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Early Regression of Severe Left Ventricular Hypertrophy After Transcatheter Aortic Valve Replacement Is Associated With Decreased Hospitalizations

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Objectives This study sought to examine the relationship between left ventricular mass (LVM) regression and clinical outcomes after transcatheter aortic valve replacement (TAVR).

Background LVM regression after valve replacement for aortic stenosis is assumed to be a favorable effect of LV unloading, but its relationship to improved clinical outcomes is unclear.

Methods Of 2,115 patients with symptomatic aortic stenosis at high surgical risk receiving TAVR in the PARTNER (Placement of Aortic Transcatheter Valves) randomized trial or continued access registry, 690 had both severe LV hypertrophy (left ventricular mass index [LVMi] $\geq$149 g/m^2 men, $\geq$122 g/m^2 women) at baseline and an LVMi measurement at 30-day post-TAVR follow-up. Clinical outcomes were compared for patients with greater than versus lesser than median percentage change in LVMi between baseline and 30 days using Cox proportional hazard models to evaluate event rates from 30 to 365 days.

Results Compared with patients with lesser regression, patients with greater LVMi regression had a similar rate of all-cause mortality (14.1% vs. 14.3%, p = 0.99), but a lower rate of rehospitalization (9.5% vs. 18.5%, hazard ratio [HR]: 0.50, 95% confidence interval [CI]: 0.32 to 0.78; p = 0.002) and a lower rate of rehospitalization specifically for heart failure (7.3% vs. 13.6%, p = 0.01). The association with a lower rate of rehospitalization was consistent across subgroups and remained significant after multivariable adjustment (HR: 0.53, 95% CI: 0.34 to 0.84; p = 0.007). Patients with greater LVMi regression had lower B-type natriuretic peptide (p = 0.002) and a trend toward better quality of life (p = 0.06) at 1-year follow-up than did those with lesser regression.

Conclusions In high-risk patients with severe aortic stenosis and severe LV hypertrophy undergoing TAVR, those with greater early LVM regression had one-half the rate of rehospitalization over the subsequent year compared to those with lesser regression. (J Am Coll Cardiol Intv 2014;7:662–73)

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Left ventricular hypertrophy (LVH), defined by increased left ventricular mass (LVM), is associated with increased mortality and morbidity in a broad spectrum of disorders, including patients with severe calcific aortic stenosis (AS) who are undergoing valve replacement surgery (1–3). LVM regression after valve replacement for AS is presumed to be a favorable effect of LV unloading (4). A number of studies have evaluated the extent and timing of LVM regression after surgical valve replacement, and it is often used as a criterion by which to compare the performance of prosthetic valves (5–9). However, the widely held axiom of a relationship between greater LVM regression and improved clinical outcomes has not been clearly established, and some findings undercut it (10). In addition, these issues have not been studied extensively in patients undergoing transcatheter aortic valve replacement (TAVR).

Accordingly, we examined the clinical outcomes of patients with severe symptomatic AS at high risk for surgery (Cohort A) enrolled in the PARTNER (Placement of Aortic Transcatheter Valves) randomized trial and those in the continued access registry to evaluate whether outcomes varied according to the amount of LVM regression after treatment with TAVR (11). Because the presence of more marked LVH prior to valve replacement portends worse clinical outcomes, we evaluated patients with severe LVH on their baseline pre-procedure echocardiogram.

Methods

Study population. The design, inclusion and exclusion criteria, and primary results of the high-risk cohort (Cohort A) of the PARTNER randomized clinical trial have been reported (11). The inclusion and exclusion criteria for patients enrolled in the high-risk continued access registry were the same as those enrolled in the Cohort A randomized trial. These patients had severe AS with an aortic valve area <0.8 cm^2 (or indexed aortic valve area <0.5 cm^2/m^2) and either resting or inducible mean gradient >40 mm Hg or peak jet velocity >4 m/s. They were symptomatic from AS (New York Heart Association functional class II or higher) and were at high surgical risk as defined by a predicted risk of death of 15% or higher by 30 days after conventional surgery. After evaluation of vascular anatomy, patients were included in either the transfemoral cohort or transapical cohort, and if enrolled in the trial, randomized to transcatheter therapy with the Edwards Sapien heart valve system (Edwards Lifesciences, Irvine, California) or surgical aortic valve replacement. For this analysis, we included only patients who received treatment with TAVR (the "as treated" population) who also had: 1) severe LVH on the baseline echocardiogram (American Society of Echocardiography sex-specific cutoffs of left ventricular mass index [LVMi] $\geq$149 g/m^2 for men, $\geq$122 g/m^2 for women); and 2) echocardiograms performed at baseline and 30 days post-TAVR with LVMi measured. Clinical characteristics were determined by the enrolling sites. The study protocol was approved by the institutional review board at each enrolling site and all patients provided written informed consent.

Abbreviations and Acronyms

AS = aortic stenosis
CI = confidence interval
HR = hazard ratio
LVH = left ventricular hypertrophy
LVM = left ventricular mass
LVMi = left ventricular mass index
TAVR = transcatheter aortic valve replacement

Echocardiography. An independent core laboratory analyzed all echocardiograms as previously described (12,13). LV mass was calculated using the formula recommended by the American Society of Echocardiography and indexed to body surface area (12,14,15). Relative wall thickness was calculated in 2 ways: [(posterior wall thickness $\times$ 2)/LV end-diastolic dimension] and [(posterior wall thickness + septal wall thickness)/LV end-diastolic dimension], in which the septal wall thickness was

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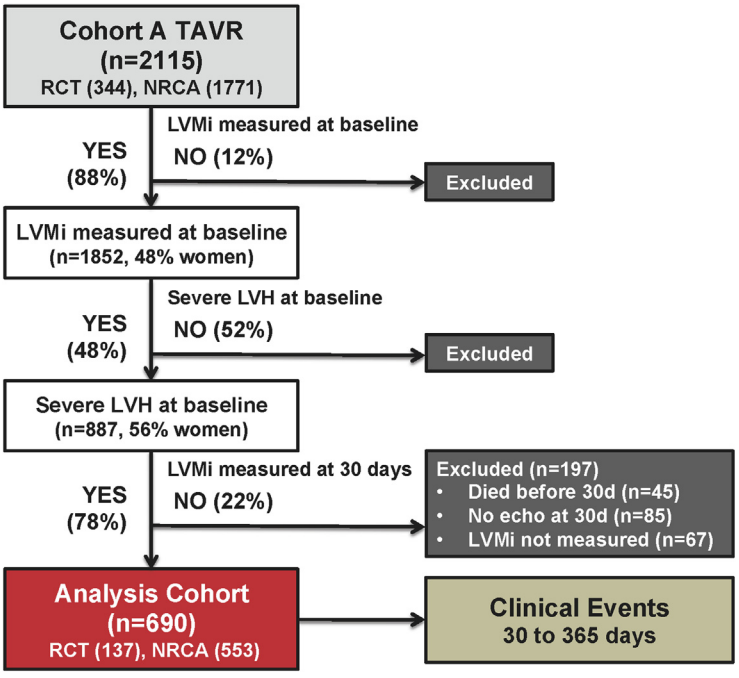

