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ORIGINAL RESEARCH

A Paradox between LV Mass Regression and Hemodynamic Improvement after Surgical and Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: Surgical aortic valve replacement (SAVR) results in higher AV gradients than transcatheter AVR (TAVR), yet calculated left ventricular (LV) mass regresses faster and greater after SAVR vs. TAVR. We examined why LV mass regression is greater after SAVR.

Methods: Serial echocardiographic studies of high-risk patients with severe aortic stenosis (AS) randomized to SAVR vs. TAVR with the CoreValve bioprosthesis were analyzed by an echocardiographic core laboratory blinded to treatment and outcomes. Measurements followed established guidelines and LV mass was calculated using the formula of Devereux and colleagues.

Results: Echo data were available in 389 TAVR and 353 SAVR patients, whose baseline LVEDD, PWT, SWT, LV mass, and stroke volume (SV) as well as AS severity were similar. At discharge after SAVR, LV mass reduction was significant (227.45 ± 65.02 to 215.08 ± 59.02 g [$p = 0.002$]) due to decreased LVEDD (5.01 ± 0.64 to 4.81 ± 0.65 cm [$p < 0.001$]) associated with reduced SV (72.6 ± 27.0 mL to 58.9 ± 21.1 mL ($p = 0.015$]). PWT and SWT were unchanged. However, after TAVR, all these variables remained similar. At 1 year, LV mass, SV and LVEDD remained smaller following SAVR vs. TAVR. There was a trend toward higher 30-day mortality in patients with greater LV mass reduction in SAVR (4.7% vs. 0.8 %; $p = 0.058$) which was not observed after TAVR.

Conclusion: The greater reduction in LV mass calculated after SAVR vs. TAVR is due to a smaller postoperative LVEDD and is associated with significantly reduced SV. There was a tendency for increased 30-day mortality associated with greater reduction in calculated LV mass after SAVR.

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KEYWORDS Aortic stenosis; echocardiography; left ventricular hypertrophy; left ventricular mass regression; surgical aortic valve replacement; transcatheter aortic valve replacement; valvular heart disease

Introduction

The left ventricle (LV) develops concentric hypertrophy and increased mass in response to pressure overload in most patients with aortic stenosis (AS). Left ventricular hypertrophy is an independent risk factor for increased cardiac morbidity and mortality.[1–3] Left ventricular mass decreases when severe AS is relieved by aortic valve replacement (AVR).[4] It is expected that LV mass regression is greater with lower aortic valve pressure gradients after AVR.[5,6] However, the Placement of Aortic Transcatheter Valve (PARTNER) Trial using a balloon-expandable bovine pericardial aortic bioprosthesis demonstrated that LV mass regression was faster and greater after surgical aortic valve replacement (SAVR) compared to transcatheter aortic valve replacement (TAVR) despite higher aortic pressure gradients and more frequent patient-prosthesis mismatch (PPM) after SAVR.[7,8] The CoreValve US Pivotal Trial using a self-expanding valve in a larger number of patients with severe AS and high surgical risk[9] yielded a similar paradoxical finding of a faster and greater reduction of LV mass in the SAVR group when LV mass was calculated by a standard mass formula.[10,11] The purpose of this analysis was to identify reasons for this paradox by using serial echocardiography data analyzed by an independent echocardiography core laboratory.

Materials and methods

Study design

The CoreValve US Pivotal High Risk Trial was a multicenter, randomized, non-inferiority trial comparing TAVR using the CoreValve self-expanding porcine pericardial aortic bioprosthesis (Medtronic, Minneapolis, MN, USA) with SAVR

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Supplemental data for this article can be accessed on the publisher's website.

in patients with symptomatic (New York Heart Association [NYHA] Class II symptoms or greater) severe AS and high surgical risk. Details of the study design and patient cohort have been published previously.[9] The study protocol was approved by the institutional review board of all participating clinical sites, and all patients provided written, informed consent.

Echocardiography

Echocardiography was performed at baseline, post-procedure, hospital discharge, and at 1-, 6-, and 12 months. All echocardiography studies were centrally analyzed using Digisonics workstation (Digisonics, Inc., Houston, TX, USA) by the echocardiography core laboratory (Echo Core Lab) at the Mayo Clinic (Rochester, MN, USA). The methods for echocardiography analysis by the Echo Core Lab have been published previously, including assessment of LV volumes, stroke volume (SV) by 2D and Doppler methods, ejection fraction (EF), AV area and pressure gradients, as well as severity of aortic regurgitation (AR).[12] Assessment of the native AV and the bioprosthesis were made according to the original Valve Academic Research Consortium, American Society of Echocardiography, and European Association of Echocardiography.[13,14] LV mass was derived from the established formula (Devereux and colleagues[15]) as follows:

$$\text{LV mass} = 0.83 \times \left[(\text{LVEDD} + \text{PWTd} + \text{SWTd})^3 - (\text{LVEDD})^3\right] + 0.6$$

Wherein LVEDD = LV end-diastolic dimension, PWTd = posterior wall thickness in diastole, and SWTd = septal wall thickness in diastole. Relative wall thickness (RWT) was calculated as (2 x PWTd) /LVEDD. LVEDD was measured towards the mid-ventricle at the largest cavity dimension, to avoid basal septal hypertrophy and maintain consistency between measurements (Figure 1).

