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Long-Term Outcomes in Patients With Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction

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ABSTRACT

BACKGROUND Chronic severe aortic regurgitation (AR) imposes significant volume and pressure overload on the left ventricle (LV), but such patients typically remain in an asymptomatic state for a very long time.

OBJECTIVES This study sought to examine long-term outcomes in a contemporary group of patients with grade III+ chronic AR and preserved left ventricular ejection fraction (LVEF) and the value of aortic valve (AV) surgery on long-term survival. We also wanted to reassess the threshold of LV dimension, beyond which mortality significantly increases.

METHODS The authors studied 1,417 such patients (mean 54 ± 16 years of age, 75% men) seen between 2002 and 2010. Clinical data were obtained and Society of Thoracic Surgeons (STS) score was calculated. The primary endpoint was mortality.

RESULTS Mean STS score was 5.5% ± 8%, and mean LVEF was 57 ± 4%, whereas 1,228 patients (87%) were asymptomatic, and 93 patients (7%) had indexed LV end-systolic dimension (iLVESD) $\geq$2.5 cm/m^2. At 6.6 ± 3 years, 933 patients (66%) underwent AV surgery (36% isolated AV surgery, 16% concomitant coronary bypass, and 58% aortic replacement), and 262 patients (19%) died. In-hospital postoperative mortality was 2% (0.6% in isolated AV surgery). On multivariate Cox survival analysis, compared to the group of iLVESD <2.5 cm/m^2 and no AV surgery, the 2 groups of iLVESD <2.5 cm/m^2 with AV surgery and iLVESD $\geq$2.5 cm/m^2 with AV surgery were associated with improved survival (hazard ratios: 0.62 and 0.42, respectively; both $p < 0.01$). Survival of patients who underwent AV surgery was similar to that of an age- and sex-matched U.S. population with 96% of deaths occurring in those with iLVESD <2.5 cm/m^2.

CONCLUSIONS At a high-volume experienced center, patients with grade III or greater AR and preserved LVEF demonstrated significantly improved long-term survival following AV surgery. The risk of death significantly increased at a lower LV dimension threshold than previously described. (J Am Coll Cardiol 2016;68:2144–53)

Chronic severe aortic regurgitation (AR) imposes significant volume and pressure overload on the left ventricle (LV), resulting in compensatory but eventually detrimental structural changes in the myocardium (1,2). Although such patients typically remain asymptomatic for a very long time, the LV eventually fails to maintain this compensated state, with a resultant drop in left ventricular ejection fraction (LVEF) and onset of heart failure symptoms. Once either happens in such patients, survival decreases significantly without surgery (3-5). Hence, the current guidelines

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recommend aortic valve (AV) surgery in symptomatic patients or those with depressed LVEF as a class I indication (6). Nonetheless, management of asymptomatic patients with severe AR and preserved LVEF is often challenging, and the appropriate timing of AV surgery in this condition remains controversial (7,8).

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Current guidelines also recommend pre-emptive AV surgery (class II indication) in asymptomatic patients with preserved LVEF in the setting of a significantly dilated LV (6). However, these recommendations were derived mostly from small studies with relatively short-term follow-up that were conducted more than 2 decades ago at a time when surgical mortality and morbidity rates were higher than those seen today, in part because myocardial protection of large ventricles was often difficult (9–12). With significant improvements in diagnostic techniques, emergence of advanced surgical techniques (minimally invasive AV surgery, AV repair, improved intraoperative myocardial protection, and postoperative care), surgical morbidity and mortality have fallen considerably. Thus, we need to reassess thresholds for intervention in such patients (13–16). The natural history for many patients may not be as benign as reported in older studies in which patients were meticulously followed (9–12). Many patients with AR who are being followed clinically may not return for follow-up as frequently as desirable. Thus, a recent report suggested an annual mortality rate of 2.2% per year in this population in contrast to the mortality rate of ~0.2% annually reported in earlier studies (9–12,17). The aim of our study, therefore, was to examine long-term outcomes in a contemporary group of patients with grade III or greater AR and preserved LVEF; to evaluate whether AV surgery positively influences long-term survival in these patients; and to reassess the threshold of LV dimension, beyond which risk of long-term mortality significantly increases.