Figure 1. Flow Diagram for Patients Included in the Analysis

d = days; LVH = left ventricular hypertrophy; LVMi = left ventricular mass index; NRCA = nonrandomized continued access registry; RCT = randomized controlled trial; TAVR = transcatheter aortic valve replacement.

measured at the basal septal bulge. Stroke volume was calculated as the LV outflow tract area multiplied by the pulsed-wave Doppler LV outflow tract velocity-time integral and indexed to body surface area. Moderate prosthesis-patient mismatch was defined as an effective orifice area index of 0.65 to 0.85 cm^2/m^2 and severe prosthesis-patient mismatch as an effective orifice area index of <0.65 cm^2/m^2. The presence and severity of post-procedural aortic regurgitation were determined according to Valve Academic Research Consortium-2 criteria (16). Per protocol, echocardiograms were obtained at baseline (within 45 days of TAVR), and post-TAVR at discharge (or 7 days), 30 days, 6 months, and 1 year (12).

Clinical endpoints. Clinical events including all-cause death, cardiac death, repeat hospitalizations, stroke, renal failure, major bleeding, and myocardial infarction; vascular complications were adjudicated by a clinical events committee (11). Repeat hospitalizations were defined as hospitalization for complications from TAVR (e.g., renal failure, infection) or symptoms of heart failure, angina, or syncope due to aortic valve disease requiring aortic valve intervention or intensified medical management. Stroke was defined as a focal neurologic deficit lasting ≥24 h or a focal neurologic deficit lasting <24 h with imaging findings of acute infarction or hemorrhage. Renal failure events were defined as the need for dialysis of any sort. The Kansas City Cardiomyopathy Questionnaire, a heart failure disease-specific health status measure, was used to assess health status (17,18).

Statistical analysis. The effect of LVMi regression was evaluated by comparing patients with severe LVH at baseline with greater versus lesser decrease in LVMi between baseline and 30 days post-TAVR. The groups were determined based on the median percentage decrease for each sex, so that women with greater than the median sex-specific percentage decrease in LVMi were combined with the men with greater than the median sex-specific percentage decrease in LVMi into a combined greater LVMi regression group. Continuous variables were summarized as mean ± SD or medians and quartiles and were compared using the Student *t*-test or Mann-Whitney rank sum test as appropriate. Categorical variables were compared with the chi-square or Fisher exact test. Changes in LVMi over time were evaluated by an overall *F* test to examine trends, and a paired *t* test was used to compare individual time points. A Student 2-sample *t* test was used to compare changes in LVMi between groups. Receiver-operating characteristic analysis was performed using Youden index criterion to determine the optimal cutpoint for percentage of LVMi regression for predicting repeat hospitalizations. Survival curves for time-to-event variables, based on all available follow-up data, were performed with the use of Kaplan-Meier estimates and were compared between groups with the use of the log-rank test. Cox

proportional hazards models were used to calculate hazard ratios and to test for interactions. Stepwise Cox models (entry/stay criteria 0.10/0.10) evaluated the relationship between greater versus lesser LVMi regression (from baseline to 30 days) and repeat hospitalizations (from 30 days to 1 year) after adjustment for clinical and echocardiographic variables that had a univariable association ($p \leq 0.10$) with repeat hospitalizations. Linear regression models evaluated clinical and echocardiographic predictors of percentage of change in LVMi from baseline to 30 days. The Kansas City Cardiomyopathy Questionnaire's overall summary scores were compared using analysis of covariance to adjust for baseline differences in the questionnaire's scores between groups. All statistical analyses were performed with SAS software (version 9.2, SAS Institute, Cary, North Carolina).

Results

Patient population. Among the 2,115 patients with symptomatic AS at high surgical risk receiving TAVR in the PARTNER randomized trial or continued access registry, 1,852 (48% women) had LVMi measured at baseline and 887 (40% of men and 57% of women with LVMi measured at baseline) had severe LVH (Fig. 1). Of those with severe LVH at baseline, 690 patients (n = 137 randomized; n = 553 registry) also had LVMi measured on the echocardiogram obtained 30 days after TAVR, which formed the population for this study; 197 patients did not have LVMi measured 30 days after TAVR for the following reasons: death (n = 45); no echocardiogram obtained (n = 85); or LVMi was not measured due to poor image quality (n = 67). A transfemoral approach was used in 55% of patients, and the remainder were treated via a transapical approach. The study population had a mean age of 85 ± 7 years, aortic valve area of 0.65 ± 0.20 cm^2, Society of Thoracic Surgeons score of 11.0 (interquartile range: 9.7, 13.0), and 56% were women.

Regression of LVMi. Among patients with severe LVH at baseline who survived 1 year after TAVR, LVMi decreased from 166 ± 31 g/m^2 (baseline) to 137 ± 35 g/m^2 (1 year) ($p < 0.001$) (Fig. 2A). LVMi regression over the first year post-TAVR occurred in both men and women ($p < 0.001$ for each) with a similar pattern of incremental regression, but the overall percentage of LVMi regression was greater among women ($p = 0.004$). Over one-half of the LVMi regression observed in this population occurred by 30 days (Fig. 2A). Compared with those with lesser LVMi regression at 30 days, those with greater LVMi regression had a higher baseline LVMi, but lower LVMi at 30 days, 6 months, and 1 year ($p < 0.05$ for each comparison) (Fig. 2B). Those with greater LVMi regression at 30 days had no change in LVMi during the remainder of the year ($p = 0.22$), whereas those with lesser LVMi regression at 30 days had significant regression during the remainder of the year ($p < 0.001$) (Fig. 2B).

