

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)

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on behalf of the PARTNER Investigators

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Transcatheter Aortic Valve Replacement

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)

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Background—The Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated similar survival after transcatheter and surgical aortic valve replacement (TAVR and SAVR, respectively) in high-risk patients with symptomatic, severe aortic stenosis. The aim of this study was to evaluate the effect of left ventricular (LV) dysfunction on clinical outcomes after TAVR and SAVR and the impact of aortic valve replacement technique on LV function.

Methods and Results—The PARTNER trial randomized high-risk patients with severe aortic stenosis to TAVR or SAVR. Patients were stratified by the presence of LV ejection fraction (LVEF) <50%. All-cause mortality was similar for TAVR and SAVR at 30-days and 1 year regardless of baseline LV function and valve replacement technique. In patients with LV dysfunction, mean LVEF increased from 35.7±8.5% to 48.6±11.3% ($P<0.0001$) 1 year after TAVR and from 38.0±8.0% to 50.1±10.8% after SAVR ($P<0.0001$). Higher baseline LVEF (odds ratio, 0.90 [95% confidence interval, 0.86, 0.95]; $P<0.0001$) and previous permanent pacemaker (odds ratio, 0.34 [95% confidence interval, 0.15, 0.81]) were independently associated with reduced likelihood of ≥10% absolute LVEF improvement by 30 days; higher mean aortic valve gradient was associated with increased odds of LVEF improvement (odds ratio, 1.04 per 1 mm Hg [95% confidence interval, 1.01, 1.08]). Failure to improve LVEF by 30 days was associated with adverse 1-year outcomes after TAVR but not SAVR.

Conclusions—In high-risk patients with severe aortic stenosis and LV dysfunction, mortality rates and LV functional recovery were comparable between valve replacement techniques. TAVR is a feasible alternative for patients with symptomatic severe aortic stenosis and LV dysfunction who are at high risk for SAVR.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00530894.

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Key Words: aortic valve replacement ■ heart failure ■ surgery ■ transcatheter aortic valve implantation ■ ventricular dysfunction, left

Left ventricular (LV) dysfunction portends an increased risk of perioperative mortality in patients undergoing surgical aortic valve replacement (SAVR) for symptomatic severe aortic stenosis (AS).¹⁻⁵ Although patients with LV dysfunction face increased early risk, SAVR for severe AS is associated with a large survival advantage and improvements in LVEF and clinical symptoms when compared with conservative management, regardless of baseline LV function.^{2,6-8} However, despite

these benefits, the operative risk attributable to LV dysfunction, in combination with advanced age and other comorbid conditions, may preclude surgical intervention.⁸

Editorial see p 596

Transcatheter aortic valve replacement (TAVR) has emerged as an effective and safe alternative for inoperable patients and those thought to possess high operative risk.⁹⁻¹¹ Evidence

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WHAT IS KNOWN

- Left ventricular dysfunction is associated with adverse outcomes after surgical aortic valve replacement, but little is known about the impact of left ventricular ejection fraction on outcomes after transcatheter aortic valve replacement.
- Data from nonrandomized analyses suggest that transcatheter aortic valve replacement is associated with superior postoperative left ventricular ejection fraction recovery compared with surgical aortic valve replacement; however, significant differences in patient characteristics make such nonrandomized comparisons difficult to interpret.

WHAT THE STUDY ADDS

- Within the Placement of Aortic Transcatheter Valves (PARTNER) trial, left ventricular dysfunction does not impact rates of all-cause mortality after either surgical aortic valve replacement or transcatheter aortic valve replacement.
- Within a randomized comparison of surgical aortic valve replacement and transcatheter aortic valve replacement, the rate and degree of left ventricular functional recovery was equivalent between both treatment modalities.
- Higher baseline left ventricular ejection fraction, low mean aortic valve gradient, and previous permanent pacemaker were each independently associated with reduced odds of early left ventricular functional recovery.

addressing the comparative risk profile and efficacy of TAVR and SAVR in patients with LV dysfunction is limited.^{10,12–15} Data from nonrandomized analyses suggest that TAVR is associated with superior postoperative LVEF recovery but similar periprocedural mortality compared with SAVR¹⁶; however, significant differences in patient characteristics make such nonrandomized comparisons difficult to interpret.¹⁷ To address these uncertainties, we evaluated the effect of LV dysfunction on clinical outcomes after TAVR and SAVR and the impact of aortic valve replacement technique on LV functional recovery in high-risk patients with symptomatic severe AS within the randomized Placement of Aortic Transcatheter Valves (PARTNER) trial.

Methods

Patients

Patient selection for cohort A of the PARTNER trial has been described previously.¹⁰ A total of 699 patients from 25 sites were randomly assigned to undergo either TAVR or SAVR; for this analysis, only patients with complete baseline echocardiographic data (97% of TAVR patients, 97% of SAVR patients) were included. Inclusion criteria included severe AS, defined as a site-measured echocardiographic aortic valve area (AVA) ≤ 0.8 cm² plus either a peak velocity ≥ 4 m/s or a mean valve gradient ≥ 40 mmHg (at rest or stress), New York Heart Association (NYHA) functional class II or greater, and high-risk status for SAVR as determined by experienced surgeons.

Patients were considered to be at high surgical risk if their predicted risk of 30-day perioperative mortality was $\geq 15\%$. The Society of Thoracic Surgery risk score was calculated for all patients and used as an additional criterion for subject eligibility for patients with no other operative contraindications.

Exclusion criteria included a bicuspid or noncalcified aortic valve, coronary artery disease requiring revascularization, an LVEF of $< 20\%$, an aortic annulus diameter of < 18 or > 25 mm, severe (4+) mitral or aortic regurgitation, a recent cardiac or neurological event, and severe renal insufficiency. The full exclusion criteria have been previously reported.¹⁰

The trial was approved by the institutional review board at each site. All patients provided written informed consent.

Study Device and Procedure

The SAPIEN heart valve system (Edwards Lifesciences, Irvine, CA) and the TAVR procedure have been described previously.^{9,10} Most procedures were performed in a hybrid operating room with the patient under general anesthesia using fluoroscopic and transesophageal echocardiographic guidance. Patients assigned to the transcatheter group underwent either transfemoral or transapical placement of the transcatheter aortic valve on the basis of whether their peripheral arteries could accommodate the large French sheaths required. Transapical placement was performed through a small intercostal incision over the LV apex with the use of a dedicated delivery catheter and the same Edwards SAPIEN valve.

Echocardiographic Assessment

Transthoracic or transesophageal echocardiography was performed at baseline to assess eligibility for enrollment in the PARTNER I trial. Follow-up transthoracic echocardiography was performed before discharge and at 1- and 6-month visits and annually thereafter. All echocardiograms were independently analyzed by the Echocardiographic Core Laboratory at the Duke Clinical Research Institute (Durham, NC) as previously described.¹⁸ All chamber parameters were measured according to the recommendations of the American Society of Echocardiography.¹⁹ Measurements were made during an average of 3 cardiac cycles for patients in sinus rhythm and an average of 5 cardiac cycles for patients with atrial fibrillation.