METHODS

From an original database of 4,176 patients, this observational cohort study evaluated 1,417 patients (asymptomatic or with mild symptoms) with grade III or greater chronic AR and preserved LVEF (≥50%) who were seen and evaluated at our tertiary care center between January 2003 and December 2010. To be included, patients had to have a comprehensive echocardiogram and, within 30 days, a thorough cardiology evaluation (>90% had both on the same day). We excluded patients whose LVEF was <50% (n = 929) and those who had acute AR (dissection or endocarditis; n = 52); any degree of aortic or mitral stenosis (n = 786); moderate or greater mitral regurgitation (n = 677); history of concomitant hypertrophic obstructive cardiomyopathy (n = 3); any congenital heart disease (except for presence of a dysmorphic aortic valve; n = 6); previous AV surgery (n = 306); and documented advanced noncardiac comorbidity (malignancy, neurological disease, or end-stage liver disease) at the time of initial visit (n = 11). At the time of initial clinical evaluation, there were no patients with an advanced noncardiac comorbidity that would preclude potential AV surgery.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AV = aortic valve

iLVESD = indexed left ventricular end-systolic dimension

LVEDD = left ventricular end-diastolic dimension

LVEF = left ventricular ejection fraction

NRI = net reclassification improvement

RVSP = right ventricular systolic function

Baseline characteristics were prospectively recorded in electronic medical records at the time of initial medical encounter and manually extracted for the current study. We recorded type of AV surgery (repair vs. replacement, type of valve prosthesis) along with concomitant procedure (coronary artery bypass graft [CABG] surgery, maze, pulmonary vein isolation, left atrial appendage ligation/excision). Additionally, concomitant aortic surgery (including the valve-sparing David and Bentall procedures and supracoronary ascending aortic grafting) was recorded. The decision to operate was made by consensus between cardiologists and cardiothoracic surgeons after a thorough discussion of risks and benefits with patients. Society of Thoracic Surgeons (STS) score was calculated in all patients.

ECHOCARDIOGRAPHY DATA. All patients underwent comprehensive baseline echocardiograms, using commercial instruments. LVEF, indexed LV dimensions, and left atrial area were measured at rest according to guidelines (18). Severity of AR was ascertained using previously described techniques (19), including measuring jet width in LV outflow tract with color Doppler, jet deceleration rate with continuous wave Doppler, presence of diastolic flow reversal in the descending aorta, vena contracta width, jet width/LV outflow tract width percent, and regurgitant volume and fraction. Morphology of AV (trileaflet vs. other) and cause of AR were also recorded. Right ventricular systolic function was measured qualitatively (normal, mild, moderate, or severe). Right ventricular systolic pressure (RVSP) was measured at rest according to guidelines (20).

OUTCOMES. The date of the patient's baseline echocardiogram at our institution was defined as the beginning of the observational period. Patients were followed by chart review with date of last follow-up

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TABLE 1 Baseline Characteristics

Age, yrs	54 ± 16
Number of males (%)	1,061 (75)
Race	
White	1,206 (85)
African-American	111 (8)
Asian	23 (2)
Hispanic	23 (2)
Other	55 (3)
Body mass index, kg/m^2	28 ± 6
Hypertension	801 (57)
Diabetes mellitus	100 (7)
Obstructive coronary artery disease	205 (15)
Atrial fibrillation	
Paroxysmal	108 (8)
Permanent	37 (3)
Hyperlipidemia	518 (3)
Smoker	435 (31)
Stroke	72 (5)
Peripheral arterial disease	25 (2)
Chronic renal failure	24 (2)
Symptom status	
Asymptomatic/atypical symptoms	1,228 (87)
Symptomatic	189 (13)
Connective tissue disorder	57 (4)
Aortic dissection	34 (2)
Prior cardiac surgery (not related to aortic valve)	88 (6)
Society of Thoracic Surgeons % score	5.5 ± 8
Aspirin	547 (39)
ACE inhibitors	669 (47)
Beta-blockers	628 (44)
Hydralazine	105 (7)
Statins	527 (37)
Oral anticoagulants	99 (7)
Serum hemoglobin, mg/dl	12.3 ± 2.6
Serum creatinine, mg/ml	1.2 ± 0.9
Low-density lipoprotein cholesterol, mg/dl	103 ± 37
High-density lipoprotein cholesterol, mg/dl	51 ± 16
Triglycerides, mg/dl	130 ± 90

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme.

or death recorded. Mortality data were obtained from medical records or state and nationally available databases (last queried December 2015). Primary outcome was all-cause mortality. During long-term follow-up, we also recorded whether patients developed a documented noncardiac comorbidity that resulted in death. In the surgical subgroup, we further recorded perioperative outcomes, including hospital length of stay, in-hospital (or within 30 days) stroke, atrial fibrillation, and readmission.