Patients with greater early LVMi regression had lower baseline prevalences of obesity ($p = 0.05$) and permanent pacemaker implantation ($p = 0.01$) than did those with lesser regression (Table 1). Baseline echocardiographic variables were also significantly different between groups (Table 2). In the greater LVMi regression group, there was greater midwall fractional shortening ($p < 0.001$), a thicker posterior wall ($p = 0.02$) resulting in greater relative wall thickness by the posterior wall thickness calculation ($p =$

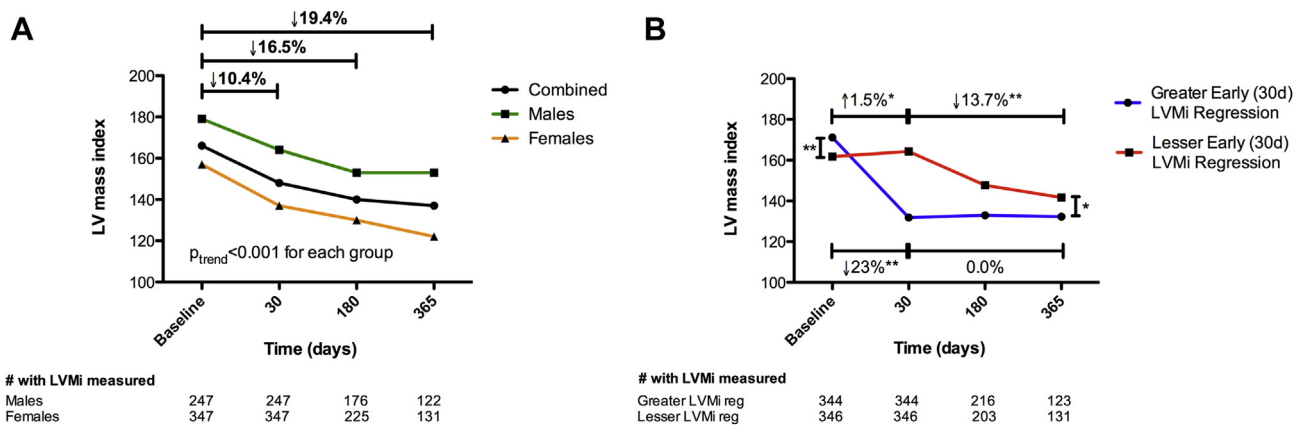

Figure 2. Regression of LVMi After TAVR in Patients With Severe LVH

(A) LVMi regression is shown for patients (combined, men, and women) who had severe LVH at baseline and survived at least 1 year after TAVR. **(B)** The pattern of change in LVMi over 1 year after TAVR is shown for patients with severe LVH at baseline who had greater versus lesser change in LVMi from baseline to 30 days post-TAVR (based on sex-specific median percentage of change in LVMi). The mean LVMi from all available echocardiograms at each time point is shown. *$p < 0.05$. **$p < 0.001$. Abbreviations as in Figure 1.

0.04), and a strong trend toward a higher mean transvalvular gradient ($p = 0.057$). There was no baseline difference in LV dimensions, ejection fraction, or stroke volume index. Following TAVR, the greater LVMi regression group had smaller LV dimensions ($p < 0.01$), wall thickness ($p < 0.001$), and relative wall thickness ($p < 0.01$). There was also significantly less moderate or severe prosthesis-patient mismatch in the greater LVMi regression group ($p = 0.04$). Greater early LVMi regression was associated with increased relative wall thickness at baseline, but decreased relative wall thickness on the 30-day post-TAVR echocardiogram, suggesting that the mass regression resulted from a relatively greater decrease in wall thickness than from a decrease in LV cavity dimension. In multivariable analysis including clinical and echocardiographic variables (at baseline and 30 days post-TAVR), female sex, absence of a pacemaker, higher LVMi, greater midwall fractional shortening at baseline, and

Table 1. Clinical Characteristics Based on Early Regression of Severe LVH After TAVR

	TAVR Cohort A (RCT + NRCA) (n = 690)		
	Greater LVMi Regression (n = 344)	Lesser LVMi Regression (n = 346)	p Value
Age	85.5 ± 6.1	84.7 ± 6.9	0.11
Female	56	56	0.99
BMI, kg/m^2	25.8 ± 5.5	27.0 ± 6.4	0.009
Obesity, BMI ≥30kg/m^2	18.9	25.1	0.05
Body surface area, m^2	1.74 ± 0.23	1.78 ± 0.24	0.02
STS score	11.7 ± 3.9	12.3 ± 5.6	0.08
STS score >10	68	70	0.44
Logistic EuroSCORE	28.0 ± 15.8	28.7 ± 17.3	0.58
Hyperlipidemia	83	83	0.95
Smoking	45	47	0.64
Hypertension	92	95	0.21
Diabetes mellitus	34	41	0.056
NYHA functional class IV	47	46	0.88
Angina	16	20	0.21
Coronary disease	74	78	0.23
Previous myocardial infarction	29	30	0.84
Previous PCI	42	38	0.26
Previous coronary artery bypass surgery	41	46	0.16
Stroke or TIA, last 6 to 12 months	26	31	0.10
Carotid disease	27	30	0.42
Peripheral vascular disease	43	43	0.96
Porcelain aorta	0.3	0.9	0.62
Pulmonary hypertension	42	40	0.59
Major arrhythmia	49	55	0.09
Permanent pacemaker	18	26	0.01
Renal disease, creatinine ≥2 mg/dl	16	20	0.15
Liver disease	1.7	2.0	0.79
Chronic obstructive lung disease	38	41	0.43
Oxygen-dependent	8.1	7.8	0.87
Anemia	71	69	0.52
Transfemoral TAVR	53	58	0.20

Values are mean ± SD or %. Greater versus lesser LVMi regression defined by sex-specific median percentage of change in LVMi from baseline to 30 days post-TAVR.