LVEF was measured using the biplane Simpson volumetric method combining apical 4-chamber and 2-chamber views. The LV endocardial border was traced contiguously from 1 side of the mitral annulus to the other, excluding the papillary muscles and trabeculations, and any apical tethering of the mitral leaflets. In the small number of images ($< 1\%$) with microbubble contrast, borders were traced similarly. LVEF was also determined by visual estimation (in 5-point increments) and, when the definition of the LV endocardial border was not adequate for biplane tracing (147/332 [44%] for TAVR, 123/304 [40%] for SAVR), was substituted to provide a single combined LVEF determination in all patients.

The core laboratory followed the American Society of Echocardiography/European Association for Echocardiography guideline for assessing the severity of native valvular stenosis and regurgitation.^{20–22} Qualitative AV assessments included leaflet thickening, calcification and mobility graded as none, mild, moderate or severe. Aortic valve peak and mean gradients were obtained using the view showing the maximal velocity. AVA or effective orifice area was calculated according to the continuity equation and indexed by BSA. Aortic and mitral regurgitation were assessed in all relevant views using color and spectral Doppler. Transvalvular regurgitation was graded according to American Society of Echocardiography recommendations as none, trace, mild, moderate, or severe.^{20,21} Echocardiographic data reported here were obtained from rest studies.

Study End Points and Statistical Analysis

The primary end point of the PARTNER trial was all-cause 1-year mortality. Prespecified secondary end points included cardiovascular mortality, stroke, repeat hospitalization, acute kidney injury,

vascular complications, bleeding events, and NYHA functional class. Crossovers between the 2 treatment groups were not permitted. A clinical events committee was responsible for adjudicating all end points. Definitions of the end points are identical to those reported previously.^{9,10} For the present analysis, LV dysfunction was defined as an LVEF <50%. Improvement in LVEF was defined as ≥10% absolute improvement in LVEF at 30 days.

For data analyses, the intention-to-treat analysis started at the time of randomization, and the as-treated analysis started at the time of induction of anesthesia in the procedure room. To measure the true effect of each respective procedure (TAVR or SAVR) on outcomes, all analyses were performed with the use of the as-treated data. Categorical variables were compared with the use of Fisher exact test. Continuous variables were presented as mean±SD and compared using the Student *t* test. Paired *t* test was used to assess changes in LVEF after aortic valve replacement. Survival curves for time-to-event variables were constructed using Kaplan–Meier estimates, which were compared using the log-rank test. To study the effect of risk factors on mortality, Cox proportional-hazards regression was performed. Multiplicative interaction terms were created to test for effect modification in the association between LV dysfunction and treatment modality. Predictors of LV functional improvement at 30 days, defined as ≥10% absolute improvement in LVEF, were identified using logistic regression models.

Multivariable models included covariates with a *P* value <0.20 in univariate analyses. Stepwise selection was used to generate final models with retention *P*<0.05. To determine the impact of LV functional improvement at 30 days on subsequent clinical outcomes, landmark analyses were performed in patients surviving beyond 30 days, in which patients with events within the first 30 days were excluded. All statistical analyses were performed with the use of SAS software, version 9.2. Statistical significance in final models was defined by a *P* value <0.05. Data extracted on October 10, 2012, were used for this analysis.

Results

Subject Characteristics

The as-treated cohort contained 657 patients, of which 332 patients underwent TAVR and 304 patients underwent SAVR and had complete baseline echocardiographic data. The echocardiographic core laboratory–measured mean LVEF was 52.8±13.0%. LV dysfunction, defined as a LVEF <50%, was present in almost a third of patients (203 out of 636 patients [31.9%]; Table 1), in whom the mean baseline LVEF was

Table 1. Baseline Patient Characteristics

	TAVR			SAVR		
	LVEF <50 (n=108)	LVEF ≥50 (n=224)	<i>P</i> Value	LVEF <50 (n=95)	LVEF ≥50 (n=209)	<i>P</i> Value
Age, y	83±7	84±7	0.26	84±7	85±6	0.37
Male sex	68.5% (74/108)	52.7% (118/224)	0.006	67.4% (64/95)	53.6% (112/209)	0.02
STS score	12.2±3.7	11.7±3.2	0.2	12.0±2.9	11.6±3.6	0.053
NYHA class			0.1			0.59
II	3.7% (4/108)	6.7% (15/224)	...	3.2% (3/95)	5.7% (12/209)	...
III or IV	96.3% (104/108)	93.3% (209/224)	...	96.8% (92/95)	94.3% (197/209)	...
CAD	80.6% (87/108)	72.8% (163/224)	0.12	84.2% (80/95)	73.7% (154/209)	0.04
Previous MI	41.7% (45/108)	19.7% (44/223)	<0.0001	48.4% (46/95)	21.4% (44/206)	<0.0001
Previous PCI	38.3% (41/107)	30.9% (69/223)	0.18	37.9% (36/95)	29.8% (62/208)	0.16
Previous CABG	49.1% (53/108)	41.1% (92/224)	0.13	51.6% (49/95)	42.1% (88/209)	0.12
Previous BAV	20.4% (22/108)	9.8% (22/224)	0.008	12.6% (12/95)	9.6% (20/209)	0.42
Cerebral vascular disease	28.0% (28/100)	31.1% (66/212)	0.57	31.4% (27/86)	25.9% (51/197)	0.34
Peripheral vascular disease	37.4% (40/107)	47.1% (105/223)	0.1	35.5% (33/93)	46.8% (96/205)	0.07
COPD	42.6% (46/108)	43.3% (97/224)	0.9	44.2% (42/95)	43.5% (91/209)	0.91
Creatinine level >2 mg/dL	22.4% (24/107)	15.6% (35/224)	0.13	17.9% (17/95)	20.1% (42/209)	0.65
Major arrhythmia	50.9% (55/108)	43.3% (97/224)	0.19	50.5% (48/95)	51.9% (108/208)	0.82
Permanent pacemaker	27.8% (30/108)	16.1% (36/224)	0.01	29.5% (28/95)	20.1% (42/209)	0.07
Pulmonary hypertension	50.0% (54/108)	50.0% (112/224)	>0.99	48.4% (46/95)	48.8% (102/209)	0.95
Liver disease	3.7% (4/108)	1.8% (4/224)	0.28	4.2% (4/95)	1.9% (4/209)	0.26
AVA, cm ²	0.63±0.2	0.67±0.2	0.1	0.62±0.2	0.65±0.2	0.27
AVA Index, cm ² /m ²	0.34±0.1	0.37±0.1	0.01	0.34±0.1	0.36±0.1	0.08
Mean AVG, mm Hg	37.5±14.1	45.5±14.0	<0.0001	38.0±13.1	45.9±14.2	<0.0001
Peak AVG, mm Hg	62.2±22.7	75.6±22.7	<0.0001	64.4±22.4	77.3±23.9	<0.0001
Peak AV velocity, m/s	3.88±0.71	4.31±0.64	<0.0001	3.96±0.64	4.34±0.70	<0.0001
AV annular diameter, mm	20.6±2.5	19.7±2.3	0.004	20.5±2.3	19.8±2.2	0.01
LVEF, %	37.1±9.2%	61.1±5.7%	<0.0001	39.3±8.4%	60.9±5.8%	<0.0001
Moderate or severe MR	27.6% (29/105)	15.6% (36/223)	0.02	25.0% (23/92)	19.5% (40/205)	0.28

AV indicates aortic valve; AVA, aortic valve area; AVG, aortic valve gradient; BAV, balloon aortic valvuloplasty; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; COPD, chronic obstructive lung disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral valve regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; and TAVR, transcatheter aortic valve replacement.