Statistics

The analysis cohort for this report comprised 742 patients implanted with either the CoreValve bioprosthesis (n = 389) or a surgical aortic valve (n = 353). Continuous variables are presented as mean ± standard deviation and categorical variables are presented as absolute number and percentage. Comparisons between continuous variables at two time points were made using the paired t-test. Comparisons between categorical variables were done using Chi-square test or Fisher's exact test where appropriate. The Student's t-test was used to assess differences in continuous variables. Data analysis was performed for the entire population first, and subsequently in those patients with normal LVEF (≥ 50%), separately. In addition, paired data were analyzed in patients with LVEF ≥ 50% who had echocardiographic data at discharge, 1 month, and 1 year for calculation of LV mass. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were done using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline data

Baseline patient characteristics have been published previously.[9,10] The population consisted of elderly patients (mean age 83 years) with slightly more men. The overall

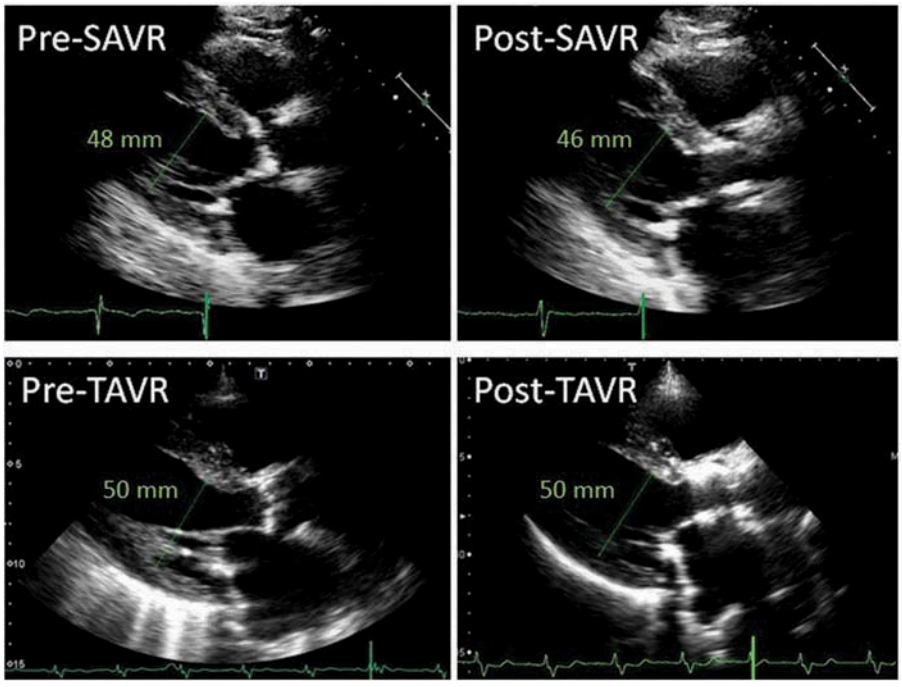

Figure 1. Left ventricular end-diastolic dimension measurement. Representative parasternal long-axis images of pre- and post- SAVR and TAVR (at 1-month follow-up) depicting the LVEDD measurement, taken at the mid-ventricular level, perpendicular to the long-axis of the ventricle, just prior to mitral valve closure or when the ventricular cavity is largest. Vertical bars on the ECG at the bottom indicates the timing of each still image used for LVEDD measurement. LVEDD, left ventricular end-diastolic dimension; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

STS PROM score was 7.4%, the majority with NYHA class III symptoms. Coronary artery disease was present in 75%, with almost half having a history of atrial fibrillation (40.7% in TAVR and 45.6% in SAVR).

Baseline echocardiographic parameters between the two groups were similar, as previously published.[10] On average, patients had a normal LVEF (58.0% in both groups), similar AV effective orifice area (EOA) of 0.7 cm^2 and mean AV gradient of 48 mm Hg in both groups, consistent with severe AV stenosis. LVEDD, PWT, and SWT were comparable between the two groups at baseline. Calculated LV mass (226.1 ± 72.5 in TAVR vs. 227.5 ± 65.0 g in SAVR) and LV mass index (122.5 ± 35.7 in TAVR vs. 123.5 ± 33.6 g/m^2 in SAVR) were increased similarly in both groups at baseline with similarly increased RWT (0.46 in both), consistent with concentric LV hypertrophy (Supplemental Table 1 available online).

Change in calculated LV mass after AVR

The entire cohort was analyzed first. Then, a sub-group analysis in those with an LVEF ≥50% was performed to avoid undue influence from a large LV dimension in those with low EF, as this may have altered the calculation of LV mass. This sub-group with LVEF ≥ 50% represented the majority of the cohort (80%). Unless specified, data represent those of the entire cohort. Upon discharge after AVR, LV mass and LV mass index decreased significantly in the SAVR group (227.45 ± 65.02 to 215.08 ± 59.02 g, $p = 0.002$; 123.54 ± 33.55 to 116.43 ± 28.94 g/m^2, $p = 0.001$, respectively), but this change was not appreciated in the TAVR group (226.07 ± 72.54 to 226.78 ± 72.98 g, $p = 0.887$; 122.45 ± 35.73 to 122.82 ± 35.97 g/m^2, $p = 0.812$). At 1 month, LV mass and LV mass index were still significantly lower in the SAVR group than in the TAVR group (200.22 ± 58.38 vs. 221.19 ± 69.63 g; $p < 0.001$ and 108.83 ± 29.31 vs. 119.45 ± 33.88 g/m^2; $p < 0.001$). At 1 year, both groups had statistically significant decreases in LV mass and LV mass index compared to baseline; however, the reduction in LV mass was significantly less in the TAVR group compared to the SAVR group ($p < 0.001$) (Figure 2).

LV mass change in patients with an LVEF ≥ 50%

Patients with an LVEF ≥ 50% at baseline constituted 80% of the cohort (316 TAVR and 281 SAVR patients, with a mean age of 83.3 in both groups). Roughly half of the patients with an LVEF <50% had an LVEDD ≥ 55 mm (53.0% in the TAVR group and 48.4% in the SAVR group, $p = 0.600$). There were significantly more patients with a large LVEDD (≥ 55 mm) in the low EF group as compared to those with preserved EF (53.0% vs. 13.2%, $p < 0.001$). Despite similar baseline values (119.76 ± 31.38 g/m^2 vs. 116.26 ± 31.36 g/m^2; $p = 0.209$, for SAVR vs. TAVR, respectively), LV mass index at discharge was again significantly less in the SAVR group compared to the TAVR group (111.21 ± 26.80 vs. 118.90 ± 34.32 g/m^2; $p = 0.013$) (Table 1).

Since the number of patients with available echocardiography data varied at each time point due to missing measurements or patient deaths, we also evaluated paired data in the subset of patients with an EF ≥ 50% (139 TAVR and 72 SAVR patients) who had LV mass data available at baseline, discharge, 1 month, and 1 year. The baseline characteristics and echocardiography data by treatment group were similar (Supplemental Tables 2 and 3 available online). The paired analysis also showed that the reduction in LV mass was significantly greater after SAVR; LV mass index regression was 8.6% in SAVR compared to only 1.1% in TAVR at 1 month ($p = 0.021$) and 16.2% compared to 7.6%, respectively, at 1 year ($p = 0.021$) (Table 2).