BMI = body mass index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVH = left ventricular hypertrophy; LVMi = left ventricular mass index; NRCA = non-randomized continued access registry; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

Table 2. Echocardiographic Characteristics Based on Early Regression of Severe LVH After TAVR

	TAVR Cohort A (RCT + NRCA) (n = 690)		
	Greater LVMi Regression (n = 344)	Lesser LVMi Regression (n = 346)	p Value
Baseline echo variables			
LVMi, g/m^2	171 ± 32	162 ± 28	<0.001
Ejection fraction, %	50 ± 13	49 ± 14	0.13
Midwall fractional shortening, %	13.5 ± 8.0	11.3 ± 6.8	<0.001
Stroke volume index, ml/m^2	38 ± 11	37 ± 11	0.17
LV end-diastolic dimension, cm	4.68 ± 0.77	4.72 ± 0.76	0.40
LV end-systolic dimension, cm	3.46 ± 0.96	3.53 ± 0.94	0.34
LV posterior wall dimension, cm	1.28 ± 0.28	1.23 ± 0.26	0.02
LV septal wall dimension, cm	1.76 ± 0.28	1.72 ± 0.33	0.09
Relative wall thickness, PWT only	0.57 ± 0.19	0.54 ± 0.18	0.04
Relative wall thickness, PWT and SWT	0.68 ± 0.19	0.65 ± 0.19	0.08
LVOT dimension, cm	2.02 ± 0.19	2.03 ± 0.19	0.46
AVA index, cm^2/m^2	0.37 ± 0.10	0.37 ± 0.11	0.67
AV mean gradient, mm Hg	47 ± 15	44 ± 15	0.057
Moderate and severe total AR	12.8	10.2	0.28
Moderate and severe MR	24.9	22.4	0.46
Post-TAVR echo variables (30 days)			
LVMi, g/m^2	132 ± 27	164 ± 32	<0.001
Ejection fraction, %	53 ± 12	52 ± 12	0.34
Midwall fractional shortening, %	13.8 ± 8.2	13.2 ± 6.9	0.27
Stroke volume index, ml/m^2	39 ± 12	39 ± 12	0.75
LV end-diastolic dimension, cm	4.58 ± 0.79	4.80 ± 0.81	<0.001
LV end-systolic dimension, cm	3.32 ± 0.94	3.51 ± 0.93	0.006
LV posterior wall dimension, cm	1.10 ± 0.23	1.22 ± 0.27	<0.001
LV septal wall dimension, cm	1.52 ± 0.27	1.69 ± 0.32	<0.001
Relative wall thickness, PWT only	0.50 ± 0.16	0.53 ± 0.18	0.01
Relative wall thickness, PWT and SWT	0.60 ± 0.17	0.63 ± 0.19	0.008
EOA index, cm^2/m^2	0.99 ± 0.29	0.96 ± 0.29	0.10
PPM, moderate and severe	33.5	41.3	0.04
PPM, severe	10.0	12.7	0.27
AV mean gradient, mm Hg	9 ± 4	10 ± 5	0.10
Mild total AR	49.4	52.3	0.45
Moderate and severe total AR	12.5	14.2	0.52
Moderate and severe MR	19.5	21.1	0.61

Values are mean ± SD or %. Greater versus lesser LVMi regression defined by sex-specific median percentage of change in LVMi from baseline to 30 days post-TAVR. Moderate PPM = EOA index 0.65 to 0.85 cm^2/m^2. Severe PPM = EOA index <0.65 cm^2/m^2.

AR = aortic regurgitation; AV = aortic valve; AVA = aortic valve area; EOA = effective orifice area; LVOT = left ventricular outflow tract; MR = mitral regurgitation; PPM = prosthesis-patient mismatch; PWT = posterior wall thickness; SWT = septal wall thickness; other abbreviations as in Table 1.

lower transvalvular mean gradient 30 days post-TAVR were independently associated with greater early LVMi regression (Table 3).

Clinical outcomes. Compared with patients with lesser regression, patients with greater LVMi regression 30 days after TAVR had a similar rate of all-cause mortality between 30 days and 1 year (14.1% vs. 14.3%, p = 0.99), but a lower rate of rehospitalization (9.5% vs. 18.5%, hazard ratio [HR]: 0.50; 95% confidence interval [CI]: 0.32 to 0.78; p = 0.002) and the composite endpoint of death or rehospitalization (19.4% vs. 27.1%, HR: 0.70, 95% CI: 0.51 to 0.97; p = 0.03) (Table 4, Fig. 3). In particular, greater early LVMi regression was associated with a lower rate of repeat hospitalizations for heart failure (7.3% vs. 13.6%, HR: 0.53, 95% CI 0.32 to 0.88, p = 0.01), which was the most common reason for repeat hospitalization in these patients (Table 4, Fig. 3C). The strong association of greater early LVMi regression with a lower rate of repeat hospitalizations was consistent across several subgroups with no significant interactions (Table 5) and remained essentially unchanged after extensive multivariable adjustment for clinical and echocardiographic factors associated with repeat hospitalizations (Table 6, Online Table 1). Receiver-operating characteristic analysis demonstrated that an early LVMi regression of 10% was the optimal cutoff for predicting repeat hospitalizations (area under the curve: 0.60, 95% CI: 0.53 to 0.66). Greater early LVMi regression was also associated with a lower rate of repeat hospitalization between 30 days and 1 year when we evaluated patients with moderate or severe baseline LVH (11.5% vs. 18.4%, HR: 0.62, 95% CI: 0.43 to 0.88, p = 0.007) or patients with any degree of baseline LVH (12.6% vs. 16.8%, HR: 0.75, 95% CI: 0.55 to 1.03; p = 0.07) (Online Tables 2 and 3).

B-type natriuretic peptide, quality of life, and functional status. Although similar at baseline, B-type natriuretic peptide levels were lower at 1 year in patients with greater early LVMi regression than in those with lesser regression (p = 0.002) (Table 7). New York Heart Association functional class was similar between the groups as was the ability to perform a 6-minute walk and the distance walked. After adjustment for baseline differences, there was a trend toward better quality of life at 1 year in patients with greater, compared with lesser, early regression of severe LVH (p = 0.06) (Table 7).