36.8±8.4%. Patients with LV dysfunction were more likely to be male (68.0 versus 53.1%; $P=0.0004$), with lower BMI (26.6±5.5 versus 27.3±6.9; $P=0.04$), and more frequently had a history of coronary artery disease (82.3 versus 73.2%; $P=0.01$), previous myocardial infarction (44.8 versus 20.5%; $P<0.0001$), coronary artery bypass grafting surgery (49.8 versus 41.1%; $P=0.04$), and balloon aortic valvuloplasty (16.7 versus 9.7%; $P=0.01$). Moderate or severe mitral regurgitation was more prevalent (25.9 versus 17.7%; $P=0.02$) in those with LV dysfunction. Patients with LVEF <50% also had lower mean (37.5±13.5 versus 45.7±14.1 mmHg; $P<0.0001$) and peak (62.9±22.4 versus 76.4±23.3 mmHg; $P<0.0001$) aortic valve gradients (AVGs), lower peak aortic valve velocities (3.91±0.67 versus 4.32±0.67 m/s; $P<0.0001$), smaller AVAs (0.63±0.2 versus 0.66±0.2 cm²; $P=0.054$; AVA index, 0.34±0.1 versus 0.37±0.1 cm²/m²; $P=0.003$), and larger aortic valve annular diameters (20.6±2.4 versus 19.8±2.2 mm; $P=0.01$) on baseline rest echocardiographic studies.

Similar trends were observed within the TAVR and SAVR cohorts with the exception of previous balloon aortic valvuloplasty, which was performed with comparable frequency in those with and without LV dysfunction undergoing SAVR (LVEF <50%, 12.6%; LVEF ≥50%, 9.6%; $P=0.42$), but with differing frequencies among patients undergoing TAVR (LVEF <50%, 20.4%; LVEF ≥50%, 9.8%; $P=0.008$).

Relationship of LV Function With Clinical Outcomes

In both TAVR and SAVR groups, a similar proportion of patients with LV dysfunction died at 30 days and at 1 year compared with those without LV dysfunction (Table 2). In patients with LVEF <50%, 30-day all-cause ($P=0.29$) and cardiac ($P=0.38$) mortality were comparable after TAVR and SAVR. In the TAVR group, 25.9% of patients with LV dysfunction died by 1 year compared with 22.9% of patients with normal LV function ($P=0.56$; Table 2). With SAVR, 23.3% and 25.2% of patients with and without LV dysfunction, respectively, died by 1 year ($P=0.79$). All-cause mortality was similar at 2 years in the TAVR and SAVR groups with and without LV dysfunction (Figure 1; log-rank P value=0.83).

Rates of repeat hospitalization within 30 days of transcatheter and surgical valve replacement were comparable whether or not LV dysfunction was present (Table 2). There was an interaction between valve replacement technique and the association of LV dysfunction with repeat hospitalization at 1 year, such that patients with LV dysfunction were at greater risk of repeat hospitalization after TAVR but not after SAVR (Table 2). Rates of rehospitalization at 1 year were significantly higher in those with LVEF <50% undergoing TAVR compared with those with normal LV function (26.0% versus 12.8%; $P=0.004$). A similar pattern was not observed with SAVR (Table 2).

Table 2. Clinical Outcomes Stratified by Baseline Left Ventricular Function

	TAVR			SAVR			Interaction P Value
	LVEF <50% (n=108)	LVEF ≥50% (n=224)	P Value	LVEF <50% (n=95)	LVEF ≥50% (n=209)	P Value	
30 d							
All-cause death	5.6% (6)	5.4% (12)	0.94	9.5% (9)	7.7% (16)	0.58	0.77
Cardiac death	3.7% (4)	4.0% (9)	0.9	6.4% (6)	1.5% (3)	0.02	0.09
Repeat hospitalization	7.7% (8)	4.6% (10)	0.27	3.4% (3)	6.6% (13)	0.28	0.13
Death or repeat hospitalization	12.0% (13)	9.8% (22)	0.54	12.6% (12)	14.0% (29)	0.8	0.54
Stroke or TIA	2.8% (3)	5.9% (13)	0.23	2.1% (2)	2.4% (5)	0.9	0.54
Stroke	1.9% (2)	5.4% (12)	0.14	2.1% (2)	2.4% (5)	0.9	0.39
TIA	0.9% (1)	0.5% (1)	0.59	0.0% (0)	0.5% (1)	0.5	>0.99
Death from any cause or major stroke	7.4% (8)	8.9% (20)	0.63	11.6% (11)	9.1% (19)	0.48	0.41
Myocardial infarction	0.0% (0)	0.0% (0)	N/A	1.1% (1)	0.0% (0)	0.13	>0.99
Dialysis lasting >30 d	0.0% (0)	0.4% (1)	0.49	0.0% (0)	3.0% (6)	0.1	>0.99
1 y							
All-cause death	25.9% (28)	22.9% (51)	0.56	23.3% (22)	25.2% (52)	0.79	0.54
Cardiac death	9.0% (9)	8.9% (19)	0.98	9.8% (9)	5.9% (11)	0.18	0.32
Repeat hospitalization	26.0% (26)	12.8% (26)	0.004	15.1% (12)	16.9% (31)	0.59	0.03
Death or repeat hospitalization	38.9% (42)	31.4% (70)	0.16	35.0% (33)	35.4% (73)	0.91	0.30
Stroke or TIA	5.0% (5)	9.6% (20)	0.17	3.5% (3)	4.3% (8)	0.78	0.57
Stroke	3.0% (3)	7.0% (15)	0.14	3.5% (3)	2.4% (5)	0.69	0.22
TIA	2.0% (2)	2.6% (5)	0.84	0.0% (0)	2.3% (4)	0.17	>0.99
Death from any cause or major stroke	26.9% (29)	25.6% (57)	0.85	26.5% (25)	26.2% (54)	0.9	0.96
Myocardial infarction	0.0% (0)	0.0% (0)	N/A	1.1% (1)	0.0% (0)	0.13	>0.99
Dialysis lasting >30 d	0.0% (0)	1.0% (2)	0.33	2.6% (2)	4.1% (8)	0.44	>0.99

Kaplan-Meier estimates (number of events) are shown. LVEF indicates left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and TIA, transient ischemic attack.