LV remodeling after SAVR and TAVR

Echocardiographic parameters of TAVR and SAVR valve function have been reported previously.[10,16] At 1 year, patients who underwent TAVR had significantly lower mean gradients (9.1 ± 3.5 mm Hg vs. 12.4 ± 7.4 mm Hg) and larger EOA (1.9 ± 0.5 cm^2 vs. 1.6 ± 0.5 cm^2) than patients who underwent SAVR.[9]

At discharge, LVEDD decreased significantly from baseline in the SAVR group (5.01 ± 0.64 to 4.81 ± 0.65 cm, $p < 0.001$) but not in the TAVR group (4.97 ± 0.63 to 4.91 ± 0.64 cm, $p = 0.094$). This decrease in LVEDD in the SAVR group persisted at 1 year, but LVEDD remained unchanged in the TAVR group (4.80 ± 0.56 cm vs. 4.98 ± 0.66 cm, $p = 0.002$) (Figure 3).

However, PWTd (11.24 ± 1.95 to 11.45 ± 1.73 mm, $p = 0.159$) and interventricular SWTd (12.00 ± 2.07 to 11.99 ± 1.94 mm, $p = 0.954$) were unchanged in the SAVR group at discharge, as well as in the TAVR group (11.19 ± 1.98 to 11.39 ± 2.05 mm; $p = 0.435$ and 11.97 ± 2.35 to 12.26 ± 2.41 mm; $p = 0.155$, respectively). By 1 year, both groups had a significant decrease in PWTd and SWTd compared to baseline ($p < 0.001$), but no difference between the two groups ($p = 0.106$ and 0.573, respectively) (Supplemental Table 1, Figure 4). The data were similar in patients with LVEF ≥ 50% and in patients who had paired data (Table 1, Table 2).

Stroke volume by 2D volumes decreased immediately after SAVR, evident at discharge (72.64 ± 27.04 to 58.93 ± 21.1 mL), but was improving by 6 months (66.34 ± 22.74 mL) and recovered by 1 year (71.45 ± 22.01 mL). In the TAVR group, SVs remained stable and even slightly increased from baseline to 1 year (70.42 ± 27.21 to 73.45 ± 23.81 mL; $p = 0.414$). Doppler-derived SV calculated by the continuity equation had a similar trend (Supplemental Table 1, Figure 5). The SV data were similar in patients with LVEF ≥50% and in patients who had paired data (Table 1 and Table 2).

Right ventricular (RV) function was similar between the two groups at baseline, but at discharge, the frequency of RV dysfunction was higher in the SAVR group compared to the TAVR group ($p < 0.001$), but there were no differences in RV function by 6 months as previously reported. Regardless of the severity of RV dysfunction, SV and LV mass were numerically lower in the SAVR group compared to the TAVR group (Table 3).

LV mass index did not differ between the groups when stratified by severity of AR at each time point (1 month, 6 months, and 1 year). When only the patients with none or trivial AR at 1 month were analyzed (156 TAVR and 201 SAVR patients), LV mass index was still significantly lower in the SAVR group (107.4 ± 28.7 vs. 115.7± 33.0 g/m^2 in the TAVR group; $p = 0.011$). There were too few patients with moderate or severe AR in follow-up, especially in the SAVR group, to determine statistically significant differences in LV mass regression.

Table 1. Left ventricular remodeling over time with baseline left ventricular ejection fraction ≥ 50%.