Table 3. Multivariable Linear Regression Models for Percentage of Change in LVMi From Baseline to 30 Days After TAVR

Variable	Beta Estimate (%)	p Value
Model 1—clinical model		
Intercept	−9.0	0.28
Age, per yr	0.1	0.48
Male	−5.7	<0.001
Baseline LVMi, per 1 g/m^2 increase	0.1	<0.001
STS score, per 1 unit increase	−0.3	0.02
Pacemaker at baseline	−3.1	0.02
Model 2—clinical + baseline echo		
Intercept	−17.9	0.04
Age, per yr	0.1	0.36
Male	−5.7	<0.001
Baseline LVMi, per 1 g/m^2 increase	0.1	<0.001
STS score, per 1 unit increase	−0.2	0.09
Pacemaker at baseline	−2.9	0.04
Midwall fractional shortening, per 1% increase	0.3	<0.001
Model 3—clinical + baseline echo + 30-day echo		
Intercept	−17.2	0.05
Age, per yr	0.1	0.30
Male	−5.7	<0.001
Baseline LVMi, per 1 g/m^2	0.1	<0.001
STS score, per 1 unit	−0.2	0.07
Pacemaker at baseline	−3.2	0.02
Midwall fractional shortening, per 1% increase	0.3	<0.001
30-Day transvalvular mean gradient, per 1 mm Hg increase	−0.3	0.05

Linear regression models evaluating variables associated with percentage of change in LVMi from baseline to 30 days post-TAVR. A positive beta estimate signifies regression/decrease in LVMi from baseline to 30 days post-TAVR. Model 1: Selection model including age, sex, and baseline LVMi (forced variables) and other variables selected from among the clinical variables (Table 1) that differ ($p \leq 0.10$) between those with greater versus lesser regression at 30 days. Model 2: Selection model including the same variables as Model 1 in addition to baseline echo variables (Table 2) that differ ($p \leq 0.10$) between those with greater versus lesser regression at 30 days (variables were excluded if they were a part of the calculation of LVMi). Model 3: Selection model including the same variables as Model 2 in addition to 30-day post-TAVR echo variables (Table 2) that differ ($p \leq 0.10$) between those with greater versus lesser regression at 30 days (variables were excluded if they were a part of the calculation of LVMi).

Abbreviations as in Table 1.

Discussion

We found that among patients with severe symptomatic AS at high surgical risk, approximately one-half of the population had severe LVH at baseline (40% of the men and 57% of the women), and that those with greater LVMi regression 30 days after TAVR had one-half the rate of repeat hospitalizations from 30 days to 1 year. This was primarily due to a significant decrease in repeat hospitalizations due to heart failure. This association of greater early LVMi regression with fewer hospitalizations was consistent across subgroups and remained significant after adjustment for clinical and echocardiographic factors associated with repeat hospitalizations. Whereas previous studies have either been inconclusive or have undercut the existing dogma, these findings support the assumption that LVH regression after valve replacement for AS is associated with a clinical benefit.

There are several novel aspects to our evaluation of LVMi regression after valve replacement in comparison to previous studies. We looked at a large number of patients, all of whom were enrolled in a multicenter clinical trial and were treated with TAVR instead of surgical AVR. Echocardiograms were performed at pre-specified consistent intervals for all patients before TAVR (baseline study) and during

Table 4. Clinical Outcomes Based on Early Regression of Severe LVH After TAVR

	Greater LVMi Regression	Lesser LVMi Regression	Hazard Ratio (95% CI)	p Value
Outcomes 30 days to 1 year, combined	n = 344	n = 346		
Death, all-cause	14.1 (47)	14.3 (48)	1.00 (0.67–1.49)	0.99
Death, cardiac	8.8 (28)	9.3 (30)	0.95 (0.57–1.59)	0.84
Repeat hospitalizations	9.5 (30)	18.5 (59)	0.50 (0.32-0.78)	0.002
Hospitalizations for CHF	7.3 (23)	13.6 (43)	0.53 (0.32–0.88)	0.01
Death or hospitalizations	19.4 (65)	27.1 (91)	0.70 (0.51–0.97)	0.03
Stroke, any	1.3 (4)	1.6 (5)	0.81 (0.22-3.03)	0.76
Outcomes 30 days to 1 year, men	n = 151	n = 152		
Death, all-cause	18.4 (27)	20.0 (29)	0.94 (0.55-1.58)	0.81
Death, cardiac	10.9 (15)	13.1 (18)	0.83 (0.42–1.66)	0.60
Repeat hospitalizations	13.6 (19)	23.3 (32)	0.57 (0.32–1.01)	0.051
Death or hospitalizations	24.4 (36)	35.5 (52)	0.67 (0.44–1.02)	0.059
Stroke, any	1.5 (2)	0.7 (1)	2.03 (0.18–22.43)	0.55
Outcomes 30 days to 1 year, women	n = 193	n = 194		
Death, all-cause	10.7 (20)	9.9 (19)	1.07 (0.57–2.00)	0.83
Death, cardiac	7.2 (13)	6.4 (12)	1.10 (0.50–2.42)	0.81
Repeat hospitalizations	6.2 (11)	15.0 (27)	0.40 (0.20–0.81)	0.009
Death or hospitalizations	15.5 (29)	20.6 (39)	0.74 (0.46–1.19)	0.21
Stroke, any	1.1 (2)	2.3 (4)	0.51 (0.09–2.78)	0.43
Outcomes 0 to 30 days, combined	n = 344	n = 346		
Post-TAVR myocardial infarct	0.9 (3)	0.6 (2)	1.51 (0.25–9.04)	0.65
Major bleeding	5.8 (20)	6.9 (24)	0.83 (0.46–1.51)	0.54
Major vascular complication	5.8 (20)	4.9 (17)	1.18 (0.62–2.26)	0.60
Renal failure requiring dialysis	2.3 (8)	0.9 (3)	2.70 (0.72–10.19)	0.13
Stroke, any	2.3 (8)	3.5 (12)	0.67 (0.27–1.64)	0.37

Values are % (n). Greater versus lesser LVMi regression defined by sex-specific median percentage of change in LVMi from baseline to 30 days post-TAVR. The event rates were calculated with the use of Kaplan-Meier methods.

CHF = congestive heart failure; CI = confidence interval; other abbreviations as in Table 1.

follow-up, and were all analyzed in a uniform manner by a core laboratory. Given the large number of patients, we were able to focus our analysis on those with severe LVH in whom the issues of LVMi regression after AVR would presumably be most important. We also had systematic echocardiographic follow-up at 30 days and were, therefore, able to evaluate the impact of early LVMi regression. Finally, a particular strength was our use of adjudicated clinical events, specifically hospitalizations, in all patients, whereas previous similar studies have been limited to mortality as the only outcome (10).

