The effect of postoperative medical treatment on left ventricular mass regression after aortic valve replacement

Meghana R. K. Helder, MD,^a Murat Ugur, MD,^a Joseph E. Bavaria, MD,^b Vibhu R. Kshetry, MD,^c Mark A. Groh, MD,^d Michael R. Petracek, MD,^e Kent W. Jones, MD,^f Rakesh M. Suri, MD,^a and Hartzell V. Schaff, MD^a

Objective: The study objective was to analyze factors associated with left ventricular mass regression in patients undergoing aortic valve replacement with a newer bioprosthesis, the Trifecta valve pericardial bioprosthesis (St Jude Medical Inc, St Paul, Minn).

Methods: A total of 444 patients underwent aortic valve replacement with the Trifecta bioprosthesis from 2007 to 2009 at 6 US institutions. The clinical and echocardiographic data of 200 of these patients who had left ventricular hypertrophy and follow-up studies 1 year postoperatively were reviewed and compared to analyze factors affecting left ventricular mass regression.

Results: Mean (standard deviation) age of the 200 study patients was 73 (9) years, 66% were men, and 92% had pure or predominant aortic valve stenosis. Complete left ventricular mass regression was observed in 102 patients (51%) by 1 year postoperatively. In univariate analysis, male sex, implantation of larger valves, larger left ventricular end-diastolic volume, and beta-blocker or calcium-channel blocker treatment at dismissal were significantly associated with complete mass regression. In the multivariate model, odds ratios (95% confidence intervals) indicated that male sex (3.38 [1.39-8.26]) and beta-blocker or calcium-channel blocker treatment at dismissal (3.41 [1.40-8.34]) were associated with increased probability of complete left ventricular mass regression. Patients with higher preoperative systolic blood pressure were less likely to have complete left ventricular mass regression (0.98 [0.97-0.99]).

Conclusions: Among patients with left ventricular hypertrophy, postoperative treatment with beta-blockers or calcium-channel blockers may enhance mass regression. This highlights the need for close medical follow-up after operation. Labeled valve size was not predictive of left ventricular mass regression. (J Thorac Cardiovasc Surg 2015;149:781-6)

See related commentary on pages 787-8.

Left ventricular (LV) hypertrophy negatively influences postoperative survival after aortic valve replacement (AVR).¹ The extent of LV mass regression after AVR

appears to be dependent on both transvalvular pressure gradients^{2,3} and aortic valve (AV) area after replacement.⁴

Newer bioprostheses may have better hemodynamic profiles than older ones, which may lead to more complete LV mass regression in patients undergoing AVR. As reported by Wendt and colleagues,⁵ AVR with bovine pericardial prostheses results in relatively low transvalvular gradients and increased AV areas. The Trifecta valve pericardial bioprosthesis (St Jude Medical Inc, St Paul, Minn) was implanted in 1014 patients between 2007 and 2009 at 31 centers worldwide. The initial results were promising; for patients with 19- and 29-mm prostheses, average mean gradients at hospital dismissal were 9.3 and 4.1 mm Hg, respectively, and effective orifice area (EOA) ranged from 1.58 to 2.50 cm².⁶ In the current study, we analyzed determinants of LV mass regression in patients undergoing AVR with this new pericardial bioprosthesis.

MATERIALS AND METHODS

To fulfill regulatory requirements of clinically evaluating the Trifecta valve, patients from 6 centers with the highest enrollment (Mayo Clinic, Rochester, Minn; Hospital of the University of Pennsylvania, Philadelphia, Pa; Minneapolis Heart Institute, Minneapolis, Minn; Mission Health and Hospitals, Asheville, NC; Vanderbilt Medical Center, Nashville, Tenn; and Intermountain Medical Center, Salt Lake City, Utah) were chosen

From the Division of Cardiovascular Surgery,^a Mayo Clinic, Rochester, Minn; Division of Cardiovascular Surgery,^b Hospital of the University of Pennsylvania, Philadelphia, Pa; Minneapolis Heart Institute,^c Minneapolis, Minn; Cardiovascular and Thoracic Surgery,^d Mission Health and Hospitals, Asheville, NC; Department of Cardiac Surgery,^e Vanderbilt Medical Center, Nashville, Tenn; and Intermountain Medical Center,^f Salt Lake City, Utah.