STATISTICAL ANALYSIS. Continuous variables are mean ± SD or median and interquartile ranges for skewed distributions and were compared using Student *t* test or analysis of variance (for normally distributed variables) or Mann-Whitney *U* test (for non-normally distributed variables). Categorical data are expressed as percentages and were compared using chi-square or Fisher exact test, as appropriate. To assess outcomes, Cox proportional hazards analysis was performed. We created a parsimonious model in which pre-specified relevant variables associated with adverse outcomes in AR patients were included. As we have previously demonstrated, even though STS score has only been validated to predict 30-day post-operative mortality, we used it in the survival analysis because it is a composite of many factors known to be associated with long-term adverse post-operative events (21). Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated and reported. Survival curves (AV surgery vs. none) for cumulative events as a function over time were obtained using the Kaplan-Meier method and compared using the log-rank statistic. Additionally, the survival of the 2 groups (AV surgery vs. none) was also compared to the survival of an age- and sex-matched U.S. population. We assessed reclassification of mortality risk using net reclassification improvement (NRI). Furthermore, discriminative abilities of various survival models were compared using c-statistic. In the subgroup of patients who did not undergo AV surgery, we further evaluated the functional relationship between indexed LV end-systolic dimension (iLVESD) and risk of death by using a parametric multiphase hazard model (22). To assess the possible nonlinear relationship between iLVESD and risk of death, covariate iLVESD was modeled as a quadratic spline with 6 knots at 5th, 23rd, 41st, 59th, 77th, and 95th percentile values of iLVESD. Statistical analysis was performed using SPSS version 11.5 (Chicago, Illinois), Stata version 10.0 (College Station, Texas), SAS version 9.4 (Cary, North Carolina) and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria) software. A p value of <0.05 was considered significant.

RESULTS

Baseline characteristics of the study sample are shown in Tables 1 and 2. By study design, all patients had preserved LVEF (≥50%) and grade III or greater AR. Also, 87% of patients were asymptomatic, whereas 13% had mild early symptoms. In the symptomatic group, the symptoms occurred <6 months prior to their clinical evaluation at our center.

SURGICAL DATA. In the current study, 933 patients (66%) underwent AV surgery at a median of 55 days (interquartile range: 19 to 435 days) from baseline echocardiogram. Indications for surgery were symptoms (n = 189), asymptomatic LV dilation

TABLE 2 Echocardiographic Variables

LV ejection fraction, %	57 ± 4
LV end-diastolic diameter	
Nonindexed, cm	5.4 ± 0.9
Indexed, cm/m^2	2.7 ± 0.6
LV end-diastolic diameter	
≥6.5 cm	154 (11)
≥7.5 cm	18 (1.3)
LV end-systolic diameter	
Nonindexed, cm	3.6 ± 0.8
Indexed, cm/m^2	1.8 ± 0.4
LV end-systolic diameter ≥5 cm	50 (3.5)
iLVSD ≥2.5 cm/m^2	93 (7)
Indexed left atrial area, cm^2/m^2	10.6 ± 3
Aortic valve morphology	
Trileaflet	877 (62)
Bicuspid	523 (37)
Unicuspid/quadricuspid	17 (1)
Cause of aortic regurgitation	
Non-trileaflet aortic valve	540 (38)
Treated infective endocarditis	145 (10)
Dilated aortic root	263 (19)
Aortic leaflet prolapse	77 (5)
Restricted leaflet motion	123 (9)
Aortic valve sclerosis without significant stenosis	166 (12)
Unknown	103 (8)
Aortic valve gradients	
Mean gradient, mm Hg	12 ± 5
Peak gradient, mm Hg	24 ± 10
Aortic valve area (continuity), cm^2	1.9 ± 0.2
Diastolic function	
Normal	604 (43)
Abnormal relaxation	699 (49)
Pseudo-normal	112 (8)
Restrictive	2 (0.1)
RV systolic pressure, mm Hg	32 ± 10
Moderate tricuspid regurgitation	102 (7)
RV systolic function	
Normal	1,398 (98.7)
Mildly reduced	11 (0.8)
Moderately reduced	8 (0.5)
Aortic root diameter, cm	4.1 ± 0.6
Aortic root ≥4.5 cm	232 (16)
Mid-ascending aortic diameter, cm	3.9 ± 0.8
Mid-ascending aorta ≥4.5 cm	241 (17)

Values are mean ± SD or n (%).

iLVESD = indexed left ventricular end-systolic dimension; LV = left ventricular; RV = right ventricular.