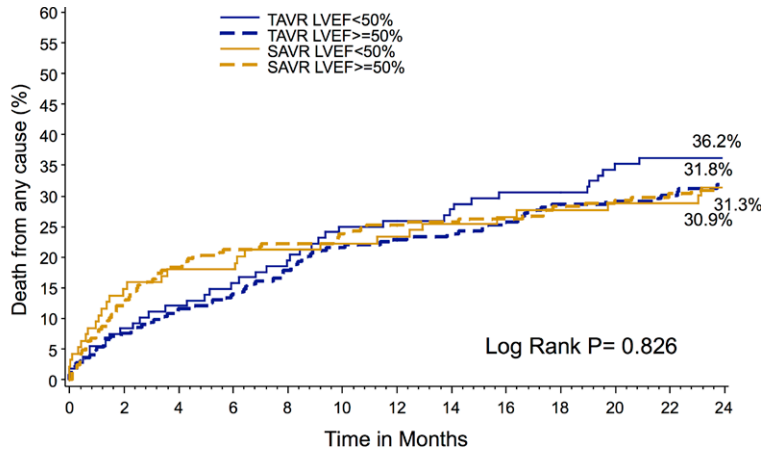


Figure 1. Time-to-event curves depicting risk of death from any cause. Time-to-event curves for risk of death from any cause are shown for transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR), stratified by baseline left ventricular (LV) function. There is no difference in 2-year survival between any of the treatment groups ($P=0.826$). The event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the Log-rank test. LVEF indicates LV ejection fraction.

Number At Risk					
TAVR LVEF<50%	108	91	80	75	57
TAVR LVEF≥50%	224	192	170	147	104
SAVR LVEF<50%	95	77	72	65	46
SAVR LVEF≥50%	209	161	152	139	104

Rates of the composite of stroke or transient ischemic attack at 30 days and at 1 year were comparable after TAVR and SAVR, regardless of baseline LV function (Table 2). There was an increased risk of stroke or transient ischemic attack at 1 year (9.6% versus 4.3%; $P=0.04$) with TAVR compared with SAVR in patients with LVEF $\geq 50\%$, but not in those with LVEF $< 50\%$ (5.0% versus 3.5%; $P=0.62$; Table 2), largely because

of a greater risk of stroke with TAVR than with SAVR in those with preserved LV function (7.0 versus 2.4%; $P=0.04$).

Symptom Status

At baseline assessment, 96.3% of patients with LVEF $< 50\%$ were classified as NYHA functional class III or IV compared with 93.3% of those with LVEF $\geq 50\%$ ($P=0.10$; Table 1).

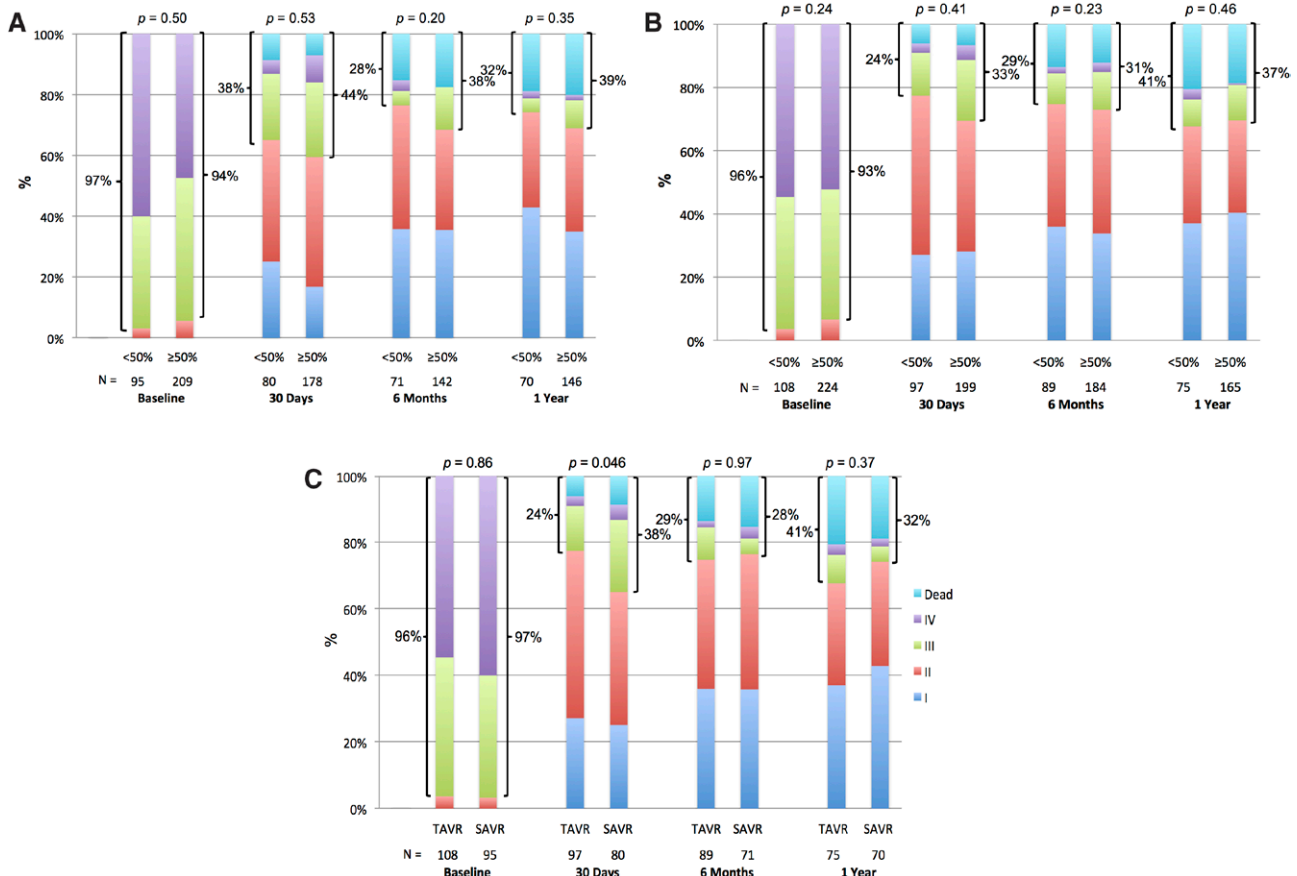


Figure 2. New York Heart Association (NYHA) functional class. Heart failure symptoms improve rapidly after both transcatheter aortic valve replacement (TAVR; **A**) and surgical aortic valve replacement (SAVR; **B**), regardless of the presence of left ventricular dysfunction. However, at 30 days, fewer patients had died or had persistent NYHA class III/IV symptoms (brackets) after TAVR than SAVR (**C**; $P=0.046$).