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Address for reprints: Hartzell V. Schaff, MD, Division of Cardiovascular Surgery, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (E-mail: schaff@mayo.edu). 0022-5223/\$36.00

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Abbreviations and Acronyms

AV	= aortic valve
AVR	= aortic valve replacement
CI	= confidence interval
EOA	= effective orifice area
LV	= left ventricular
OR	= odds ratio
SD	= standard deviation

(n = 444) as a subset of patients from the 31 centers in the initial investigation device exemption study (n = 1014) for long-term follow-up. In addition to initial consent to participate in the study, all subjects signed consent for follow-up visits, clinical evaluation, and echocardiography. Institutional review board approval was obtained at each participating site. Details of bioprosthetic AV implantation and definition of adverse events have been published.⁶ Briefly, early adverse events were those that occurred before 30 days postimplantation, and late events occurred after 30 days.

For the entire group of patients, we examined clinical data to determine hemodynamic outcomes, valve gradients, and survival during a follow-up period of 5 years. We also analyzed determinants of LV mass regression. Among the 444 available patients, 405 had sufficient echocardiographic information to calculate LV mass, as follows:

$$\text{LV mass (in grams)} = (0.832 \times 1.04 [\{\text{interventricular septal thickness} + \text{LV end - diastolic dimension (in millimeters)} + \text{LV posterior wall thickness}\}^3 - (\text{LV end - diastolic dimension})^3]) / 1000 + 0.6 \text{ g.}^7$$

LV mass index (in grams/meters squared) was calculated by dividing LV mass by body surface area. LV hypertrophy was defined as an LV mass index greater than 95 g/m² for women and greater than 115 g/m² for men.⁸ Postoperative predissmissal echocardiograms and all subsequent echocardiograms were read in a central core laboratory, and we used data from the predissmissal echocardiogram for baseline data on LV hypertrophy.

Continuous variables are presented as mean (standard deviation [SD]), and categorical variables are presented as number of patients (percentage). All *P* values for comparisons between groups are based on the 2-sample *t* test, chi-square test, or Fisher exact test. No adjustments for multiple comparisons were made. We analyzed LV mass regression by 2 methods. First, we categorized patients with LV hypertrophy as having complete or incomplete regression of hypertrophy 1 year postoperatively on the basis of the cut-off values given earlier. In a second analysis, we used the absolute change in LV hypertrophy from the initial echocardiogram to the 1-year time point. For both end points, we performed univariate and multivariate analyses on clinical variables. All variables with a *P* value less than .2 in the univariate analysis were included in the multivariate analysis. In the multivariate analysis, *P* < .05 was considered significant. The Kaplan-Meier method was used to estimate survival for patients who had complete LV mass regression compared with those who did not. However, because data at 1 year were required to compose the groups, only deaths after 1 year were included. St Jude Medical Inc was involved in the collection of data and provided statistical support.

RESULTS

The mean (SD) age of all 444 patients was 73.5 (8.9) years. Demographics and preoperative findings for these patients are detailed in Table 1. Implanted AV sizes ranged from 19 to 29 mm, with 31.5% of patients (n = 140) receiving a 23-mm valve. Total duration of follow-up was 1333.5 patient-years.

Hemodynamic Performance

The mean (SD) initial AV gradient was 7.4 (3.3) mm Hg. The gradient increased slightly to 9.4 (4.6) mm Hg at 3 years and 9.8 (5.0) mm Hg at 5 years. Mean (SD) initial EOA was 1.95 (0.37) cm², compared with 1.60 (0.37) cm² at 3 years and 1.58 (0.37) cm² at 5 years postoperatively. Initial indexed EOA was 0.98 (0.18) cm²/m², compared with 0.80 (0.17) cm²/m² at 3 years and 0.80 (0.18) cm²/m² at 5 years postoperatively.

Most patients (n = 441, 99.3%) had no or trivial aortic insufficiency at dismissal. At 3 years (258 patients at risk), 66.3% of patients (n = 171) had no aortic regurgitation, 19.8% of patients (n = 51) had trivial regurgitation, and 11.2% of patients (n = 29) had mild regurgitation. At 5 years (34 patients at risk), 50% of patients (n = 17) had no regurgitation, 29.4% of patients (n = 10) had trivial regurgitation, 14.7% of patients (n = 5) had mild regurgitation, and 5.9% of patients (n = 2) had moderate regurgitation.