TABLE 3 Predictors of Long-Term Mortality*

	Hazard Ratio (95% CI)	p Value
Model A: Individual known predictors of long-term mortality		
Age (for every 10-yr increase)	1.58 (1.41–1.81)	<0.001
Chronic kidney disease	2.70 (1.69–4.27)	<0.001
Prior cardiac surgery	1.91 (1.16–3.23)	<0.001
Symptomatic versus asymptomatic	2.06 (1.76–2.49)	<0.001
RVSP (for every 10 mm Hg increase)	1.35 (1.17–1.51)	<0.001
iLVESD <2.5 cm/m^2 (reference group)		
Aortic valve surgery and iLVESD <2.5 cm/m^2	0.62 (0.44–0.89)	<0.001
Aortic valve surgery and iLVESD ≥2.5 cm/m^2	0.42 (0.29–0.68)	<0.001
Model B: With STS score as a surrogate of multiple known predictors of long-term mortality†		
STS score (for 1% increase)	1.41 (1.29–1.49)	<0.001
RVSP (for every 10 mm Hg increase)	1.35 (1.21–1.51)	<0.001
iLVESD < 2.5 cm/m^2 (reference group)		
Aortic valve surgery and iLVESD <2.5 cm/m^2	0.64 (0.40–0.88)	<0.001
Aortic valve surgery and iLVESD ≥2.5 cm/m^2	0.46 (0.28–0.72)	<0.001

*Multivariate Cox proportional hazard analysis for predictors of long-term mortality in the entire study sample (262 deaths). †In model B, individual variables that constituted part of STS score were not considered for analysis. Variables analyzed in model A: age, sex, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease, smoking, connective tissue disorder, chronic kidney disease, prior cardiac surgery, symptom status, bicuspid vs. trileaflet aortic valve, aspirin, statin, beta-blockers, ACE inhibitor, LV ejection fraction, iLVESD, RVSP, aortic valve surgery, concomitant aortic/coronary bypass surgery, and time to surgery. Variables analyzed in model B: STS score, connective tissue disorder, bicuspid vs. trileaflet aortic valve, aspirin, statin, beta-blockers, ACE inhibitor, iLVESD, RVSP, aortic valve surgery, concomitant aortic and coronary bypass surgery, and time to aortic valve surgery.

ACE = angiotensin-converting enzyme; CI = confidence interval; iLVESD = indexed LV end-systolic dimension; RVSP = right ventricular systolic pressure; STS = Society of Thoracic Surgeons; other abbreviations as in Tables 1 and 2.

(LV end-diastolic dimension [LVEDD] ≥6.5 cm, LVESD ≥5 cm, or iLVESD ≥2.5 cm/m^2; n = 153), concomitant aortic aneurysm (root or ascending; n = 446), or previously treated infective endocarditis (n = 145). There were 677 patients who underwent AV replacement (522 bioprosthetic, 111 mechanical, and 43 homografts), and 256 had AV repair. There were 334 patients who underwent minimally invasive isolated AV surgeries (107 isolated AV repair and 227 AV replacement). Concomitantly, there were 540 aortic surgeries (78 valve-sparing aortic root replacements, 56 aortoplasties, 21 composite grafts, and 385 supracoronary grafts). Additional procedures performed at the time of AV surgery were left atrial appendage ligation/excision (n = 59), maze procedure/pulmonary vein isolation (n = 48), tricuspid valve repair (n = 17), and CABG surgery (n = 152).

OUTCOMES. Total follow-up time was 9,384 patient-years with 72% of patients having at least 5 years of follow-up (82% 5-year follow-up in survivors). During a mean follow-up of 6.6 ± 3 years, 262 patients (19%) died. At long-term follow-up, 19 patients experienced noncardiac comorbidity. In the surgical group, post-operative outcomes (30 days or during post-surgical admission) included 19 deaths (2%), 11 strokes (1%), 26 patients (26%) who had cardiogenic shock (requiring vasopressors for >24 h), 44 patients (3%) who required prolonged intubation (>48 h), and 244 patients (26%) with transient post-operative atrial fibrillation. Additionally, 45 patients (3%) were readmitted within 30 days post-operatively for congestive heart failure. In the isolated AV surgery subgroup, 2 patients (0.6%) died in hospital.

For the entire study sample, we performed Cox proportional hazards survival analysis for the primary outcome of death. Neither sex (HR: 1.37; 95% CI: 0.93 to

1.96; $p = 0.09$), nor presence of bicuspid versus trileaflet aortic valve (HR: 0.92; 95% CI: 0.82 to 1.03; $p = 0.13$), nor pre-operative atrial fibrillation (HR: 1.45; 95% CI: 0.96 to 2.16; $p = 0.11$), nor concomitant aortic and CABG surgery (HR: 1.06; 95% CI: 0.92 to 1.23; $p = 0.60$) were significantly associated with the primary outcome, even on univariate analysis. However, on univariate Cox proportional hazards survival analysis, higher iLVESD (HR: 0.39; 95% CI: 0.28 to 0.54; $p < 0.001$) was paradoxically associated with lower long-term mortality, likely because all patients with iLVESD $\geq$2.5 cm/m^2 underwent AV surgery, which improved long-term survival. To further elucidate the association between iLVESD and AV surgery, we created 3 categories, patients with iLVESD <2.5 cm/m^2 with no AV surgery (reference group); those with iLVESD <2.5 cm/m^2 with AV surgery; and those with iLVESD $\geq$2.5 cm/m^2 with AV surgery. In the final multivariate analysis, older age (HR: 1.57), symptomatic versus nonsymptomatic (HR: 2.06), and chronic kidney disease (HR: 2.70), prior cardiac surgery (HR: 1.91), and RVSP (HR: 1.35) were independently associated with higher mortality (all $p < 0.01$) (**Table 3**, Model A). However, compared to the reference group, the 2 groups of iLVESD involving AV surgery were significantly associated with improved survival (both $p < 0.001$). Results were similar when STS score was substituted in the multivariate model for its constituent variables (**Table 3**, Model B).