Functional status improved markedly by 30 days after both TAVR and SAVR, regardless of the presence of baseline LV dysfunction (Figure 2A and 2B). However, in patients with baseline LV dysfunction, the proportion of patients who died or remained with NYHA class III/IV symptoms at 30 days was lower with TAVR than with SAVR (Figure 2C; $P=0.046$).

LV Function After Aortic Valve Replacement

The mean LVEF was $52.4\pm 13.6\%$ in the TAVR group and $53.3\pm 12.4\%$ in the SAVR group ($P=0.40$). In those with LV dysfunction, mean baseline LVEF was $39.3\pm 8.4\%$ and $37.1\pm 9.2\%$ in the SAVR and TAVR groups, respectively ($P=0.06$). LV dysfunction improved equally after both transcatheter and surgical valve replacement with most improvement occurring within the first 30 days (Figure 3). By 1 year, 37 (53.6%) patients with LV dysfunction had normalized their LV function (reached LVEF $\geq 50\%$) after TAVR compared with 33 (62.3%) patients after SAVR ($P=0.34$). LVEF improved to $48.6\pm 11.3\%$ with TAVR ($P<0.0001$) and $50.1\pm 10.8\%$ with SAVR ($P=0.0001$; between group $P=0.45$). LVEF remained stable after both TAVR and SAVR in those with preserved LV function (Figure 3).

Improvement in LVEF in those patients with LV dysfunction at baseline, defined as an absolute increase in LVEF $\geq 10\%$ at the 30-day echocardiogram, was observed in 48 (51.6%) TAVR patients and 27 (40.9%) SAVR patients ($P=0.18$). Among TAVR patients with LVEF improvement, LVEF markedly increased within the first 30 days (33.6 ± 9.3 – $52.9\pm 10.1\%$), with no further improvement noted at 1 year (LVEF, $52.7\pm 10.2\%$ at 1 year; $P=0.82$ versus 30-day LVEF; Figure 4A). In TAVR patients without LVEF improvement,

LVEF remained stable at 30 days (37.4 ± 8.0 – $38.8\pm 8.6\%$) but demonstrated a modest increase during the subsequent 11 months (LVEF, $43.5\pm 11.1\%$ at 1 year; $P=0.048$ versus 30-day LVEF; Figure 4A). After SAVR, patients with LVEF improvement experienced dramatic LVEF recovery within the first 30 days (35.0 ± 9.0 – $51.2\pm 12.7\%$) followed by continued modest improvement during the remainder of the first post-operative year (LVEF, $55.9\pm 6.8\%$ at 1 year; $P=0.0015$ versus 30-day LVEF). As with TAVR, LVEF remained stable in SAVR patients without early LVEF improvement (41.2 ± 6.0 – $39.2\pm 9.0\%$) and then slowly and modestly improved by 1-year follow-up ($43.7\pm 10.7\%$ at 1 year; $P=0.002$ versus 30-day LVEF; Figure 4B). To exclude the possibility that late LVEF improvement is influenced by survival bias, an exploratory analysis limited to patients surviving to 1-year was performed. After TAVR, patients that did not experience early LVEF improvement but survived to 1 year demonstrated a slow increase in LVEF from $36.9\pm 7.3\%$ at baseline to $43.6\pm 11.1\%$ at 1 year ($P=0.004$; Figure 4C). After SAVR, an initial decrement in LVEF was observed in patients without early LVEF improvement that survived to 1 year followed by a slow increase to baseline levels ($41.2\pm 6.5\%$ at baseline to $43.4\pm 11.4\%$ at 1 year; $P=0.37$; Figure 4D).

Predictors of LVEF Improvement

In an analysis limited to patients with baseline LV dysfunction, univariable logistic regression analyses identified higher baseline LVEF (odds ratio [OR], 0.93 [95% confidence interval [CI], 0.89, 0.97]; $P=0.0004$), previous myocardial infarction (OR, 0.53 [95% CI, 0.28, 1.00]; $P=0.048$), previous coronary artery bypass grafting surgery (OR, 0.43 [95% CI,

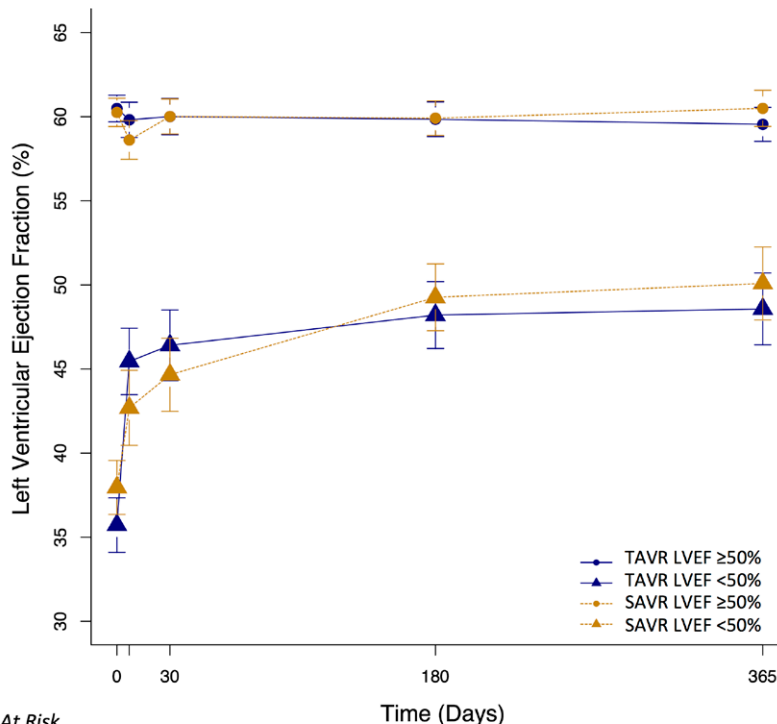


Figure 3. Left ventricular functional recovery with time. Left ventricular ejection fraction (LVEF) remained stable in those with normal baseline function. In subjects with baseline LV dysfunction, LVEF improved quickly and equally after surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR), with most LV functional improvement occurring within the first 30 days. Points represent mean values with error bars depicting SD.