Adverse Events and Survival Among All Patients

Adverse events after AVR are shown in Table 2. At 3 years, cumulative freedom from embolism, endocarditis, nonstructural dysfunction, and structural valve deterioration was 95.4%, 99.1%, 99.2%, and 99.7%, respectively. The same measures at 5 years (30 patients at risk) were 94.9%, 99.1%, 99.2%, and 99.7%, respectively. Seven patients required reoperation for replacement of the prosthesis; 1 of these events occurred early and was due to partial obstruction of the left main coronary artery. The 6 late implantations were due to endocarditis (n = 2), structural valve deterioration (n = 1), and nonstructural dysfunction (n = 3). Freedom from AV reoperation 3 years postoperatively was 98.6%. At 3 years, cumulative freedom from overall mortality was 93.2%, and freedom from valve-related mortality was 99.5%. No valve thrombosis, minor paravalvular leak, or clinically significant hemolysis occurred.

Left Ventricular Mass Regression

The average initial LV mass index for all 405 patients with data available (including those who did not have LV hypertrophy) was 113.6 g/m². By 1 year postoperatively, the LV mass index had decreased to 102.6 g/m² with little further decrease during the subsequent 4 years (5-year average, 101.7 g/m²). Thus, the 1-year follow-up time point was chosen for our analysis to identify determinants of LV mass regression.

A total of 200 patients who had LV hypertrophy at the time of operation and sufficient echocardiographic data to allow determination of LV mass index 1 year postoperatively were analyzed further. These patients had a mean (SD) age of 73 (9) years, and 132 (66%) were men. Ninety-two percent (n = 184) had pure or predominant AV stenosis.

We compared the patient subsets of approximately 50% each who had complete (n = 102) and incomplete (n = 98)

TABLE 1. Demographics and preoperative findings

Variable	Value* (N = 444)
Age at implant, y	73.5 (8.9)
Men	299 (67.3)
BMI, kg/m ²	29.5 (5.2)
Body surface area, m ²	2 (0.2)
History of smoking	249 (56.1)
Diagnosis of hypertension	364 (82.0)
History of diabetes mellitus	109 (24.5)
Atrial fibrillation/flutter	39 (8.8)
History of CHF	154 (34.7)
History of PVD	53 (11.9)
History of CVD	24 (5.4)
NYHA class	
I	26 (5.9)
II	190 (42.8)
III	209 (47.1)
IV	19 (4.3)
Previous cardiovascular surgery/procedure	128 (28.8)
Previous AVR	4 (0.9)
Previous CABG	27 (6.1)
History of coronary artery disease	274 (61.7)
Aortic crossclamp time, min	84.4 (37.1)
For isolated AVR	64.4 (27.8)
Cardiopulmonary bypass time, min	114.3 (51.6)
For isolated AVR	87.6 (40.2)

AVR, Aortic valve replacement; BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CVD, cardiovascular disease; NYHA, New York Heart Association; PVD, peripheral vascular disease. *Values are mean (SD) or number of patients (%).

regression of LV hypertrophy. Multiple clinical variables were analyzed as predictors of complete LV mass regression (Table 3). In this unadjusted comparison, male sex ($P < .001$), larger implanted valve sizes ($P = .01$), larger

TABLE 2. Early and late adverse events

Adverse event	Early events, no. (%) (N = 444)	Late events, no.	Linearized rate, per 100 patient-y
Thromboembolism	10 (2.3)	12	0.90
Neurologic	8 (1.8)	11	0.82
TIA	0 (0.0)	7	0.52
RIND	5 (1.1)	1	0.07
Stroke	3 (0.7)	3	0.22
Systemic	2 (0.5)	1	0.07
Major bleeding	31 (7.0)	20	1.50
Nonstructural dysfunction	0 (0.0)	3	0.22
PV leak, major	0 (0.0)	1	0.07
Endocarditis	0 (0.0)	4	0.30
Structural deterioration	0 (0.0)	1	0.07
Reoperation for valve replacement	1 (0.2)	6	0.45
All-cause mortality	6 (1.4)	26	1.95
Valve-related	1 (0.2)	1	0.07
Other cardiac	1 (0.2)	7	0.52
Other cause	4 (0.9)	18	1.35

PV, Paravalvular; RIND, reversible ischemic neurologic deficit; TIA, transient ischemic attack.