Regression of LVH after valve replacement for AS and its clinical implications. LV hypertrophy commonly occurs in patients with chronic LV pressure overload from severe AS. It regresses over months to years after valve replacement (6–8), and some studies have shown that significant LVM regression occurs even earlier (19,20). We showed that in patients with severe LVH treated with TAVR, more than 50% of the 1-year LVMi regression occurred by 30 days. This pattern was consistent for men and women and highlights the remarkable plasticity of the heart, even in this elderly cohort with many comorbidities (21). It was also interesting that those with greater LVMi regression at 30 days did not regress further over the remainder of the year. In contrast, those who had less or no LVMi regression by 30 days experienced LVMi regression between 30 days and 1 year, although they failed to achieve an equivalent degree of regression over the year. LVM is a function of chamber dimensions and wall thickness. We observed that whereas those with more early regression had smaller LV chamber dimensions and thinner walls at 30 days, the relative wall thickness measurements at baseline and 30 days indicate that there was a greater reduction in the muscle (wall thickness) than in the LV chamber dimensions in those patients. After adjusting for baseline LVMi, clinical and echocardiographic variables associated with greater early LVMi regression included female sex, absence of a pacemaker pre-operatively, increased pre-operative midwall fractional shortening, and lower transvalvular mean gradient at 30 days.

Many studies have evaluated LVMi regression after AVR, using it as a surrogate endpoint to compare different valve prostheses; this attests to the widespread assumption that LVMi regression after AVR is a clinically beneficial effect of valve replacement (4,5,9). A few studies suggest clinical

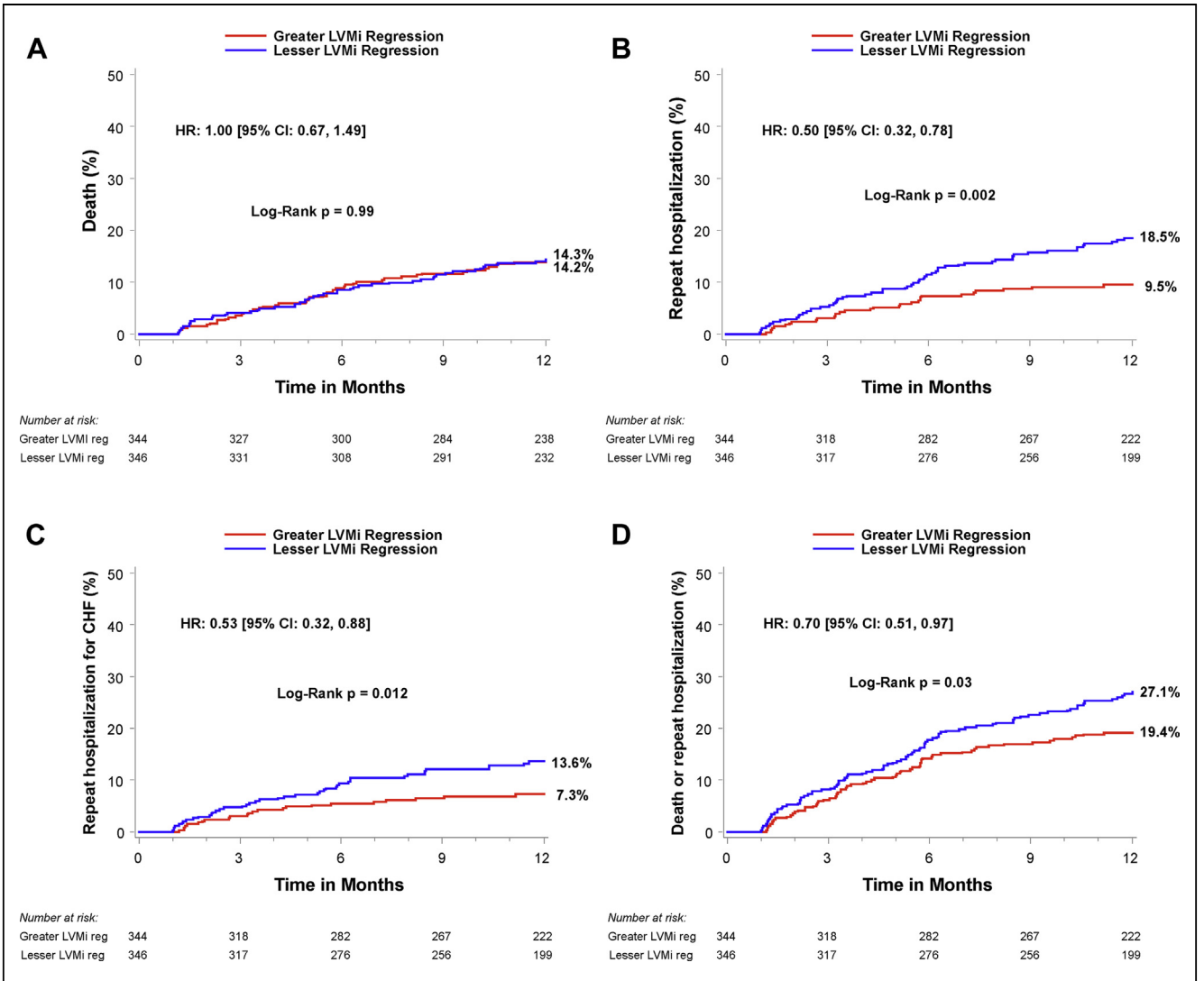

Figure 3. Time-to-Event Curves for Death or Repeat Hospitalizations From 30 Days to 1 Year

Time-to-event curves are shown from 30 days to 1 year for **(A)** death (all-cause), **(B)** repeat hospitalizations, **(C)** repeat hospitalizations for heart failure, and **(D)** death (all-cause) or repeat hospitalizations for patients with symptomatic aortic stenosis and severe left ventricular hypertrophy at high surgical risk receiving TAVR in the PARTNER randomized trial or continued access registry. The curves compare patients with greater versus lesser LVMi regression from baseline to 30 days after TAVR (based on sex-specific median percentage of change in LVMi). The event rates were calculated with the use of Kaplan-Meier methods and compared with the use of the log-rank. CHF = congestive heart failure; CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

benefit from greater post-operative LVMi regression, but significant methodological flaws or small sample size led to inconclusive findings (22,23). In contrast, some studies have reported that greater LVMi regression after AVR is not associated with improved outcome, thus questioning the prevailing dogma (10). For hypertensive patients with LVH, regression of LVH with antihypertensive medical therapy has been associated with improved clinical outcomes (24,25). However, such an association has not previously been demonstrated for patients with AS experiencing LVM regression after valve replacement. As such, our finding that greater early LVMi regression is associated with one-half the rate of repeat hospitalization during the first year after TAVR provides a novel and important insight into the connection between regression of LVH and clinical outcomes after valve replacement for AS.

