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ORIGINAL INVESTIGATIONS

Outcomes in Chronic Hemodynamically Significant Aortic Regurgitation and Limitations of Current Guidelines

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ABSTRACT

BACKGROUND Few data exist on the contemporary profiles and outcomes of patients with significant aortic regurgitation (AR).

OBJECTIVES This study sought to assess the benefits of aortic valve repair or replacement (AVR) and the prognostic value of left ventricular (LV) dimensions in significant AR.

METHODS From 2006 to 2017, consecutive patients with ≥moderate-severe chronic AR without prior heart surgery, myocardial infarction, or overt coronary artery disease were included.

RESULTS Of 748 participants (58 ± 17 years of age; 82% men), 387 (52%) were medically treated, and 361 (48%) had AVR. Of 361 patients having AVR, 334 (93%) met guideline criteria: Class I indications in 284 (79%) patients, which included symptoms in 236, and Class II indications in 50 (14%). The remaining 27 (7%) opted for surgery without Class I or II indications. At a median follow-up of 4.9 years (interquartile range: 2.3 to 8.3 years), 125 (17%) patients had died. Age, comorbidities, baseline symptoms, and higher LV end-systolic dimension index (LVESDi) were associated with all-cause mortality (all $p \leq 0.01$). Compared with patients having LVESDi <20 mm/m^2, those with LVESDi 20 to 25 mm/m^2 (hazard ratio: 1.53; 95% confidence interval: 1.01 to 2.31) and ≥25 mm/m^2 (HR: 2.23; 95% confidence interval: 1.32 to 3.77) had increased risks of death. AVR was associated with better survival ($p < 0.0001$). Patients with Class I indications for surgery had inferior post-operative survival ($p < 0.003$).

CONCLUSIONS Class I indications for surgery, mainly symptoms, are the most common triggers for AVR. Class II indications were associated with better post-operative outcome and thus merit more attention. LVESDi was the only LV parameter independently associated with all-cause mortality and the ideal cutoff seems to be lower than previously recommended. (J Am Coll Cardiol 2019;73:1741–52) © 2019 by the American College of Cardiology Foundation.

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Compared with the 2006 guidelines, the 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on valvular heart disease (VHD) recommended a reduction in the left ventricular (LV) dimensions for surgical intervention for severe aortic regurgitation (AR) (1,2). However, most of the studies that laid the foundation of guideline recommendations were published more than a decade ago and included patients managed more than 20 years ago. Furthermore, many

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ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

AR = aortic regurgitation

AVR = aortic valve repair or replacement

CABG = coronary artery bypass grafting

CAD = coronary artery disease

EROA = effective regurgitant orifice area

HR = hazard ratio

IQR = interquartile range

LV = left ventricular

LVEDD = left ventricular end-diastolic dimension

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic dimension

LVESDi = left ventricular end-systolic dimension index

NYHA = New York Heart Association

OR = odds ratio

TTE = transthoracic echocardiogram

VHD = valvular heart disease

prior investigations in AR only included patients with aortic valve repair or replacement (AVR) (3-6). However, AVR eliminates excess risk of death and improves LV function (1,2,7). Therefore, to understand the influence of baseline LV function on outcome in the natural history of AR, it is crucial to include nonsurgical populations. Prior studies also included patients with overt coronary artery disease (CAD) and previous coronary artery bypass grafting (CABG) (3-5). It is thus unclear to what extent myocardial ischemia contributed to chamber enlargement and mortality among patients with AR (3-5,8). Additionally, parameters of comprehensive AR quantification and diastolic function were not yet standardized and were not included in earlier analyses. Over time, quantitative diagnostic tools and surgical techniques have advanced, experience in aortic valve repair has expanded, the etiologies of AR have changed (9), and the threshold for surgical referrals has decreased (10). Moreover, new therapies continue to evolve (11).

Accordingly, in this study of patients with pure chronic AR of at least moderately severe grade, we sought to determine the following: 1) indications for surgery according to 2014 AHA/ACC VHD guidelines; 2) determinants of survival, including the impact of AVR; and 3) echocardiographic correlates of symptomatic status.