Number At Risk	0	30	180	365
TAVR LVEF $\geq 50\%$	224	185	161	150
TAVR LVEF $< 50\%$	108	93	79	69
SAVR LVEF $\geq 50\%$	209	160	119	105
SAVR LVEF $< 50\%$	95	66	52	53

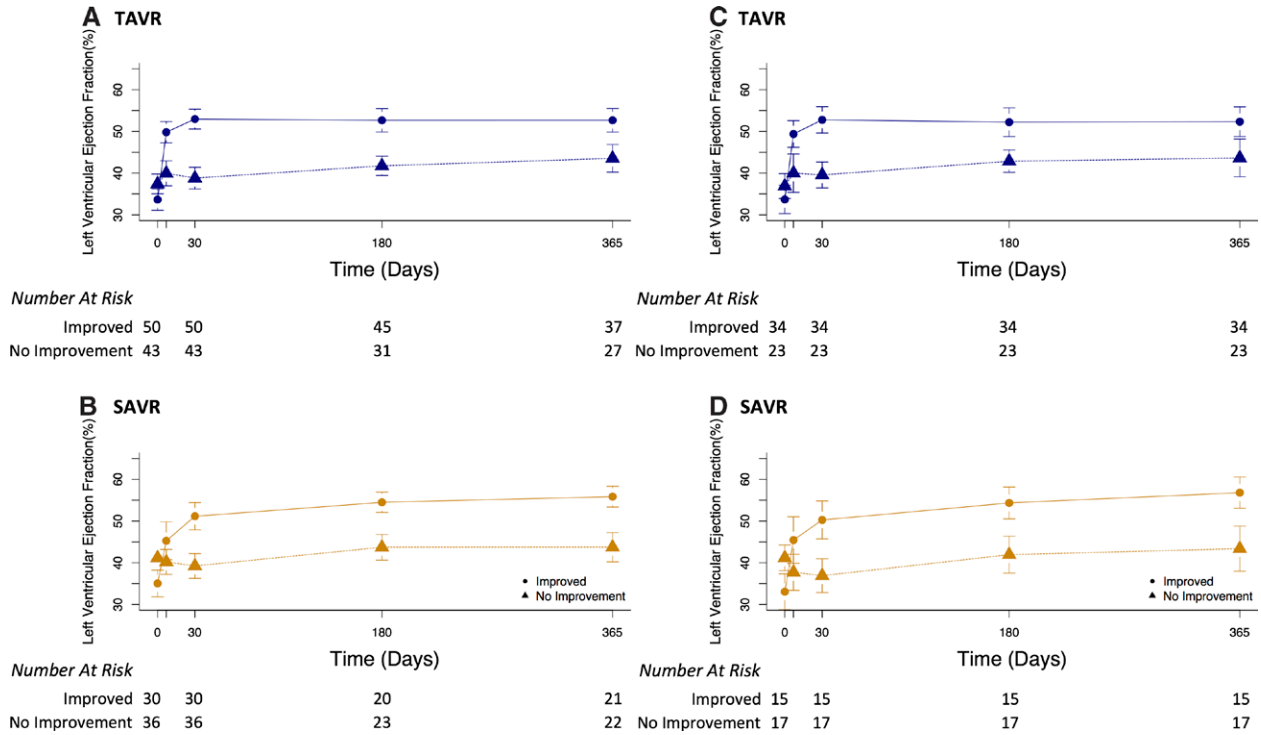


Figure 4. Left ventricular functional recovery in patients with left ventricular dysfunction. Left ventricular ejection fraction (LVEF) is plotted versus time in patients with LV dysfunction stratified by improvement in LVEF $\geq 10\%$ by 30-day follow-up after transcatheter aortic valve replacement (TAVR; **A**) and surgical aortic valve replacement (SAVR; **B**). An exploratory analysis limited to subjects surviving to 1-year similarly demonstrates similar patterns of change in LVEF after TAVR (**C**) and SAVR (**D**). Points represent mean values with error bars depicting SD.

0.23, 0.81]; $P=0.0094$), and previous permanent pacemaker (OR, 0.41 [95% CI, 0.20, 0.83]; $P=0.014$) to be associated with a reduced odds of LV functional improvement after valve replacement (Table 3). Older age (OR, 1.05 [95% CI, 1.00, 1.10]; $P=0.052$), higher baseline mean AVG (OR, 1.03 [95% CI, 1.01, 1.06]; $P=0.016$), and transfemoral TAVR (OR versus SAVR, 1.76 [0.89, 3.48]; $P=0.036$) were associated with increased likelihood of LVEF improvement. In a parallel analysis, there was no difference in the rates of moderate or severe paravalvular aortic regurgitation in those who improved compared with those who did not at hospital discharge (4.2 versus 7.5%; $P=0.83$) or at 30 days (10.0 versus 7.1%; $P=0.91$). In multivariable analyses, only baseline LVEF (OR, 0.90 [95% CI, 0.86, 0.95]; $P<0.0001$), previous permanent pacemaker (OR, 0.34 [95% CI, 0.15, 0.81]; $P=0.015$), and higher mean AVG (OR, 1.04 [95% CI, 1.01, 1.08]; $P=0.015$) were independently associated with the likelihood of 30-day LVEF improvement (Table 3).

Impact of LV Functional Recovery on Clinical Outcomes

Further analyses were performed to determine the impact of LV functional improvement at 30 days on subsequent clinical outcomes. Early LV functional improvement was associated with reduced rates of all-cause death in TAVR patients at 1 year (hazard ratio, 0.28 [95% CI, 0.10, 0.79]; $P=0.01$) but not in SAVR patients (hazard ratio, 1.19 [95% CI, 0.34, 4.11]; $P=0.78$; Interaction $P=0.07$; Table 4). Similarly, cardiac mortality was reduced in TAVR patients with LV improvement (hazard ratio, 0.18 [95% CI, 0.02, 1.58]; $P=0.08$) but

not in SAVR patients (hazard ratio, 0.59 [95% CI, 0.05, 6.52]; $P=0.66$; Interaction $P=0.047$). Moreover, patients who did not demonstrate early LVEF improvement had greater all-cause mortality after TAVR but not SAVR (Figure 5A and 5B). Poor LV functional recovery after TAVR was also associated with increased risk of repeat hospitalization (Interaction $P=0.051$) and the composite end points of death from any cause or repeat hospitalization (Interaction $P=0.02$) and of death from any cause or major stroke at 1 year (Interaction $P=0.08$; Table 4). No differences in 1-year clinical outcomes were observed between those with and without LV functional improvement after SAVR, although these analyses possessed less statistical power (Table 4).

Discussion

In this study, we found that in high-risk patients with symptomatic severe AS, baseline LV dysfunction (LVEF, $>20\%$ and $<50\%$) does not impact survival after either SAVR or TAVR. However, there was a borderline association of LV dysfunction with 30-day cardiac death after SAVR and with an increased risk of repeat hospitalization within the first year after TAVR. The lack of influence of LV dysfunction on periprocedural mortality is probably because of the exclusion of patients with severe LV dysfunction (LVEF $<20\%$), in whom the bulk of the risk is thought to exist.^{1,2,4,5} Evidence suggests that the relationship between LVEF and mortality is not linear. Data from the EuroSCORE study and others indicate that perioperative risk markedly increases with LVEF $<30\%$.^{1,2,4} Similarly, in patients with chronic heart failure, mild LV dysfunction has

Table 3. Unadjusted and Multivariable Predictors of Left Ventricular Functional Improvement at 30 Days in Patients With Baseline Left Ventricular Dysfunction (LVEF <50%)