Potential mechanisms for the relationship between LVMi regression and hospitalizations. Greater LVMi regression was associated with a lower rate of repeat hospitalization, and the majority of these hospitalizations were related to heart failure. B-type natriuretic peptide levels were lower at 180 and 365 days in patients who had greater early LVMi regression, which is consistent with improved LV function and less heart failure in these patients. We hypothesize that

Table 5. Subgroup Analyses for Repeat Hospitalizations

	Greater LVMi Regression	Lesser LVMi Regression	Hazard Ratio (95% CI)	p Value
Overall population	n = 344	n = 346		
Repeat hospitalizations	9.5 (30)	18.5 (59)	0.50 (0.32–0.78)	0.002
Trial group			p for interaction = 0.16	
TAVR Cohort A RCT	n = 63	n = 74		
	13.8 (8)	16.3 (11)	0.90 (0.36–2.24)	0.82
TAVR Cohort A NRCA	n = 281	n = 272		
	8.6 (22)	19.0 (48)	0.43 (0.26–0.71)	0.0007
Access route			p for interaction = 0.54	
Transfemoral	n = 179	n = 197		
	8.9 (15)	15.4 (28)	0.57 (0.30–1.06)	0.07
Transapical	n = 165	n = 149		
	10.1 (15)	22.6 (31)	0.43 (0.23–0.80)	0.006
Sex			p for interaction = 0.46	
Male	n = 151	n = 152		
	13.5 (19)	23.3 (32)	0.57 (0.32–1.01)	0.05
Female	n = 193	n = 194		
	6.2 (11)	15.0 (27)	0.41 (0.20–0.82)	0.009
Relative wall thickness			p for interaction = 0.12	
≥ Median	n = 186	n = 159		
	11.0 (19)	15.5 (23)	0.71 (0.39–1.30)	0.26
< Median	n = 158	n = 187		
	7.5 (11)	21.0 (36)	0.35 (0.18–0.68)	0.001
LV end-diastolic dimension			p for interaction = 0.40	
≥ Median	n = 166	n = 177		
	14.4 (22)	24.5 (40)	0.58 (0.35–0.98)	0.04
< Median	n = 178	n = 169		
	4.9 (8)	12.2 (19)	0.38 (0.17–0.88)	0.02
Ejection fraction			p for interaction = 0.14	
≥50%	n = 216	n = 195		
	9.6 (19)	13.6 (24)	0.71 (0.39–1.30)	0.27
<50%	n = 127	n = 151		
	9.3 (11)	24.8 (35)	0.36 (0.18–0.71)	0.002
Midwall fractional shortening			p for interaction = 0.48	
≥ Median	n = 177	n = 149		
	8.5 (14)	19.0 (26)	0.45 (0.23–0.86)	0.01
< Median	n = 141	n = 185		
	10.8 (14)	17.0 (29)	0.62 (0.33–1.18)	0.14
Stroke volume index			p for interaction = 0.23	
≥35 ml/m^2	n = 194	n = 175		
	7.3 (13)	18.0 (29)	0.39 (0.20–0.75)	0.003
<35 ml/m^2	n = 144	n = 165		
	13.0 (17)	18.9 (29)	0.68 (0.37–1.24)	0.2

Continued on the next page

more mass regression might have caused improved diastolic function (26,27), but assessment of diastolic function was not included in the core laboratory echocardiographic measurements (12). Related to this, we speculate that more early LVMi regression might result from less myocardial fibrosis, as suggested by greater midwall fractional shortening at baseline in these patients. LV fibrosis has been associated with impaired systolic function in patients with AS and associated with increased mortality and less symptomatic improvement and LV functional recovery after AVR (28,29).

The event rates for repeat hospitalizations between patients with greater versus lesser early LVMi regression continued to separate during the entire period from 30 days to 1 year (Fig. 1B), suggesting that greater early LVMi regression is associated with ongoing and accumulating clinical benefits. Whether early (30 days) versus intermediate

Table 5. Continued

	Greater LVMi Regression	Lesser LVMi Regression	Hazard Ratio (95% CI)	p Value
Mean gradient			p for interaction = 0.28	
≥40 mm Hg	n = 216	n = 191		
	6.4 (13)	15.3 (27)	0.40 (0.21–0.78)	0.005
<40 mm Hg	n = 122	n = 150		
	14.6 (16)	22.5 (31)	0.66 (0.36–1.22)	0.18
30-day paravalvular AR			p for interaction = 0.18	
Moderate/severe paravalvular AR	n = 38	n = 44		
	22.4 (8)	24.6 (10)	0.92 (0.36–2.32)	0.85
No/trace/mild paravalvular AR	n = 306	n = 299		
	7.8 (22)	17.4 (48)	0.44 (0.27–0.73)	0.001

Cox proportional hazards models were used to evaluate the hazard ratios for patients in each subgroup for the outcome of repeat hospitalizations and the interaction between each subgroup and LVMi regression (greater vs. lesser regression from baseline to 30 days post-TAVR based on sex-specific median percentage of change in LVMI) for repeat hospitalizations.

Abbreviations as in Tables 1, 2, and 4.

Table 6. Predictors of Repeat Hospitalization (30 Days to 1 Year) Based on Early Regression of Severe LVH After TAVR

Variable	Hazard Ratio (95% CI)	p Value
Model 1—clinical model		
Greater early LVMi regression, baseline to 30 days	0.52 (0.33–0.81)	0.004
Age, per yr	0.98 (0.95–1.01)	0.12
Male	1.37 (0.87–2.17)	0.18
Baseline LVMi, per 1 g/m^2 increase	1.00 (1.00–1.01)	0.39
Major arrhythmia	1.91 (1.23–2.96)	0.004
Previous PCI	1.70 (1.11–2.59)	0.01
Smoking	1.77 (1.14–2.76)	0.01
Model 2—clinical and echocardiographic model		
Greater early LVMi regression, baseline to 30 days	0.53 (0.34–0.84)	0.007
Age, per yr	0.97 (0.94–1.00)	0.055
Male	1.32 (0.83–2.10)	0.23
Baseline LVMi, per 1 g/m^2 increase	1.00 (1.00–1.01)	0.35
Major arrhythmia	1.74 (1.12–2.71)	0.01
Previous PCI	1.52 (0.99–2.35)	0.06
Smoking	1.81 (1.16–2.82)	0.009
Baseline mean gradient, per 1 mm Hg increase	0.98 (0.96–1.00)	0.02
Moderate/severe AR at 30 days	1.59 (0.99–2.57)	0.06

Cox proportional hazards models evaluating whether greater early LVMi from baseline to 30 days post-TAVR (based on sex-specific median percentage of change in LVMi) is an independent predictor of the clinical endpoint of repeat hospitalization from 30 to 365 days.