Echocardiographic parameters	TAVR (*N* = 316)	SAVR (*N* = 281)	*p*-value
LVED dimension (cm)			
Baseline	4.84 ± 0.56 (280)	4.91 ± 0.58 (249)	0.187
Discharge	4.79 ± 0.56 (242)	4.71 ± 0.61 (174)	0.174
30 day	4.89 ± 0.59 (263)	4.62 ± 0.58 (195)	<0.001
6 month	4.91 ± 0.61 (229)	4.66 ± 0.59 (165)	<0.001
1 year	4.90 ± 0.61 (218)	4.75 ± 0.55 (148)	0.020
p-value for change from baseline to 1 year	0.960	< 0.001	
Concentric remodeling (RWTm)			
Baseline	0.48 ± 0.10 (266)	0.48 ± 0.10 (244)	0.867
Discharge	0.50 ± 0.11 (233)	0.51 ± 0.10 (165)	0.591
30 day	0.47 ± 0.09 (251)	0.50 ± 0.11 (184)	0.007
6 month	0.45 ± 0.10 (213)	0.50 ± 0.11 (158)	<0.001
1 year	0.45 ± 0.10 (205)	0.46 ± 0.10 (144)	0.461
p-value for change from baseline to 1 year	0.004	0.009	
Concentric remodeling (RWTp)			
Baseline	0.47 ± 0.10 (270)	0.47 ± 0.10 (248)	0.923
Discharge	0.48 ± 0.10 (237)	0.49 ± 0.10 (166)	0.289
30 day	0.46 ± 0.09 (254)	0.48 ± 0.10 (187)	0.014
6 month	0.43 ± 0.09 (217)	0.49 ± 0.11 (160)	<0.001
1 year	0.43 ± 0.10 (213)	0.43 ± 0.10 (147)	0.688
p-value for change from baseline to 1 year	0.002	0.005	
LV mass (gm)			
Baseline	213.20 ± 63.54 (266)	220.59 ± 61.60 (244)	0.1849
Discharge	217.83 ± 69.10 (233)	205.15 ± 53.89 (165)	0.041
30 day	212.66 ± 64.31 (251)	190.13 ± 52.29 (184)	<0.001
6 month	206.07 ± 63.39 (213)	198.20 ± 58.13 (158)	0.222
1 year	201.35 ± 60.11 (205)	187.10 ± 57.84 (144)	0.028
p-value for change from baseline to 1 year	< 0.001	< 0.001	
LV mass index (gm/m^2)			
Baseline	116.26 ± 31.36 (266)	119.76 ± 31.38 (244)	0.209
Discharge	118.90 ± 34.32 (233)	111.21 ± 26.80 (165)	0.013
30 day	115.29 ± 30.49 (251)	103.22 ± 26.13 (184)	<0.001
6 month	110.69 ± 28.92 (213)	106.71 ± 27.15 (158)	0.180
1 year	108.09 ± 27.18 (205)	99.63 ± 27.32 (144)	0.005
p-value for change from baseline to 1 year	< 0.001	< 0.001	
LV mass index regression (%)			
Discharge	−3.95 ± 26.95 (207)	2.20 ± 26.88 (152)	0.033
30 day	−2.18 ± 30.48 (224)	10.10 ± 23.74 (171)	<0.001
6 month	3.33 ± 26.98 (184)	9.69 ± 26.21 (145)	0.032
1 year	5.24 ± 27.47 (181)	15.54 ± 26.45 (129)	0.001
p-value for change from baseline to 1 year	0.011	< 0.001	
Doppler stroke volume (mL)			
Baseline	78.10 ± 23.50 (285)	77.40 ± 20.36 (246)	0.714
Discharge	76.06 ± 19.30 (272)	63.89 ± 19.06 (199)	<0.001
30 day	78.71 ± 23.33 (288)	68.44 ± 20.23 (224)	<0.001
6 month	80.07 ± 22.69 (245)	74.49 ± 19.89 (181)	0.009
1 year	80.53 ± 21.83 (231)	76.32 ± 21.03 (162)	0.057
p-value for change from baseline to 1 year	0.192	0.023	
Posterior wall thickness (mm)			
Baseline	11.12 ± 1.97 (271)	11.27 ± 1.95 (249)	0.381
Discharge	11.43 ± 2.05 (237)	11.38 ± 1.74 (167)	0.821
30 day	11.04 ± 1.82 (254)	10.88 ± 1.80 (188)	0.383
6 month	10.56 ± 1.79 (218)	11.18 ± 1.95 (160)	0.002
1 year	10.47 ± 1.93 (213)	10.06 ± 2.03 (147)	0.054
p-value for change from baseline to 1 year	< 0.001	< 0.001	
Septal wall thickness (mm)			
Baseline	11.88 ± 2.29 (274)	12.02 ± 2.10 (246)	0.456
Discharge	12.19 ± 2.41 (237)	11.93 ± 1.87 (172)	0.220
30 day	11.70 ± 2.03 (259)	11.66 ± 2.16 (193)	0.837
6 month	11.42 ± 2.23 (220)	11.65 ± 2.04 (164)	0.300
1 year	11.31 ± 2.17 (212)	11.40 ± 2.43 (148)	0.720
p-value for change from baseline to 1 year	0.002	< 0.001	

Note. LVEDD, left ventricular end-diastolic dimension; RWT, relative wall thickness.

The degree of mitral regurgitation (MR) did not differ between the two groups at baseline (approximately 10% had moderate or greater MR; $p = 0.699$). Although TAVR patients had more MR at discharge and 1 month, by 6 months there was no difference between the two groups ($p = 0.264$), with greater than 90% of patients with mild or less MR (Supplemental Table 4 available online).

Impact of LV mass regression on outcome

To assess clinical outcomes, all-cause mortality was evaluated using the absolute reduction in LV mass (g) from baseline to post-procedure stratified by the median reduction (29.4 g for TAVR and 36.4 g for SAVR) for each group (Figure 6). There were no differences in mortality in TAVR patients with a median

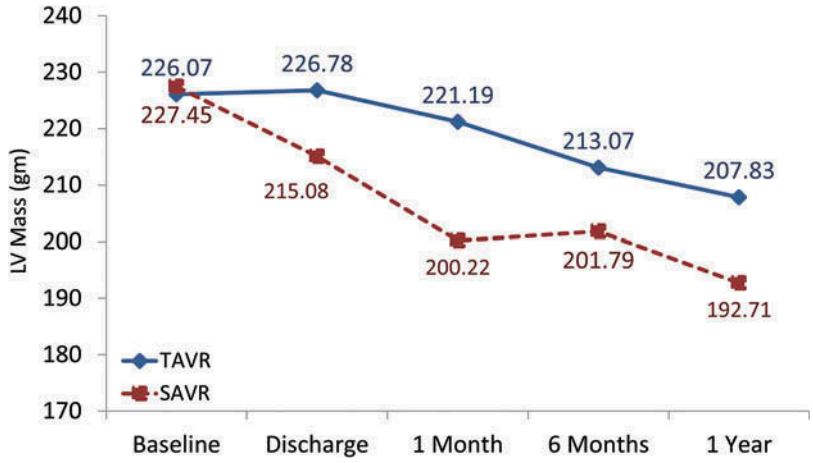

Figure 2. Left ventricular mass for all patients to 1 year. At discharge, LV mass was significantly decreased compared to baseline in the SAVR (dotted red line) patients ($p = 0.002$), but not in the TAVR (blue line) patients ($p = 0.887$). $p = 0.05$ TAVR vs. SAVR at discharge. At 1 year, LV mass was significantly decreased compared to baseline for both TAVR and SAVR, and was significantly less in the SAVR group ($p < 0.001$). SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Table 2. Left ventricular remodeling over time in patients with baseline EF ≥ 50% who had LV mass data available at baseline, discharge, 1 month, and 1 year.