	Unadjusted		Multivariable	
	OR [95% CI]	P Value	OR [95% CI]	P Value
Baseline characteristics				
Age	1.05 [1.00, 1.10]	0.052
Male sex	0.65 [0.33, 1.26]	0.20
STS score	1.02 [0.93, 1.13]	0.62
Diabetes mellitus	0.93 [0.50, 1.74]	0.82
Hypertension	0.90 [0.34, 2.35]	0.83
Peripheral arterial disease	0.71 [0.37, 1.35]	0.29
Previous MI	0.53 [0.28, 1.00]	0.048
Previous PCI	0.78 [0.41, 1.47]	0.44
Previous CABG	0.43 [0.23, 0.81]	0.0094
Previous BAV	1.15 [0.53, 2.50]	0.72
Permanent pacemaker	0.41 [0.20, 0.83]	0.014	0.34 [0.15, 0.77]	0.01
Baseline creatinine	0.76 [0.43, 1.32]	0.29
Echocardiographic measures				
AVA	0.28 [0.05, 1.42]	0.12
Peak AV gradient	1.00 [1.00, 1.01]	0.10
Mean AVG	1.03 [1.01, 1.06]	0.016	1.03 [1.01, 1.06]	0.03
Baseline LVEF	0.93 [0.89, 0.97]	0.0004	0.91 [0.86, 0.95]	<0.0001
Mod/severe MR	1.65 [0.78, 3.49]	0.19
Valve replacement technique				
Transapical TAVR (vs SAVR)	0.72 [0.28, 1.88]	0.18
Transfemoral TAVR (vs SAVR)	1.76 [0.89, 3.48]	0.036

AV indicates aortic valve; AVA, aortic valve area; AVG, aortic valve gradient; BAV, balloon aortic valvuloplasty; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CI, confidence interval; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral valve regurgitation; OR, odds ratio; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; and TAVR, transcatheter aortic valve replacement.

no impact on survival.²³ The association between LV function and mortality is modulated by comorbid conditions and the pathogenesis of cardiomyopathy.²³ We suspect that the exclusion of patients with nonrevascularized coronary artery disease, low AVGs, and other severe valve lesions from the PARTNER trial mitigates the impact of LVEF on clinical outcomes. In this cohort of patients with symptomatic severe AS, those with normal LV function notably have myopathic ventricles clinically manifesting as heart failure with preserved EF and therefore have diminished survival similar to that seen with reduced EF.²⁴ The impact of LVEF on survival may consequently be diminished. Nevertheless, our findings confirm the efficacy and safety of TAVR in patients with LV dysfunction and indicate that TAVR should be considered a feasible option in patients with symptomatic severe AS and LV dysfunction who are at high risk for SAVR.

Previous evidence from Clavel et al¹⁶ suggests greater improvements in LVEF with TAVR when compared with SAVR. In part, this advantage of TAVR was thought to be because of the superior hemodynamic profile of transcatheter heart valves and the more complete relief of AS. In addition, the avoidance of surgical insults related to cardioplegia, ischemia-reperfusion, inflammation, apoptosis, and surgical trauma was anticipated to add to the likelihood of myocardial

functional recovery after TAVR.^{16,25} However, we found no difference in the rate or degree of LV functional recovery after TAVR and SAVR. With both treatment modalities, we observed a rapid and substantial improvement in LVEF in patients with baseline LV dysfunction, with 40% to 50% of patients experiencing a >10% absolute increase in their LVEF by 30-day follow-up. The discrepancy may be a consequence of the concomitant performance of coronary artery bypass grafting surgery with SAVR in ≈60% of patients in the previous study.¹⁶ The presence of nonrevascularized coronary artery disease at the initiation of surgery in addition to prolonged cardiopulmonary bypass with concomitant coronary artery bypass grafting surgery may play a role. Alternatively, because patients with severe LV dysfunction (LVEF <20%) are exquisitely sensitive to LV afterload, they may reap an advantage from the superior hemodynamic profile of transcatheter heart valves.²⁶ Patients with such severe LV dysfunction, as well as those requiring coronary revascularization, were excluded from the PARTNER trial; therefore, it remains possible that improvements in LVEF will be more robust after TAVR than after SAVR in such patients.

We identified a proportion of patients (≈50%) with LV dysfunction who do not experience an early improvement in LVEF after valve replacement. After both TAVR and SAVR,

Table 4. Clinical Outcomes at 1 Year by 30-Day Improvement in Left Ventricular Ejection Fraction in Those With Baseline Left Ventricular Dysfunction (LVEF <50%)

	Improvement	No Improvement	Hazard Ratio [95% CI]	P Value
TAVR	(n=50)	(n=43)		
All-cause death	10.0% (5)	30.2% (13)	0.28 [0.10, 0.79]	0.01
Cardiac death	2.1% (1)	11.2% (4)	0.18 [0.02, 1.58]	0.08
Repeat hospitalization	14.2% (7)	42.4% (17)	0.28 [0.11, 0.67]	0.002
Death or repeat hospitalization	20.0% (10)	51.2% (22)	0.30 [0.14, 0.63]	0.0008
Stroke or TIA	2.1% (1)	7.6% (3)	0.26 [0.03, 2.48]	0.20
Stroke	0.0% (0)	5.3% (2)	N/A	0.20
TIA	2.1% (1)	2.3% (1)	0.79 [0.05, 12.69]	0.87
Death from any cause or major stroke	10.0% (5)	32.6% (14)	0.26 [0.09, 0.72]	0.005
Myocardial infarction	0.0% (0)	0.0% (0)	N/A	N/A
Dialysis lasting >30 d	0.0% (0)	0.0% (0)	N/A	N/A
SAVR	(n=30)	(n=36)		
All-cause death	16.7% (5)	13.9% (5)	1.19 [0.34, 4.11]	0.78
Cardiac death	3.6% (1)	5.6% (2)	0.59 [0.05, 6.52]	0.66
Repeat hospitalization	21.5% (6)	8.9% (3)	2.43 [0.61, 9.73]	0.19
Death or repeat hospitalization	33.3% (10)	22.2% (8)	1.53 [0.60, 3.88]	0.36
Stroke or TIA	0.0% (0)	6.0% (2)	N/A	0.19
Stroke	0.0% (0)	6.0% (2)	N/A	0.19
TIA	0.0% (0)	0.0% (0)	N/A	N/A
Death from any cause or major stroke	16.7% (5)	19.4% (7)	0.82 [0.26, 2.60]	0.74
Myocardial infarction	0.0% (0)	0.0% (0)	N/A	N/A
Dialysis lasting >30 d	0.0% (0)	2.9% (1)	N/A	0.36

Kaplan-Meier estimates (number of events) are shown. CI indicates confidence interval; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and TIA, transient ischemic attack.

