92-2.43)	.10	1.87 (1.09-3.19)	.02

Abbreviations: AS, aortic stenosis; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LF, low flow; MLF, moderate LF; ND, not done; NF, normal flow; SLF, severe LF; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

[a] Score indicates the probability of mortality at 30 days by measuring patient risk at the time of surgery on a scale from 0% to 100%. An STS score of less than 4% is generally considered low risk; 4% to 8%, intermediate risk; and higher than 8%, high risk.

noted on their discharge echocardiogram had persistent LF during 1 year of follow-up, but those with MLF and NF achieved normalized flow by 6 months. Second, patients with severe LF AS had significantly lower 1-year survival compared with those with higher discharge LVSVI levels. Third, in both classic and paradoxical LF AS, patients with severe LF had the worst clinical outcomes. Fourth, sex, pre-TAVR transvalvular gradient, atrial fibrillation, presence of moderate or severe mitral regurgitation, STS score, and effective orifice area index were other multivariate indicators of higher 1-year mortality. Fifth, patients with both persistent LF and moderate to severe mitral regurgitation at discharge had particularly poor outcomes.

Mortality in Patients With LF AS Undergoing TAVR

As previously reported,[1] patients with LF AS in the PARTNER trial (cohorts A and B only) had a significantly higher 1-year mortality rate compared with NF AS patients undergoing TAVR (37% vs 28%). The lower 1-year mortality rates for patients undergoing TAVR observed in our present study is likely related to improved operator experience, patient selection, and advances in device technology, since a large number patients were included from the later continuing-access registry.

In patients with LF AS, postprocedure assessment of LVSVI has not been characterized as a method of risk stratifying patients undergoing TAVR. Instead, the SAVR and TAVR literature[2,20-22] has emphasized the importance of preprocedure patient selection. Preoperative risk scores, atrial fibrillation, low preoperative mean transvalvular gradient, lack of contractile reserve, multivessel coronary artery disease, and LF all indicate the probability of late mortality in patients undergoing AVR. Our study confirms the importance of patient selection since sex and STS score were independent predictors of 1-year outcome.

In patients undergoing TAVR, preprocedural hemodynamic markers (eg, LF and mean transvalvular gradient) and procedural characteristics (eg, transapical access) are indicators of poor outcomes.[1,13,23] In our study, patients with persistent SLF after TAVR were more likely to have undergone a transapical procedure. The transapical approach may contribute to a delay in LV function recovery, but when it was included in the multivariate analysis it was not an indicator of 1-year mortality.[24] Recently, Le Ven et al[25] demonstrated among all AS patients that an LVSVI of 35 mL/m^2 or less after TAVR was indicative of 6-month and 1-year mortality. Combining these results with those of our study suggests that patients with preprocedural NF who develop LF, as well as patients with preprocedural LF and persistent LF after the procedure, have worse outcomes. Specifically among patients with LF AS, our study also indicates that a low discharge LVSVI may be a signal of concomitant untreated abnormalities (eg, mitral regurgitation) that can provide additional prognostic information.

Changes in LVSVI After TAVR

Previous studies have focused on improvement in left ventricular ejection fraction in patients with classic LF AS. Clavel et al[12] demonstrated that female sex, lack of atrial fibrillation, change in aortic valve area, and the absence of preprocedural coronary artery disease were multivariate predictors of improvement in ejection fraction after TAVR, which in turn, resulted in better functional capacity and long-term outcomes. Patients with decreased ejection fraction and AS undergoing TAVR have an increase in ejection fraction by hospital discharge that continues to improve at 1-year follow-up.[12,26] Unlike ejection fraction, changes in LVSVI among patients with LF AS after TAVR have not been well characterized. Our findings correlate with those of a recent study[25] demonstrating that, within the LF AS subgroup, some patients have normalized LVSVI at hospital discharge, but others exhibit persistent LF (with a decline in LVSVI), which is associated with worse outcome. Similarly, in our analysis, these differences remained over time. The SLF group had persistent LF during 1 year of follow-up and the MLF and NF groups had normalized LVSVI between 30 days and 6 months. We observed that a lower baseline EF was indicative of lower LVSVI after TAVR, but the presence of moderate to severe aortic regurgitation and a higher transvalvular gradient were indicative of an increase in LVSVI.