Echocardiographic parameters	TAVR (*N* = 139)	SAVR (*N* = 72)	*p*-value
LV mass (gm)			
Baseline	221.88 ± 61.67 (139)	223.68 ± 50.09 (72)	0.831
Discharge	223.07 ± 65.85 (139)	214.17 ± 49.00 (72)	0.269
1 month	213.55 ± 55.97 (139)	198.76 ± 41.56 (72)	0.031
1 year	198.48 ± 56.02 (139)	182.13 ± 43.09 (72)	0.020
p-value for change from baseline to 1 year	< 0.001	< 0.001	
LV mass index (gm/m^2)			
Baseline	120.73 ± 30.47 (139)	123.45 ± 28.64 (72)	0.531
Discharge	121.20 ± 33.36 (139)	117.72 ± 25.84 (72)	0.403
1 month	116.10 ± 28.25 (139)	109.40 ± 22.53 (72)	0.063
1 year	107.34 ± 25.82 (139)	99.81 ± 20.66 (72)	0.023
p-value for change from baseline to 1 year	< 0.001	< 0.001	
LV mass index regression (%)			
Discharge	−3.01 ± 25.54 (139)	1.90 ± 23.55 (72)	0.176
1 month	1.14 ± 22.06 (139)	8.55 ± 21.62 (72)	0.021
1 year	7.56 ± 26.98 (139)	16.18 ± 22.63 (72)	0.021
p-value for change from baseline to 1 year	0.001	< 0.001	
Posterior wall thickness (mm)			
Baseline	11.29 ± 1.94 (148)	11.24 ± 1.97 (76)	0.846
Discharge	11.54 ± 2.09 (148)	11.49 ± 1.76 (76)	0.848
1 month	11.01 ± 1.72 (148)	11.11 ± 1.45 (76)	0.669
1 year	10.53 ± 1.91 (148)	10.12 ± 2.05 (76)	0.134
p-value for change from baseline to 1 year	< 0.001	0.003	
Septal wall thickness (mm)			
Baseline	11.94 ± 2.18 (150)	12.35 ± 1.90 (81)	0.161
Discharge	12.29 ± 2.38 (150)	12.17 ± 1.86 (81)	0.689
1 month	11.68 ± 1.87 (150)	11.83 ± 1.98 (81)	0.577
1 year	11.25 ± 2.12 (150)	11.49 ± 2.20 (81)	0.405
p-value for change from baseline to 1 year	< 0.001	< 0.001	
Concentric remodeling (RWTm)			
Baseline	0.48 ± 0.09 (139)	0.48 ± 0.09 (72)	0.984
Discharge	0.50 ± 0.10 (139)	0.50 ± 0.10 (72)	0.806
30 day	0.47 ± 0.08 (139)	0.50 ± 0.09 (72)	0.026
1 year	0.46 ± 0.11 (139)	0.46 ± 0.10 (72)	0.539
p-value for change from baseline to 1 year	0.010	0.203	
Concentric remodeling (RWTp)			
Baseline	0.47 ± 0.09 (147)	0.46 ± 0.10 (74)	0.522
Discharge	0.49 ± 0.10 (147)	0.49 ± 0.10 (74)	0.973
30 day	0.46 ± 0.08 (147)	0.48 ± 0.08 (74)	0.051
1 year	0.44 ± 0.11 (147)	0.44 ± 0.11 (74)	0.753
p-value for change from baseline to 1 year	0.020	0.205	
Doppler stroke volume (mL)			
Baseline	78.80 ± 21.35	81.49 ± 22.28	0.313
Discharge	76.15 ± 19.36	65.09 ± 18.59	<0.001
1 month	80.00 ± 22.96	69.87 ± 20.66	<0.001
1 year	81.09 ± 21.33	75.39 ± 19.68	0.026
p-value for change from baseline to 1 year	0.210	0.011	

Table 3. Echocardiographic findings and right ventricular function at 1 month.

	TAVR[a]			SAVR[a]			
	Normal RV n = 310	Mild dysfunction n = 42	Mod dysfunction n = 7	Normal RV n = 237	Mild dysfunction n = 56	Mod dysfunction n = 14	Severe dysfunction n = 1
LVEDD (cm)	4.95 ± 0.59	5.32 ± 0.83	5.24 ± 0.91	4.71 ± 0.62	4.87 ± 0.76	4.51 ± 0.70	0
LVEDV (mL)	129.81 ± 44.94	159.12 ± 51.15	201.50 ± 108.60	111.66 ± 40.74	130.79 ± 49.79	114.33 ± 44.55	344.00
SWT (mm)	11.76 ± 2.05	11.91 ± 2.72	12.43 ± 1.81	11.55 ± 2.03	11.97 ± 1.96	11.50 ± 2.88	0
PWT (mm)	11.08 ± 1.84	10.85 ± 1.89	11.14 ± 1.46	10.79 ± 1.69	11.35 ± 1.75	11.89 ± 3.22	0
RWT	0.45 ± 0.09	0.43 ± 0.12	0.44 ± 0.12	0.47 ± 0.10	0.48 ± 0.10	0.55 ± 0.20	0
2DE SV (mL)[b]	74.14 ± 24.95	74.90 ± 24.02	81.00 ± 26.24	61.91 ± 21.13	55.16 ± 19.64	48.33 ± 15.11	74.00
Doppler SV (mL)	78.76 ± 23.03	74.96 ± 26.42	69.87 ± 25.02	69.20 ± 20.23	65.56 ± 19.07	43.87 ± 12.25	0
LV mass (gm)	218.41 ± 69.02	237.63 ± 75.89	246.43 ± 60.12	194.98 ± 55.07	219.66 ± 66.64	190.53 ± 61.61	0
LV mass index (gm/m^2)	118.90 ± 33.80	122.90 ± 37.57	128.88 ± 22.31	106.79 ± 28.10	117.04 ± 32.20	106.13 ± 32.86	0

Note. There were no TAVR patients with severe right ventricular dysfunction. LVEDV, left ventricular end = diastolic volume.
[a]In six TAVR patients and nine SAVR patients RV dysfunction could not be determined.
[b]Calculated.