TABLE 3. Clinical features by mass regression (n = 200)

Variable	Mass regression*		P value
	Complete (n = 102)	Incomplete (n = 98)	
Men	81 (79.4)	51 (52.0)	<.001
Age, y	72.3 (9.9)	74.7 (8.8)	.07
Preoperative NYHA class III or IV	47 (46.1)	49 (50.0)	.69
Valve size category			.01
Small (19 or 21 mm)	28 (27.5)	47 (48.0)	
Medium (23 or 25 mm)	62 (60.8)	44 (44.9)	
Large (27 or 29 mm)	12 (11.8)	7 (7.1)	
Ejection fraction, %	57.9 (10.8)	58.4 (11.4)	.76
Initial mean gradient, mm Hg	7.2 (3.1)	7.9 (3.8)	.20
Initial LV mass index, g/m ²	133.0 (23.8)	134.0 (24.7)	.76
Indexed EOA, cm ² /m ²	0.98 (0.19)	0.96 (0.19)	.38
Discharge EOAi category	(n = 100)	(n = 94)	.53
<0.65	3 (3.0)	3 (3.2)	
0.65-0.85	22 (22.0)	27 (28.7)	
>0.85	75 (75.0)	64 (68.1)	
LV end-diastolic volume, mL	98.7 (33.1)	88.6 (28.8)	.02
LV end-systolic volume, mL	43.7 (24.9)	38.1 (19.9)	.08
Concomitant CABG	31 (30.4)	36 (36.7)	.34
History of hypertension	82 (80.4)	81 (82.7)	.68
Systolic blood pressure, mm Hg			
Preoperative	131.9 (18.5)	138.3 (21.4)	.02
At 1 y	133.4 (16.0)	136.3 (19.4)	.26
Taking BB or CCB			
At dismissal	92 (90.2)	78 (79.6)	.04
At 1 y	82 (80.4)	80 (81.6)	.82
Preoperative body surface area, m ²	2.0 (0.2)	1.9 (0.2)	.001

BB, Beta-blocker; CABG, coronary artery bypass grafting; CCB, calcium-channel blocker; EOA, effective orifice area; EOAi, indexed effective orifice area; LV, left ventricular; NYHA, New York Heart Association. *Values are mean (SD) or number of patients (%).

LV end-diastolic volume ($P = .02$), lower preoperative systolic blood pressure ($P = .02$), treatment with beta-blockers or calcium-channel blockers at dismissal

TABLE 4. Multivariate analysis

Variable	Odds ratio (95% CI)	P value
Men	3.38 (1.39-8.26)	.007
Age, y*	0.98 (0.94-1.01)	.21
Valve size		.96
Small vs large	0.83 (0.20-3.39)	
Medium vs large	0.84 (0.26-2.72)	
Discharge LV end-diastolic volume, mL*	1.00 (0.97-1.02)	.71
Discharge LV end-systolic volume, mL*	1.00 (0.97-1.03)	.85
Higher preoperative systolic blood pressure*	0.98 (0.97-0.99)	.04
Preoperative BSA, m ² *	2.18 (0.35-13.61)	.40
Taking CCB at 1 y	1.35 (0.64-2.83)	.43
Taking BB or CCB at discharge	3.41 (1.40-8.34)	.007

BB, Beta-blocker; BSA, body surface area; CCB, calcium-channel blocker; CI, confidence interval; LV, left ventricular. *Calculated as a continuous variable.

FIGURE 1. Kaplan–Meier survival curves. Probability of survival for patients who had complete ($n = 102$) and incomplete ($n = 98$) regression of LV hypertrophy after AVR. At 5 years, probability of survival was 94.5% for patients with complete regression and 83.5% for patients with incomplete regression ($P = .67$). AVR, Aortic valve replacement.

($P = .04$), and higher preoperative body surface area ($P = .001$) were all associated with complete mass regression.

In the multivariate analysis (Table 4), male sex (odds ratio [OR], 3.38; 95% confidence interval [CI], 1.39–8.26) and treatment with beta-blockers or calcium-channel blockers at dismissal (OR, 3.41; 95% CI, 1.40–8.34) were independently associated with increased probability of complete LV mass regression. Patients with higher preoperative systolic blood pressure were less likely to have complete LV mass regression (OR, 0.98; 95% CI, 0.97–0.99). Valve size was not predictive of complete LV mass regression in the multivariate model (OR, 0.83; 95% CI, 0.20–3.39).