In terms of long-term survival, patients undergoing AV surgery demonstrated significantly less mortality than those who did not have surgery (124 [13%] vs. 138 [29%], respectively; log-rank $p < 0.001$) and exhibited a survival curve similar to the age- and sex-matched U.S. population (**Central Illustration**).

Addition of iLVESD and AV surgery to the clinical model (STS score + RVSP) provided incremental prognostic value for long-term mortality. With sequential addition of iLVESD and AV surgery, the c-statistic for long-term mortality for the clinical model (STS score + RVSP) increased from 0.63 (95% CI: 0.51 to 0.76) to 0.70 (95% CI: 0.60 to 0.87) and further to 0.76 (95% CI: 0.64 to 0.89), respectively ($p < 0.001$ for both). Similarly, adding iLVESD and AV surgery to the clinical model sequentially improved reclassification for long-term mortality as follows: clinical model + ILVESD (NRI: 0.13 [95% CI: 0.04 to 0.24]; $p = 0.008$); and clinical model + iLVESD + AV surgery (NRI: 0.24 [95% CI: 0.13 to 0.33], $p < 0.001$).

For the entire study sample, most of the deaths occurred long term in patients who were below the various guideline-recommended LV dimension cutoffs for AV surgery at baseline: 258 (98%) in LVESD <5 cm, 251 (96%) in iLVESD <2.5 cm/m^2, or 252 (96%) in those with LVEDD <6.5 cm. We evaluated the association between LV dimensions and long-term mortality, separated by AV surgery status, during follow-up (**Table 4**). Even within the subgroups who did not meet the guideline-recommended LV dimension cutoffs for AV surgery, patients undergoing AV surgery had significantly better long-term survival versus those who did not.

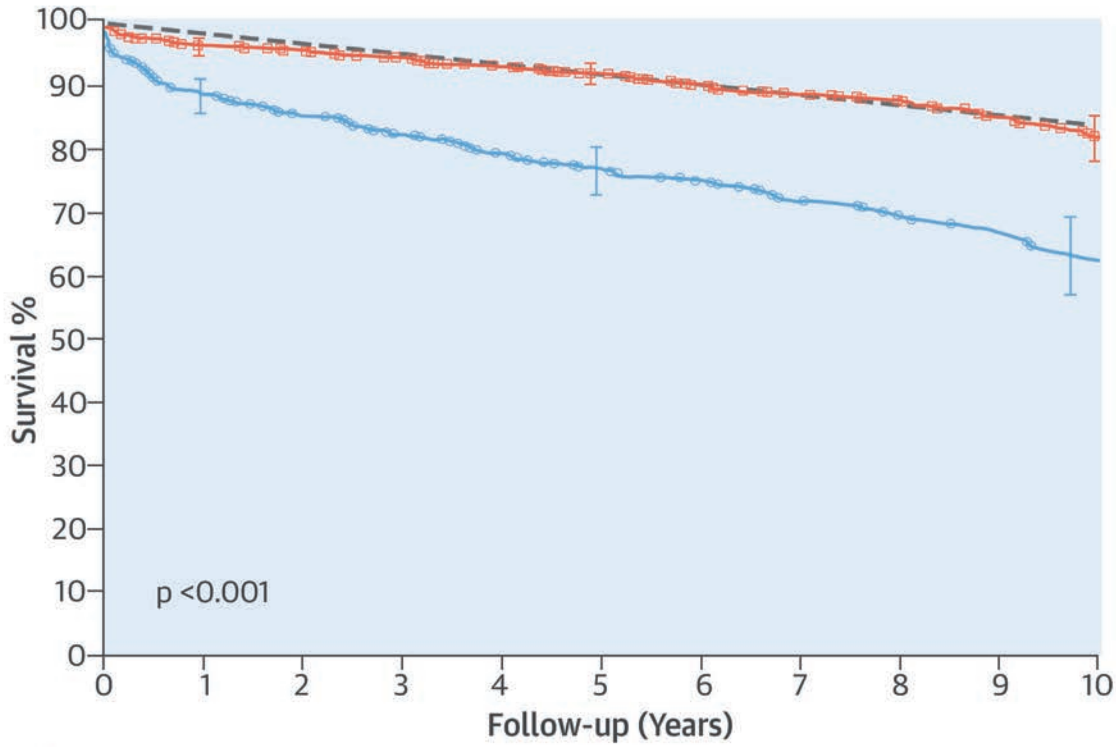
In a further subgroup analysis of asymptomatic patients with preserved iLVESD <2.5 cm/m^2 (n = 1,146; 167 deaths), the results of multivariate Cox proportional hazard survival analysis were similar. Higher STS score (HR: 1.23; 95% CI: 1.12 to 1.36) and higher RVSP (HR: 1.24; 95% CI: 1.07 to 1.62) were associated with higher mortality, whereas AV surgery (HR: 0.51; 95% CI: 0.24 to 0.80) was associated with improved survival (all $p < 0.01$). Even in this subgroup of asymptomatic patients with preserved iLVESD, increasing iLVESD was paradoxically associated with lower long-term mortality, likely due to a significant interaction between increasing iLVESD and AV surgery (HR: 0.60; 95% CI: 0.32 to 0.89; $p < 0.01$).