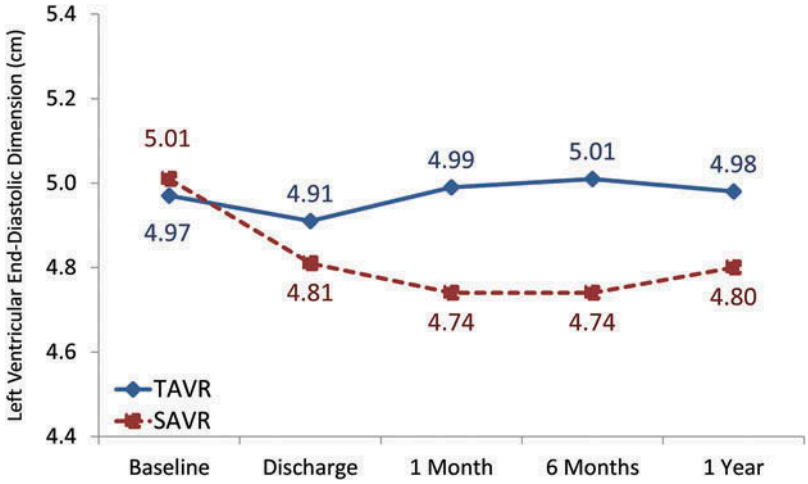

Figure 3. Left ventricular end-diastolic dimension for all patients to 1 year. The LVEDD significantly decreased from baseline to 1 year in the SAVR patients (red dotted line) (p = 0.001), but not in the TAVR patients (blue line) (p = 0.991). LV mass = 0.83 × [(LVEDD + PWTd + SWTd)^3 – (LVEDD)^3] +0.6. LVEDD, left ventricular end-diastolic dimension; PWT, posterior wall thickness; SWT, septal wall thickness; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

LVM reduction of ≥ 29.4 g vs. < 29.4 g at 30 days (1.3% vs. 0.7%, p = 0.565) or at 6 months (5.3% vs. 8.7%, p = 0.258). There were also no differences at 1 year (12.7% vs. 12.8%, p = 0.928; Figure 6A). There was a trend toward higher 30-day mortality in patients with more LV mass reduction, ≥ 36.4 g vs. < 36.4 g, following SAVR (4.7% vs. 0.8%; p = 0.058, but this was not statistically significant at 6 months (14.2 vs. 10.2%, p = 0.325) or at 1 year (19.1% vs. 17.8%, p = 0.698; Figure 6B).

Discussion

This study shows that LV mass, as calculated by the standard Devereux formula, appears to decrease immediately after SAVR, and its calculated reduction is greater after SAVR compared to TAVR with the CoreValve self-expanding aortic valve bioprosthesis which continues up to 1 year, similar to earlier data from the PARTNER trial.[7] This is paradoxical given the fact that prosthetic aortic valve gradients are higher and severe PPM is more frequent after SAVR compared to TAVR, again demonstrated in this cohort.[11,17] The degree of LV mass regression seen after TAVR in our study was comparable to a similar study evaluating LV remodeling after CoreValve bioprosthesis implantation.[18] This paradox appears to be related to significant reductions in LVEDD and SV soon after SAVR which did not occur after TAVR. Moreover, septal and posterior wall thickness regressed similarly in both groups. Hence, the immediate, faster and greater reduction in LV mass calculated after SAVR is likely due to the LV mass formula in which LVEDD is a major component, rather than actual regression of LV mass. In addition, when those patients with reduced EF and enlarged LVEDD were excluded, the results were similar to the entire cohort.

Two-dimensional echocardiography using the linear method as demonstrated here is the mainstay for clinical assessment of LV mass, but has reduced accuracy and reproducibility compared to 3D methods. It also has not been well validated in a large cohort of patients with varying degrees of cardiac remodeling.[15] Our paradoxical findings of greater LV mass regression after SAVR may have been driven by a small number of "outliers" in LVEDD. However, we specifically analyzed the data in patients with preserved EF to eliminate the undue influence of a large LVEDD on the LV mass calculation; only 13% of patients with normal EF had LVEDD >55 mm. Measuring LVEDD is challenging (Figure 1) and can be highly variable if the measurement is not perpendicular to the long-axis of the LV, as can occur in a

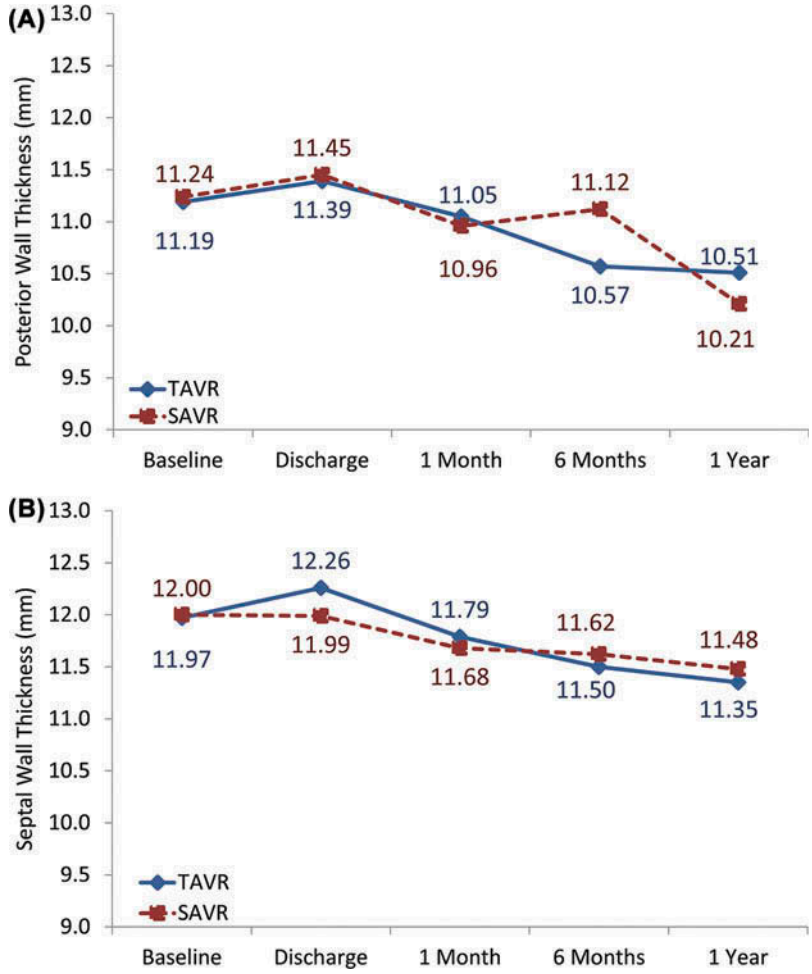

Figure 4. Changes in left ventricular wall thickness following transcatheter or surgical aortic valve replacement. Posterior wall thickness (A); and septal wall thickness (B) over time in all patients. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

low parasternal window. Selection of end-diastole may also be variable, especially in cases with paradoxical septal motion from pacing or bundle branch block. The linear dimensions are raised to the power of 3, such that even small errors in measurement can create big differences in calculated LV mass. It is also important to note that large population studies using two-dimensional harmonic imaging to establish normal LV mass are limited. However, these pitfalls should have affected the SAVR and TAVR groups equally, so measurement error alone cannot explain our findings. Furthermore, similar faster LV mass regression due to smaller LVEDD and reduced SV after surgery compared to TAVR was shown in the PARTNER trial, again suggesting these findings are not likely related to measurement error.[7]