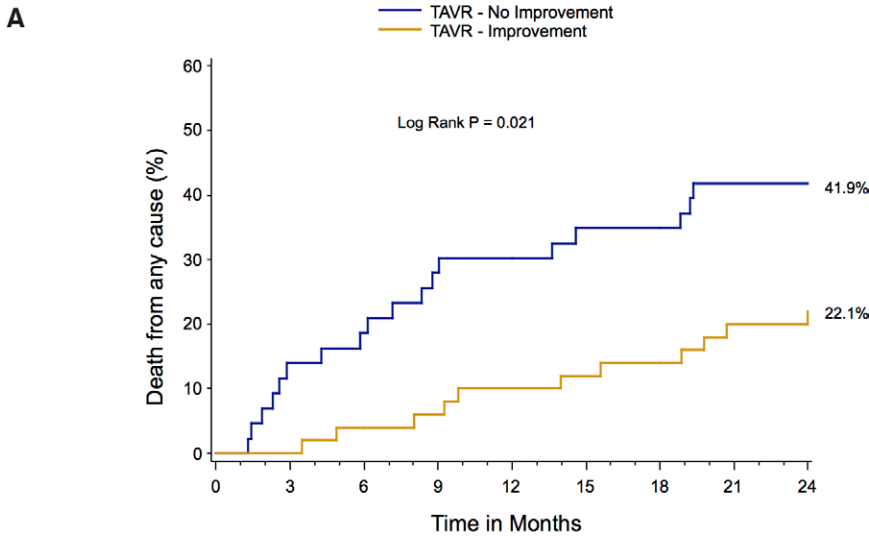
these patients experience a gradual, but modest, increase in LVEF during the first year. Higher baseline LVEF, low mean AVG, and previous permanent pacemaker were each independently associated with reduced odds of early LV functional improvement. The association of higher baseline LVEF with reduced LVEF improvement is because of a ceiling effect (ie, LVEF cannot improve beyond a certain point), whereas low AVGs and previous pacemaker likely reflect the impact of an advanced cardiomyopathic process and cardiac dyssynchrony on LV functional recover. Interestingly in univariable analyses, transfemoral TAVR was associated with improved LV function when compared with the transapical approach and to SAVR, suggesting that procedural trauma to the LV apex may hinder LV functional recovery in those with baseline dysfunction. Less robust LVEF improvement has previously been described after transapical TAVR, although this difference diminished after adjustment for baseline LVEF.¹⁶ The severity of baseline mitral regurgitation was not associated with myocardial recovery, and with TAVR, paravalvular aortic regurgitation was not associated with lesser LV functional improvement despite recent evidence associating it with increased late mortality.¹¹

The clinical consequences of the lack of early LV functional recovery seem to be greater with TAVR than with SAVR. All-cause mortality, repeat hospitalization, and the composite end points of death or repeat hospitalization and of death or major stroke were each markedly increased in patients that had

undergone TAVR and failed to demonstrate early improvement in LVEF. The pathophysiologic mechanism mediating this increased risk is not readily apparent. Further exploration of possible mediators, such as procedural LV injury, conduction abnormalities, or arrhythmias is warranted in larger cohorts.

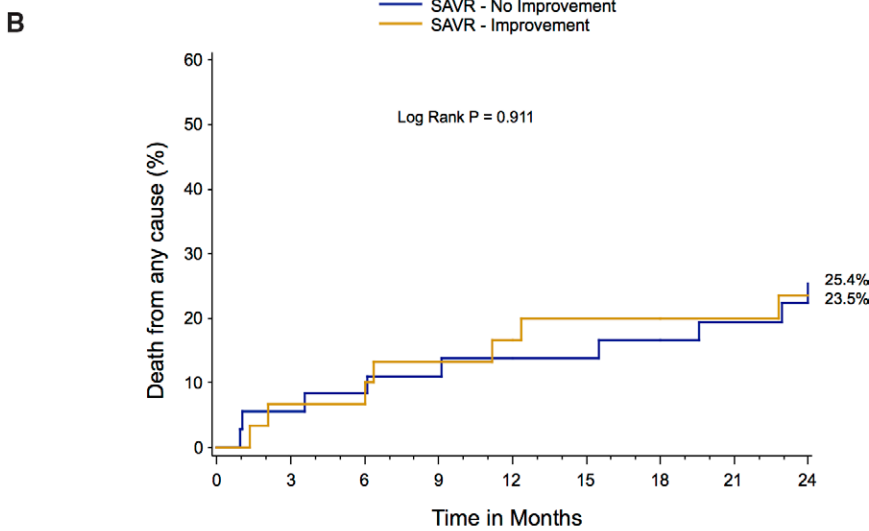
Finally, we observed substantial improvements in NYHA functional class after both TAVR and SAVR, regardless of baseline LV dysfunction, and moreover demonstrated that reduced LV function does not attenuate symptomatic recovery after either TAVR or SAVR. However, a larger proportion of patients with LV dysfunction died or had persistent class III/IV symptoms at 30-days after SAVR compared with TAVR. This finding reflects the early hazard of surgery and slower recovery afterward as previously described in the PARTNER trial.¹⁰

The randomized comparison of TAVR versus SAVR, the use of an echocardiographic core laboratory, and the independent adjudication of clinical events are significant strengths of this analysis; however, several limitations must also be acknowledged. First, patients with severe LV dysfunction, defined as an LVEF <20%, and with low gradient AS, defined as mean AVG <40 mm Hg, were excluded from the PARTNER trial. Consequently, our results may not extend to patients with more severe LV dysfunction or with low AVGs. Second, the number of patients without LVEF improvement was relatively small and did not allow for additional analyses to delineate the pathogenesis of increased mortality with TAVR but not SAVR. Third, given the relatively small number of transapical TAVR



Number at risk:

TAVR - No Improvement	43	35	30	28	24
TAVR - Improvement	50	48	45	43	38



Number at risk:

SAVR - No Improvement	36	33	31	30	25
SAVR - Improvement	30	28	25	23	21

Figure 5. Time-to-event curves depicting risk of death from any cause in patients with left ventricular (LV) dysfunction. Those who failed to improve by 30-days after transcatheter aortic valve replacement (TAVR) possessed an increased risk of death at 2-years (A), whereas lack of LV functional improvement after surgical aortic valve replacement (SAVR) did not influence survival (B). The event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test. Patients surviving <30 days were excluded from these analyses.

within the PARTNER trial, our analysis was not sufficiently powered to definitively assess the impact of TAVR approach on LV function. Fourth, our analyses are prone to survival selection bias given that follow-up LVEF was only available in those that survived. Fifth, we do not possess sufficient data to assess loading conditions at the time of echocardiography. Finally, the PARTNER trial included highly selected high-risk patients. Whether these results are applicable to the larger population of AS patients warrants further investigation.

In conclusion, we found that in high-risk patients with symptomatic severe AS, baseline LV dysfunction (LVEF, 20%–50%) had no impact on survival after either TAVR or SAVR. Rapid LV functional improvement occurred within 30 days of TAVR and SAVR in most patients, but failure to do

so was associated with adverse clinical outcomes only after TAVR. Higher baseline LVEF, low mean AVG, and presence of a previous permanent pacemaker were associated with reduced likelihood of early LV functional improvement. These data suggest that TAVR should be considered a feasible alternative for patients with symptomatic severe AS and LV dysfunction that are at high risk for SAVR. Future efforts should be directed toward clarifying the impact of more severe LV dysfunction after aortic valve replacement and toward predicting and augmenting LV functional recovery.

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