To further study the association of iLVESD and long-term mortality, independent of AV surgery, we excluded patients who underwent AV surgery during follow-up (n = 484; 128 deaths). On multivariate Cox proportional hazard analysis, iLVESD (HR: 2.44; 95% CI: 1.57 to 3.78), along with higher STS score (HR: 1.49; 95% CI: 1.32 to 1.68) and higher RVSP (HR: 1.12; 95% CI: 1.06 to 1.24) were significantly associated with long-term mortality (all $p < 0.01$). Without the interaction between AV surgery and iLVESD, there was an expected association between higher mortality and increasing iLVESD in this subgroup. Within this subgroup of nonoperated patients, according to the data for 5-year hazard using quadratic spline with 6 knots, patients with iLVESD $\leq$2.0 cm/m^2 had excellent 5-year survival (**Figure 1**). However, the risk of death continuously increased beyond iLVESD >2 cm/m^2 (significantly lower than the currently recommended surgical threshold $\geq$2.5 cm/m^2). Of note, in this subgroup, the decision to not operate was made by the evaluating cardiologists, and there were no patients with a documented noncardiac comorbidity at the time of initial clinical evaluation that would have precluded them from having AV surgery. The results of additional survival analyses are shown in Online Appendix 1.

DISCUSSION

In this large study of mostly asymptomatic or minimally symptomatic patients with grade III or greater chronic AR and preserved LVEF, ~65% of patients

CENTRAL ILLUSTRATION Long-Term Survival



Number at Risk

AV Surgery During Follow-up						
No	484	414	359	234	122	44
Yes	933	821	821	598	259	171

AV Surgery During Follow-up — No AV Surgery During Follow-up

Normal Age-Gender Matched U.S. Population

Mentias, A. et al. J Am Coll Cardiol. 2016;68(20):2144–53.

This study sought to determine whether aortic valve surgery would impact long-term survival in patients with chronic aortic regurgitation and preserved left ventricular ejection fraction. Not only did patients with aortic valve surgery experience significantly better long-term survival than those patients who did not undergo surgery, the rate was similar to that in a normal age- and sex-matched U.S. population **(gray dotted line)**.

underwent AV surgery with low (2%) in-hospital postoperative mortality (0.6% for isolated AV surgery). Additionally, AV surgery was associated with significantly improved long-term survival independent of other established factors. In the entire study sample, higher iLVESD was paradoxically associated with lower long-term mortality, because all patients with LVESD >2.5 cm/m^2 underwent AV surgery, which was associated with improved survival. In terms of long-term mortality, the findings were similar if STS score was substituted for its individual component predictors. Furthermore, addition of iLVESD and AV surgery to the clinical model (STS score + RVSP) provided incremental prognostic value and improved reclassification for long-term mortality. The long-term survival of the subgroup that underwent AV surgery was significantly better than those who did not undergo surgery (and very similar to an age- and sex-matched U.S. population). Also, >95% of long-term deaths occurred in patients who were below guideline-recommended LV dimension cutoffs for AV surgery. Our findings were similar in a