In a second analysis, LV mass regression was expressed as change in LV mass from baseline. On univariate analysis, male sex, younger age, larger initial LV mass index, lower initial ejection fraction, larger initial LV end-diastolic and end-systolic volumes, higher preoperative systolic blood pressure, and smaller preoperative body surface area were associated with greater LV mass regression ($P < .05$) (data not shown). When these and other variables with a P value less than .2 were included in a multivariate analysis, independent determinants of LV mass regression were larger initial LV mass index (parameter estimate, -0.75 ; 95% CI, -0.88 to 0.61) and higher preoperative systolic blood pressure (parameter estimate, 0.23 ; 95% CI, 0.07 – 0.40). Thus, the final model suggests that a higher initial LV mass index results in a greater decrease in LV mass and that higher preoperative systolic blood pressure is associated with less LV mass reduction.

We analyzed blood pressure at follow-up intervals and found no difference in mean systolic pressure in patients who had complete versus incomplete LV mass regression.

Mean (SD) values for the 2 groups, respectively, were 133 (16) versus 136 (19) mm Hg at 1 year ($P = .26$), 132 (16) versus 133 (16) mm Hg at 3 years ($P = .73$), and 136 (20) versus 128 (20) mm Hg at 5 years ($P = .30$). Also, there was no difference in symptomatic status, as reflected by New York Heart Association class, between patients with complete regression and patients with incomplete regression. The percentage of patients with class III or IV status for the 2 groups, respectively, was 0% versus 1.1% at 1 year ($P = .49$), 0% versus 0% at 3 years, and 6.3% versus 0% at 5 years ($P > .99$). Survival at 5 years was similar among patients with complete or incomplete LV mass regression ($P = .67$) (Figure 1).

DISCUSSION

An important finding in this study was the benefit of treatment with beta-blockers and calcium-channel blockers in LV mass regression after AVR. Patients who at dismissal were taking 1 or both of these medications were more likely to have complete LV mass regression compared with untreated patients. To our knowledge, this effect of medical treatment on regression of LV hypertrophy after AVR has not been reported. Tomoeda and colleagues⁹ found that prevention of postoperative hypertension in select patients without LV dilatation and indexed EOA greater than $0.77 \text{ cm}^2/\text{m}^2$ could prevent postoperative LV hypertrophy. However, we believe that the effect of beta-blockers extends beyond treatment of hypertension. Beta-blockade has been used in patients with heart failure for approximately 2 decades to prevent maladaptive remodeling of the LV and to promote regression of LV hypertrophy. Indeed, beta-blockers have been shown to improve LV function in patients with systolic heart failure.¹⁰ The mechanism may be related to improved cardiac calcium release channel function.¹¹

Calcium-channel blocker use should theoretically decrease afterload and help with diastolic function.¹² However, as studies in heart failure have shown,^{13,14} other risks may be associated with calcium-channel blockers that should be analyzed before prescribing them for LV hypertrophy associated with aortic stenosis.

Another important finding in our series was that most of the regression of LV mass occurred during the first postoperative year. This is similar to the findings of Tomoeda and colleagues,⁹ who studied 48 consecutive patients undergoing AVR for aortic stenosis in whom the average LV mass index was 250 g/m². In their patients, LV mass was decreased to a plateau of 150 g/m² by 1 year postoperatively. Therefore, it seems likely that LV hypertrophy after 1 year in patients with normally functioning AV prostheses is due to other cardiovascular diseases, such as systemic arterial hypertension.

We analyzed LV mass regression by 2 different methods, using LV mass as a dichotomous or continuous variable. Expressing LV mass regression as a dichotomous variable, complete or incomplete, may be more relevant clinically than using the change in LV mass. For example, in a patient with a greatly hypertrophied LV, mass may regress substantially, resulting in a sizeable absolute reduction in LV mass, but hypertrophy could still remain and the patient may have residual symptoms due to diastolic dysfunction. In our multivariate analysis using LV mass regression as a dichotomous variable, the factors contributing most to complete regression of LV mass were male sex, lower preoperative systolic blood pressure, and treatment with beta-blockers or calcium-channel blockers at dismissal. Prosthesis–patient mismatch and preoperative LV hypertrophy were not factors contributing to complete LV mass regression.

In our study, men were more likely than women to achieve complete LV mass regression. This finding was similar to results reported by Del Rizzo and colleagues.¹⁵ In contrast, Hanayama and colleagues¹⁶ and Beach and colleagues¹⁷ suggested that LV mass regression after AVR for AV disease is more complete in women than in men. In our series, definition of LV hypertrophy was stratified by sex,⁷ which may explain some differences between our findings and those in previous reports.