Model 1: Selection model including age, sex, baseline LVMi, and LVMi regression (greater vs. lesser change in LVMi from baseline to 30 days) (forced variables) and other variables selected from among the baseline clinical variables and clinical events from 0 to 30 days (myocardial infarction, any stroke, major vascular complication, major bleeding, renal failure requiring dialysis) that have a significant ($p \leq 0.10$) univariable relationship with the clinical endpoint of repeat hospitalization from 30 to 365 days (Online Table 1). Model 2: Selection model including the same variables as Model 1 in addition to baseline or 30 day echo variables that have a significant ($p \leq 0.10$) univariable relationship with the clinical endpoint of repeat hospitalization from 30 to 365 days (Online Table 1). Echocardiographic variables were excluded if they were a part of the calculation of LVMi (LV cavity dimensions and wall thickness).

Abbreviations as in Tables 1, 2, and 4.

(6 months) LVMi regression has differential associations with clinical outcomes requires further study. Despite the association between greater LVM regression and fewer hospitalizations, there was no association with cardiac or all-cause mortality. This may be because a 1-year follow-up time frame is too short to detect differences in mortality, but further studies with longer term follow-up are needed to evaluate this relationship.

Clinical implications. Repeat hospitalizations are a major contributor to healthcare costs and a particular focus of efforts to reduce spending. Our findings demonstrate that greater LVMi regression after valve replacement has important clinical and economic implications. Because of its favorable impact on clinical outcomes, we need to better understand what predicts LVMi regression as well as what may augment it. Our findings suggest that LVMi regression after valve replacement may be a therapeutic target and provide a rationale for identifying adjunctive medical therapy that, in addition to valvular unloading, could accentuate LVMi regression after valve replacement. It is also important to note that in addition to decreasing repeat hospitalizations, greater early LVMi regression was associated with a trend toward improved quality of life at 1 year, an important patient-centered metric of the clinical benefit of TAVR. To our knowledge, this is also the first analysis that specifically evaluates clinical and echocardiographic factors associated with repeat hospitalizations after TAVR and offers insights into other potentially modifiable factors.

Study limitations. Echocardiography is not as accurate for assessment of LVM as magnetic resonance imaging, but magnetic resonance imaging is much more expensive and was not available in this randomized clinical trial. There may be minor problems with the accuracy of some of the echocardiographic measurements due to image quality or distortions in LV geometry, and evaluating the change in LVM

Table 7. BNP, Symptoms, Quality of Life, and 6-Min Walk

	Greater LVMi Regression (n = 344)	Lesser LVMi Regression (n = 346)	p Value
BNP			
Baseline	862 (398, 2,258)	932 (450, 1,927)	0.92
30 days	624 (305, 1,497)	727 (350, 1,599)	0.27
6 months	421 (211, 1,024)	562 (243, 1,287)	0.08
1 year	356 (186, 824)	533 (268, 1,068)	0.002
NYHA class III/IV			
Baseline	94	94	0.98
Discharge	35	42	0.09
30 days	18	19	0.87
6 months	10	11	0.60
1 year	8	13	0.11
KCCQ			
Baseline			
Patients with KCCQ data	313	318	
Overall summary score	42.3 ± 21.8	44.7 ± 22.6	0.18
30 days			
Patients with KCCQ data	318	314	
Overall summary score adjusted for baseline score	61.0 ± 24.5	62.7 ± 24.4	0.75*
6 months			
Patients with KCCQ data	278	277	
Overall summary score adjusted for baseline score	73.2 ± 21.4	70.5 ± 23.9	0.44*
1 year			
Patients with KCCQ data	228	236	
Overall summary score adjusted for baseline score	73.0 ± 21.2	71.5 ± 22.3	0.06*
6-Min walk			
Baseline			
Could not perform	32	34	0.61
Distance walked, m†	151 ± 101	166 ± 96	0.12
30 days			
Could not perform	29	29	0.19
Distance walked, m	187 ± 110	180 ± 110	0.48
6 months			
Could not perform	22	24	0.55
Distance walked, m	206 ± 114	209 ± 114	0.79
1 year			
Could not perform	20	22	0.47
Distance walked, m	201 ± 97	200 ± 123	0.92

Values are median (25th, 75th percentile), %, or mean ± SD. *Follow-up KCCQ overall summary scores were compared using analysis of covariance to adjust for baseline differences in KCCQ scores between groups. †Excluding those who could not perform the 6-min walk.

BNP = B-type natriuretic peptide; KCCQ = Kansas City Cardiomyopathy Questionnaire; other abbreviations as in Table 1.

may have a wider range of error than evaluating a single measurement does. However, these inaccuracies should affect all patients in the study, and all echocardiographic measurements were made by a core laboratory (12). Our findings apply to elderly patients at high surgical risk treated with TAVR; however, they may not apply to younger lower risk patients, those without severe LVH at baseline, or those treated with surgical valve replacement. Selection bias may also have influenced our results insofar as patients that did not survive 30 days or patients with poor image quality, which precluded measurement of LVMi, were not included in our analysis. Finally, the follow-up time was limited to 1 year because events were not adjudicated beyond this point, which may explain the lack of a relationship between LVMi regression and mortality.

Conclusions

In high-risk patients with severe LVH undergoing TAVR, those with greater early LVMi regression had one-half the rate of repeat hospitalizations, principally for heart failure, over the first post-procedure year. This association was consistent across subgroups and remained significant after multivariable adjustment. These findings support the dogma that LVMi regression after valve replacement is associated with clinical benefits, which had previously lacked supporting evidence. The strong association between LVMi regression and reduced hospitalizations has important economic and clinical implications. Further study is needed to elucidate factors associated with LVMi regression and to identify adjunctive medical therapies and other interventions that may optimize regression of LVH after valve replacement.

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Key Words: aortic stenosis ■ heart failure ■ hospitalizations ■ hypertrophic left ventricular remodeling ■ transcatheter aortic valve replacement.

APPENDIX

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