TABLE 4 Association Between LV Dimensions and Mortality*

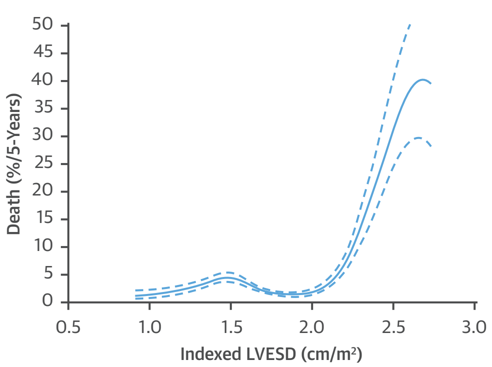
	LV End-systolic Dimension					
	3–4 cm		4–5 cm		>5 cm	
	Surgery (n = 644)	No Surgery (n = 416)	Surgery (n = 241)	No Surgery (n = 66)	Surgery (n = 50)	No Surgery (n = 0)
Dead	107 (17)	126 (30)	13 (5)	12 (18)	4 (8)	NA
	iLVESD					
	<2 cm/m²		2–2.5 cm/m²		>2.5 cm/m²	
	Surgery (n = 635)	No Surgery (n = 411)	Surgery (n = 215)	No Surgery (n = 63)	Surgery (n = 93)	No Surgery (n = 0)
Dead	97 (15)	101 (25)	19 (9)	14 (22)	11 (12)	NA
	LV End-diastolic Dimension					
	<5.5 cm		5.5–6.5 cm		>6.5 cm	
	Surgery (n = 414)	No Surgery (n = 322)	Surgery (n = 377)	No Surgery (n = 150)	Surgery (n = 154)	No Surgery (n = 0)
Dead	50 (12)	92 (29)	68 (18)	42 (28)	10 (6)	NA

Values are n (%). *Within each subgroup, aortic valve surgery was associated with improved survival.
NA = not available; Abbreviations as in Tables 1 and 2.

subgroup of asymptomatic patients with preserved iLVESD <2.5 cm/m².

We further studied the independent association of iLVESD and mortality in a subgroup that excluded patients undergoing AV surgery during follow-up. In these patients, without the interaction between AV surgery and iLVESD, there was an expected association between higher long-term mortality and increasing iLVESD. Within this subgroup, patients with iLVESD ≤2.0 cm/m² had an excellent 5-year survival; however, risk of death significantly and continuously increased beyond iLVESD >2 cm/m² (which is lower than the currently recommended surgical threshold of ≥2.5 cm/m²).

FIGURE 1 Mortality Risk



In the subgroup that did not undergo aortic valve surgery, in order to assess the possible nonlinear relationship between iLVESD and risk of death, we modeled the covariate predicted iLVESD as a quadratic spline. Based upon the visual analysis of the curves, patients with iLVESD <2 cm/m² had excellent 5-year survival. However, the risk of death significantly and continuously rose as iLVESD increased beyond 2 cm/m². **Solid line** = 5-year parametric estimates of instantaneous risk of death; **dotted lines** = 68% confidence interval. iLVESD = indexed left ventricular end-systolic dimension.

Chronic severe AR results in LV volume overload as the regurgitant AR jet increases LV diastolic filling. Subsequently, the LV undergoes progressive and eccentric hypertrophy with increase in its dimensions to counter high LV wall stress, thus initially keeping LV diastolic pressure low. Additionally, the LV is exposed to a higher afterload through increased systemic hypertension due to high stroke volume, resulting in further LV hypertrophy (1,2). Patients with severe chronic AR remain in this compensated and usually asymptomatic state for a very long time. Eventually, the LV fails to maintain this compensated state, with a resultant rise in end-diastolic pressure, fall in LVEF, and development of symptoms. It has been previously described that once symptoms develop or LVEF drops, long-term survival decreases dramatically in the absence of surgical intervention (3–5).

Based on these pathophysiological principles, the current guidelines recommend AV surgery in symptomatic patients or those with depressed LVEF as a Class I indication (6). They also recommend preemptive AV surgery in asymptomatic patients with preserved LVEF, in the setting of a dilated LV (LVEDD >6.5 cm [Class IIb indication] or LVESD >5 cm/iLVESD >2.5 cm/m² [Class IIa indication]) (6). However, these recommendations were derived mostly from small studies (32 to 104 patients) with relatively short-term follow-up, performed more than 2 decades ago (9–12). These recommendations may need to be revisited in the current era of advanced diagnostic techniques and emergence of advanced surgical techniques and improved post-operative care (13-16). Additionally, natural history of asymptomatic severe AR with preserved LVEF might not be as benign as previously reported (9-12). Detaint et al. (17) recently reported a 10-year survival of 78% (suggesting an annual mortality rate of 2.2% per year) in contrast to the annual mortality rate of ~0.2% reported in earlier studies (9-12).

Similar to our results, Park et al. (23) showed that in severe asymptomatic AR patients with normal LVEF, early surgery at a cut-off value of LVESD 4.5 cm was associated with better outcomes. However, their study sample was relatively small (n = 284) with a much shorter follow-up of up to 3 years. In another small study of 170 patients, Tornos et al. (24) showed that patients who underwent early AV surgery had significantly better survival compared to patients who underwent surgery timed according to the current guidelines (mean 90% vs. 75%, respectively, at 1 year and 86% vs. 64%, respectively, at 5-year follow-up).