Older patients with aortic stenosis can have a prominent basal septum that makes defining the septal edge of the LVEDD measurement difficult, and can lead to overestimating LV mass. Imaging modalities such as 3D echocardiography or cardiac magnetic resonance imaging (MRI), which do not rely on geometric assumptions regarding LV shape or distribution of wall thickness, may provide a more accurate assessment of LV mass in these scenarios. 2D echocardiography tends to underestimate LV volume compared to MRI[19] and is likely inferior to MRI for assessment of LV mass. In addition, echocardiography is unable to provide reliable information on the presence and progression of myocardial fibrosis. Although not yet adopted in routine clinical practice, the latest 2015 American Society of Echocardiography guidelines recommends 3D assessment for LV mass in those patients with abnormally shaped ventricles or in patients with asymmetric hypertrophy.[20] However, 2D linear assessment remains advantageous in studying large populations given the wealth of published data on this quick and simple method.

We demonstrated that LVEDD and left ventricular end diastolic volume (LVEDV) decrease after SAVR, but remain stable after TAVR, similar to findings from Tzikas and colleagues.[18] This is mirrored by a decrease in SV immediately after SAVR. Given differences in LVOT measurements between laboratories, SV was calculated by both 2D volumetric and Doppler-derived methods, which showed similar findings between the two groups at each time point. Although both posterior and septal wall thickness decreased after AVR, the degree to which this occurred was not different between the two groups. Thus, the finding of greater LV mass reduction after SAVR is related to a statistically significant reduction in LVEDD along with a reduction in SV after SAVR compared to TAVR. This is supported by the paradoxical trend towards reduced survival after SAVR in those patients with apparent greater LV mass regression.

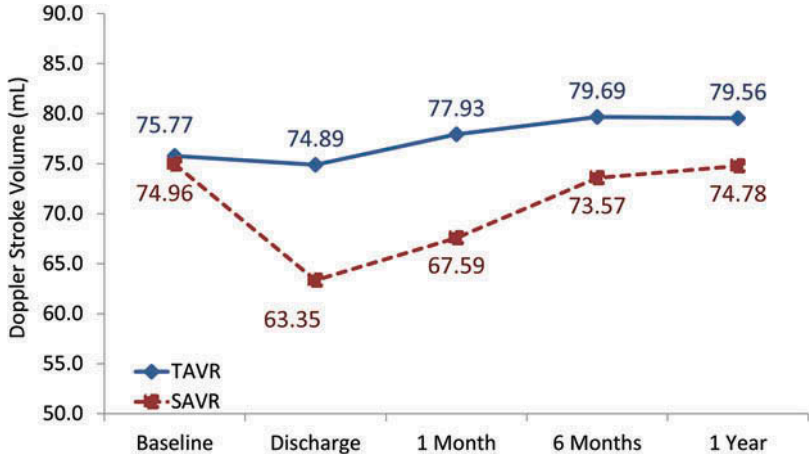

Figure 5. Doppler-derived stroke volume for all patients through 1 year. From baseline to discharge, there was a significant reduction in Doppler-derived stroke volume for SAVR patients ($p < 0.001$), not seen with the TAVR patients ($p = 0.392$). At 1 year, compared to baseline, stroke volume had recovered for the SAVR patients ($p = 0.072$), and there was an increase in stroke volume for TAVR patients ($p = 0.050$). SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