Determining which patients achieve normalization of their LVSVI after TAVR may depend on the degree of myocardial disease due predominantly to AS rather than other abnormalities. Patients with more intrinsic myocardial disease as evidenced by a lower ejection fraction, lower baseline transvalvular gradient, and lower baseline LVSVI were less likely to exhibit an immediate increase in LVSVI. The preferred clinical method for distinguishing these entities in patients with classic LF AS is preprocedure dobutamine stress echocardiography for assessment of contractile or flow reserve; however, many patients without contractile reserve still benefit from AVR compared with medical treatment.[27] These differences in concomitant myocardial disease and contractile reserve likely represent the source for later normalization of LVSVI seen in the MLF and NF groups and may contribute to the higher 1-year mortality rates noted in patients with SLF. However, making this distinction in patients with paradoxical LF AS is more difficult. These patients tend to have a higher global LV hemodynamic load as measured by valvuloarterial impedance. Currently, these patients are not stratified by any preprocedure hemodynamic measurements, such as by valvuloarterial impedance or systemic vascular resistance, which may explain why a mortality difference was seen in the paradoxical group but not in the classic group.[4]

Finally, when evaluating causes for higher and lower LVSVI after TAVR, it is important to recognize concurrent valvular disease. As expected, the presence of moderate to severe aortic regurgitation at discharge was indicative of an increase in postprocedural LVSVI. However, aortic regurgitation was not an independent predictor of 1-year mortality because it was likely masked by other comorbidities in this higher-risk LF population. When patients with moderate to severe aortic regurgitation at discharge were excluded from the analysis, there was a similar trend in mortality (eFigure 6A in the Supplement). However, an increase in LVSVI alone does not account for the better outcomes observed, since there was not a mortality difference among patients with none, trace, or mild aortic regurgitation with and without a 20% increase in LVSVI (eFigure 6B in the Supplement). We also found that effective orifice area index was an independent predictor of mortality, consistent with previous studies of the effect of patient-prosthesis mismatch after both SAVR and TAVR.[4,11,12,21]

Role of Concomitant Mitral Regurgitation

In our multivariate analysis, we found that postprocedural moderate to severe mitral regurgitation was indicative of 1-year mortality among patients with LF AS. We also found that patients with persistent LF at discharge (SLF and MLF groups) with moderate to severe mitral regurgitation had worse 1-year clinical outcomes compared with patients in the same group with none, trace, or mild mitral regurgitation.

The effect of mitral regurgitation in patients undergoing TAVR remains controversial. Previous studies[28,29] have demonstrated that moderate or severe mitral regurgitation was an indicator of late mortality among patients with low-ejection fraction, low-gradient AS undergoing TAVR. However, in a recent PARTNER trial analysis,[29] the presence of moderate or severe mitral regurgitation did not predict 2-year outcomes among all patients undergoing TAVR. The prevalence of moderate or severe mitral regurgitation is higher among patients with classic LF AS compared with those who had high-gradient NF AS. Patients with classic LF AS tend to have dilated LV cavities with annular dilatation leading to functional mitral regurgitation.[27] Previous analyses[30] in TAVR cohorts have shown that patients with functional mitral regurgitation, decreased ejection fraction, and increased LV cavity sizes exhibit the most improvement in mitral regurgitation severity after TAVR. Therefore, patients with predominantly functional mitral regurgitation in the presence of LF AS may represent an identifiable therapeutic target for TAVR. It is not surprising that moderate and severe mitral regurgitation continue to persist from baseline to discharge echocardiogram since TAVR does not address mitral regurgitation severity immediately and can affect functional mitral regurgitation only after significant reverse LV remodeling has occurred. Consequently, persistent mitral regurgitation will continue to reduce forward stroke volume despite the therapeutic benefit of TAVR, which may cause LF AS to persist. The benefit of percutaneous mitral valve therapies after TAVR in this patient population has yet to be shown and may represent an area for further investigation.

Limitations

The patients with LF AS included in this analysis represent a mixed population of those with a resting transvalvular gradient greater than or equal to 40 mm Hg or less than 40 mm Hg on baseline echocardiogram. Data regarding dobutamine stress echocardiography were not collected prospectively for patients with a resting transvalvular gradient less than 40 mm Hg and were not available for this analysis. We analyzed LF using the Doppler-derived, 2-dimensional, LV outflow tract diameter and velocity-time integral. The definition of LF is not standardized in the literature, but we chose a definition (LVSVI ≤35 mL/m^2) that has been commonly used. It is possible that a 3-dimensional echocardiographic or computed tomographic assessment of the outflow tract dimensions or invasive hemodynamic assessment could lead to different values and conclusions.[31,32] Finally, our analysis was retrospective and subject to the limitations of an observational study. All patients with LF received the same treatment modality with TAVR and were not compared with patients who underwent other treatments, so the comparisons and conclusions should be validated in a prospective trial. Nonetheless, the present study is an analysis of a large randomized trial with core laboratory-assessed echocardiographic data.

Conclusions

Patients with LF AS undergoing TAVR represent a heterogeneous population with a higher mortality rate than patients with NF high-gradient AS. Many of the differences observed within this subset of patients stem from preexisting cardiac disease and its interaction with AS. Although flow improved in most patients by 6 months after TAVR, severe LF at discharge persisted in up to one-third of the patients and was independently associated with higher 1-year mortality rates. The identification of remedial causes of persistent LF after TAVR may represent an opportunity to improve the outcome of these patients.

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