Several studies have shown that subclinical LV myocardial dysfunction occurs early in the compensated stage with preserved LVEF, prior to development of overt symptoms and often before reaching the current guideline-recommended surgical thresholds (25,26). Furthermore, myocardial injury in chronic AR is thought to occur in a heterogeneous distribution, not affecting all LV segments equally (27). In asymptomatic patients with significant AR and preserved LVEF, along with considering lower thresholds of LV dimensions for surgical referral, we may need to evaluate newer, more sensitive markers of early LV systolic dysfunction. Indeed, when myocardial biopsy was performed in early stages of severe chronic AR, nonphysiological increase in interstitial fibrosis and myocardial fiber diameter were evident (28). Multiple smaller reports have evaluated the potential role of newer echocardiographic indexes like strain, tissue Doppler, and torsion in such patients (29-32). Pizarro et al. (33) demonstrated that subclinical LV dysfunction in these patients is also evident by high resting serum B-type natriuretic protein, which was associated with a composite endpoint of LV dysfunction, development of symptoms, and death. However, large-scale studies need to be conducted to evaluate the incremental prognostic utility of strain on the hard outcome of death.

To the best of our knowledge, our study is the largest to date, including more than 1,400 patients with severe chronic AR and preserved LVEF, with a relatively long follow-up, permitting us to study the hard endpoint of death. It reinforced the value of AV surgery to improve survival in these patients, lowering it to a level similar to a normal age- and sex-matched U.S. population. Also, there is a need to underscore the importance of a multidisciplinary management strategy (along with the availability of the full surgical spectrum, including AV repair and minimally invasive options) at an experienced center (15,16,34). The current study suggested that LV dimension thresholds, above which the hazard of death significantly increases, are much lower than that currently endorsed by practice guidelines (6). Hence, considering AV surgery earlier than recommended, especially in an experienced center, may be associated with improved long-term survival. Our findings are hypothesis generating and require prospective validation.

STUDY LIMITATIONS. This was a retrospective observational study from a tertiary referral center with its inherent selection biases, including potential underreporting of post-operative arrhythmia. Our primary aim was not to test the natural history of AR from its initial diagnosis to time of surgery. Our institution is experienced and performs a high volume of AV surgeries with a low rate of adverse events. As a result, our data may not be generalized across all other centers (15,16,34). Additionally, in the group without surgery, it was difficult to ascertain the actual LV size or LVEF at the time of death. Within this subgroup, early surgery (in those with potential for loss of follow-up) or regular follow-up at an experienced center might be warranted. For the current study, advanced quantitative echocardiographic parameters like indexed LV volumes were not uniformly available (especially during the earlier part of the study) and hence, not reported. Indeed, Detaint et al. (17) showed that quantitative grading of AR and LV end-systolic volume index were much better factors to predict mortality than the conventional AR grading and LV diameters currently used. Our retrospective study demonstrated only associations and not causality. We report all-cause, not cardiac, mortality as the primary endpoint. However, on secondary outcomes analysis, where documented noncardiac deaths were excluded, the basic results were similar. Furthermore, it has been demonstrated previously that all-cause mortality is less biased than cardiac mortality (35).

CONCLUSIONS

At a high-volume, experienced center, asymptomatic or minimally symptomatic patients with grade III or greater AR and preserved LVEF demonstrated significantly improved long-term survival following AV surgery, similar to that of the normal age- and sex-matched U.S. population. Addition of iLVESD and AV surgery provided incremental prognostic value and improved reclassification for long-term mortality. Nonsurgical patients with iLVESD ≤2.0 cm/m² had an excellent 5-year survival; however, the risk of death significantly and continuously increased beyond iLVESD >2 cm/m² (a value much lower than the currently recommended surgical threshold of ≥2.5 cm/m²). These findings need prospective validation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Asymptomatic or minimally symptomatic patients with chronic, severe aortic regurgitation and preserved LVEF undergoing initial aortic valve replacement at a high-volume surgical center exhibited long-term survival similar to that of age- and sex-matched individuals without valvular heart disease. The risk of death increased when the indexed left ventricular end-systolic diameter exceeded 2 cm/m², a threshold lower than the currently recommended value of ≥2.5 cm/m².

TRANSLATIONAL OUTLOOK: Replication of this experience in other settings might warrant revision of current recommendations for the timing of surgical intervention based on LV dimensions in asymptomatic patients with chronic aortic regurgitation and preserved ejection fraction.

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KEY WORDS aortic valve surgery, indexed left ventricular end-systolic dimension, mortality, outcomes

APPENDIX For an expanded results section, please see the online version of this article.