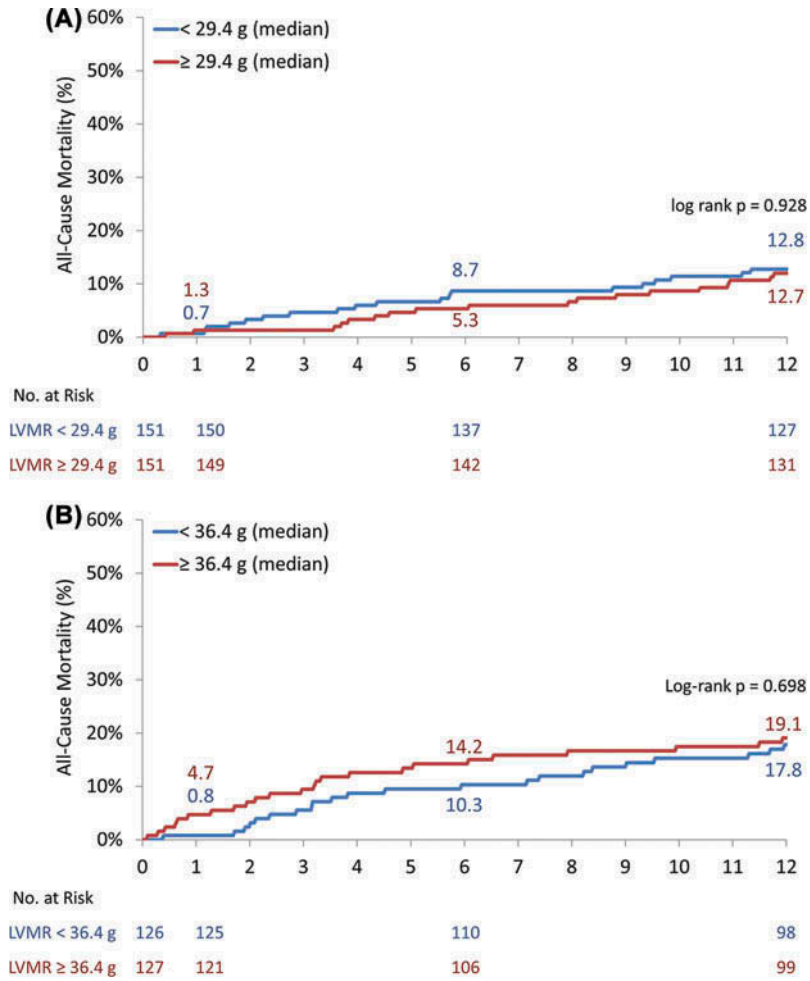

Figure 6. The 1-year all-cause mortality. All-cause mortality to 1 year based on treatment-specific median reduction in LV mass for (A) TAVR and for (B) SAVR. LVMR, left ventricular mass regression; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Older data support the notion that LV mass regression occurs early after SAVR, and that the type or size of the aortic prosthesis does not affect the extent of early regression.[21] In addition, measures of prosthetic hemodynamics may not affect the degree of LV mass regression after SAVR, with only pre-operative LV hypertrophy demonstrated as a significant predictor.[22,23] Reduced LVEDD was likely a large factor for reduced LV mass after SAVR in previous studies. However, new data suggests that the type of prosthesis can affect the degree of LV mass regression and survival.[6]

A key initiative in designing new valve prostheses is creating a favorable hemodynamic effect on the ventricle and ventricular reverse remodeling.[6] This focus in prosthesis development is further fueled by the finding that PPM (prosthesis considered too small for the patient, introducing functional obstruction to flow) increases mortality after AVR,[24] and impairs LV mass regression after both SAVR and TAVR.[17,25] This complicates the finding that LV mass regression is greater after SAVR given the significantly lower rate of PPM in TAVR and higher survival after CoreValve implantation compared to SAVR.[9]

The majority of LV mass regression after AVR (10% to 30%) is complete by 1 year, but this process of reverse remodeling continues for several years after AVR,[26,27] despite the presence of a constant, albeit smaller, pressure gradient with the prosthesis. Available data, although limited, suggest that residual LV hypertrophy has a negative impact on long-term survival after AVR in patients with severe aortic stenosis,[25,28] but other findings indicate that only a high preoperative LV mass, and not the extent of LV mass regression, determine clinical outcomes.[29] Greater early regression of LV mass index seen at 1 month post-TAVR with the SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA) was associated with significantly decreased re-hospitalizations.[30] In a study with longer-term follow-up, enhanced LV mass regression was independently associated with improved long-term survival,[31] and thus should be an important focus when we alleviate severe aortic stenosis. A recent study reiterated the finding that lower mean gradients after AVR are associated with greater LV mass regression and improved patient outcomes and survival.[6] These findings stress that LV mass regression is a good thing and the way in which we measure LV mass should be accurate.

Several hypotheses might explain this apparent paradox in LV mass regression and the differences in LVEDD after TAVR vs. SAVR. First, ventricular remodeling may introduce an error into the Devereux formula used to calculate LV mass from 2D echocardiography,[15] which relies on geometric assumptions of LV shape as a prolate ellipsoid. Interestingly, as LV mass decreased, wall thickness (represented by PWTd and SWTd in formula) did not change between the two groups (but did decrease compared to baseline), but LVEDD significantly decreased in the SAVR group only. Concomitant with this decrease in LVEDD, SV dropped after SAVR, though did improve by 1 year. Thus, the Devereux formula may not hold when LVEDD changes rapidly.

Secondly, this early decrease in SV may be due to a peri-operative insult to the LV including, but not limited to, diffuse subendocardial ischemia, to which the hypertrophied LV is more vulnerable. Alternatively, cardiopulmonary bypass may cause RV dysfunction and enlargement that causes decreased SV,[32] as RV dysfunction was more frequent after SAVR. However, as RV function worsens, there is no trend in LVEDD in the SAVR group. Stroke volume was lower in the SAVR group regardless of RV dysfunction (Table 3). It appears that RV dysfunction is due to a combination of a primary RV abnormality and a reflection of LV dysfunction, rather than being a prime culprit for reduced LVEDD and SV. Cold cardioplegia may also have a negative effect on biventricular function.[33] In addition, paradoxical septal motion and dyssynchrony of ventricular contraction is common post-bypass, an additional element likely contributing to decreased SV after SAVR.

Lastly, another explanation may be the greater frequency of paravalvular leak after TAVR vs. SAVR[34] that may alter LV remodeling and limit LV mass regression; however even when the patients with moderate to severe AR were excluded, there was still a greater decrease in LV mass with SAVR compared to TAVR. Furthermore, there was no significant difference in the degree of MR at baseline and by 6 months to explain the difference in LV mass regression.

Limitations of this study include methods for LV measurements used in the LV mass calculation. As previously mentioned, using linear measurements from a single 2D echocardiographic slice of the LV may not be completely accurate in the setting of abnormal ventricular remodeling. Also, since linear measurements are cubed in the Devereux formula, even small measurement errors in dimensions or thickness have a high impact on accuracy. The Devereux formula is possibly inaccurate in the presence of asymmetric hypertrophy and other diseases with regional variations in wall thickness (i.e. previous myocardial infarction and/or coronary artery disease). However, the majority of patients had an LVEF ≥50% and, it is unlikely that these patients had a burden of cardiac fibrosis that limited LV mass regression.[35] Bias may have also influenced our findings, given the study was not blinded to valve group. However, the sonographers and echocardiologists evaluating these studies were unaware of this particular research question. Another limitation is the lack of a gold standard for LV mass assessment which could be used to compare with our LV mass calculated from the Devereux formula. Further comparison studies with 3D echocardiography (or other 2D methods such as the area-length or truncated ellipsoid method)[20] or cardiac MRI will be helpful to validate our observations.

Conclusion

This echocardiographic study from the CoreValve US Pivotal High Risk Study shows that although significant LV mass reduction occurs after both TAVR and SAVR at 1 year when calculated by the Devereux formula, the change occurs sooner and is greater after SAVR. This paradoxical finding is due to reduced LVEDD in the SAVR group, a major component of the mass formula, associated with reduced SV. The rapidity of LV mass reduction after SAVR is not favorable as it indicates a lower SV rather than a truly faster regression of LV mass and may increase peri-operative mortality.

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Clinical Trial Registration

ClinicalTrials.gov NCT01240902

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