In contrast to previous publications,^{16,17} the current study found that lower preoperative systolic blood pressure was associated with complete LV mass regression. Some of the discrepancy in the findings may arise from definitions of hypertension. In univariate analysis, we examined the relationship between complete mass regression and multiple definitions of hypertension, including diagnosis of hypertension preoperatively, treatment of hypertension at dismissal, diagnosis of hypertension at 1 year postoperatively, and systolic blood pressure preoperatively and at 1 year. Among these variables, only preoperative systolic blood pressure as a continuous variable was found

to be associated significantly with complete mass regression. The variables used in other studies¹⁷ were based on patient-reported diagnosis, which potentially introduces error in interpretation and medical recording. Quantitative variables are more likely to be reliable than diagnostic labels.

Our patient cohort is representative of elderly patients who have senescent AV stenosis, and these patients typically have less LV hypertrophy than younger patients with congenitally bicuspid or unicuspid AV disease. In this study, only 55% of patients had LV hypertrophy at the time of AVR, and this prevalence of LV hypertrophy in patients undergoing AVR for aortic stenosis is somewhat higher than other investigators have described. Hanayama and colleagues¹⁶ reported that only 25% of patients with aortic stenosis had LV hypertrophy at the time of operation. However, these authors did not use a sex-based definition of LV hypertrophy and thus may have underestimated the frequency of hypertrophy in women.

LV hypertrophy at the time of AVR confers a poor prognosis postoperatively. In the experience of Mihaljevic and colleagues,¹⁸ survival at 10 years after AVR in patients with LV hypertrophy was 50%, compared with 70% for patients without LV hypertrophy ($P = .03$). Therefore, it is reasonable to hypothesize that complete regression of LV hypertrophy after AVR might improve late survival, but this has not been demonstrated conclusively. Gaudino and colleagues¹⁹ found that the extent of LV mass regression did not affect postoperative survival after AVR. Our study also shows no survival benefit among patients who achieved complete LV mass regression compared with those who had incomplete LV mass regression. However, it is clear that regression of LV mass is closely associated with increased LV contractility postoperatively,²⁰ which would be expected to improve late outcomes.¹⁹

In our study, prosthesis–patient mismatch and extent of preoperative LV hypertrophy were not found to be predictors of LV mass regression as a dichotomous variable. Poor hemodynamic function of the AV prosthesis might be expected to affect LV mass regression after AVR, but studies of this are conflicting.^{15-17,21,22} The differing results may be related, in part, to the outcome used, for example, absolute LV mass, change in LV mass, or regression of hypertrophy to normal LV mass. In our patients, complete LV mass regression (dichotomous variable) was not related to prosthesis–patient mismatch. The influence of residual obstruction to flow through the prosthesis is mitigated in this study of the Trifecta valve because few patients had severe prosthesis–patient mismatch, and the valve has good hemodynamic performance. Indeed, informal comparison suggests that transvalvular gradients are lower and orifice areas are greater with the Trifecta prosthesis versus other stented bioprostheses and newer valve models designed for rapid deployment.^{6,23-25}

Severity of preoperative LV hypertrophy has been reported to be an important determinant of postoperative LV

mass regression in multiple studies.^{16,17,22} These prior investigations differed from ours, however, by expressing LV mass regression as a continuous variable or using non-sex-based definitions of LV hypertrophy. In our patients, preoperative LV mass was positively correlated with absolute reduction in LV hypertrophy but not with complete LV mass regression.

Study Limitations

This is a multi-institutional study of patients undergoing AVR with the Trifecta prosthesis, and this analysis has several limitations. First, baseline echocardiograms were studies performed at hospital dismissal early after surgery. Evidence suggests that there may be a small degree of LV mass regression in the few days early after surgery before the postoperative study.²⁶ Thus, our baseline measurements may slightly underestimate the overall degree of LV hypertrophy. Second, we did not have detailed information on dosage, duration of treatment, and compliance with beta-blockers and calcium-channel blockers prescribed at dismissal. Third, because this is a newer prosthesis, patient follow-up data are limited at the longer time points, as indicated by the numbers of patients at risk.

CONCLUSIONS

In this study of patients with LV hypertrophy undergoing AVR with the Trifecta bioprosthesis, most LV mass regression occurred within the first year after operation. Several variables were independently associated with complete mass regression, including male sex, lower preoperative systolic blood pressure, and postoperative treatment with beta-blockers and calcium-channel blockers. This highlights the importance of continued careful medical follow-up of patients undergoing AVR for aortic stenosis.

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