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METHODS

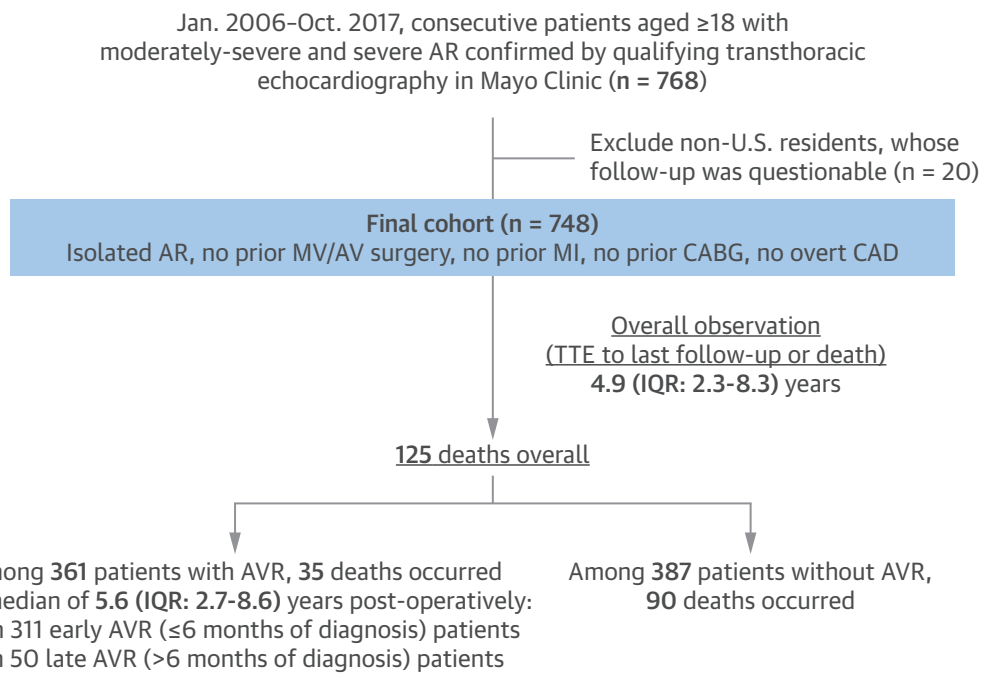
STUDY POPULATION. Between January 2006 and October 2017, we identified all consecutive patients with moderate-severe and severe AR evaluated by comprehensive transthoracic echocardiogram (TTE) and excluded those with acute aortic dissection, active endocarditis, aortic or mitral stenosis and mitral regurgitation of more than mild degree, previous aortic or mitral valve surgery, hypertrophic cardiomyopathy, terminal malignancies, and carcinoid heart disease. To eliminate possible effects of ischemic cardiomyopathy on LV chamber enlargement and mortality, we used International Classification of Diseases codes and chart review to identify and exclude patients with prior myocardial infarction, prior CABG, and overt coronary artery disease (left main stenosis >50%, 2- or 3-vessel CAD requiring intervention) (**Figure 1**). All included patients had a thorough cardiology or cardiovascular surgery evaluation within 30 days of first qualifying TTE, and in patients with more than 1 qualifying TTE, the first study was used for analysis. Shared decision for AVR was made between the treating physician and the patient based on consideration of the risks and benefits and guideline recommendations (2). We extracted the medical history and baseline characteristics of each patient from electronic medical records (chart review and International Classification of Diseases-9th Revision and -10th Revision code extraction), which were prospectively recorded during cardiovascular consultation for AR. Charlson comorbidity index was calculated (12). This study was approved by the Institutional Review Board.

ECHOCARDIOGRAPHY. TTE with chamber quantification was performed according to recommendations from the American Society of Echocardiography (13). An integrated approach for diagnosis of AR severity used a combination of quantitative and semi-quantitative measurements, including proximal isovelocity surface area-derived regurgitant volume, vena contracta width, and time-velocity integral of the reversed flow in the descending aorta (14). All echocardiograms were interpreted by experienced cardiologists with level III training. Assessment of diastolic function was based on guideline recommendations (15). Advanced diastolic dysfunction was defined as pseudonormalization of mitral inflow pattern or restrictive LV filling. Measurements were from the average of ≤3 and 5 beats in patients with sinus rhythm and atrial fibrillation, respectively.

SYMPTOMS AND THE USE OF 2014 AHA/ACC SURGICAL INDICATIONS. Symptomatic patients were those who had symptoms recorded in the electronic health record by treating cardiologists or cardiovascular surgeons during consultation. The 2014 AHA/ACC VHD guidelines were used for the definitions of surgical indications, including: 1) symptoms (Class I indication); 2) LV ejection fraction (LVEF) <50% (Class I); 3) surgery for aortic dilatation or aneurysms (other cardiac surgery; Class I); 4) LV end-systolic dimension index (LVESDi) >25 mm/m^2 (Class IIa); 5) LVESD >50 mm (Class IIa); and 6) LV end-diastolic dimension (LVEDD) >65 mm (Class IIb) (2).

OUTCOMES. The endpoint was all-cause mortality. This rather than cardiac mortality was selected as the most robust endpoint because of the limitations of death certificates in accurately defining and recording cause of death (16). The survival status in all participants was retrieved using Accurint (LexisNexis, RELX Group, New York, New York), a proprietary resource

FIGURE 1 Study Flow Chart



AR = aortic regurgitation; AV = aortic valve; AVR = aortic valve repair or replacement; CABG = coronary artery bypass grafting; CAD = coronary artery disease; IQR = interquartile range; MI = myocardial infarction; MV = mitral valve; TTE = transthoracic echocardiography.

combining multiple national sources (queried May 2018). The observation was between the date of the qualifying TTE and death, or last follow-up.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD according to data distribution, and were compared using the Student's *t*-test or Wilcoxon rank sum test whenever appropriate. Categorical data were presented as percentages and were compared using chi-square or Fisher exact test. Generalized linear and logistic regression models, both binary and ordinal, were used for continuous and categorical variables, respectively, when adjustment for covariates was needed. Linear regression analysis was used to study the relationships between age and LV chamber dimensions. Cox proportional hazards modeling was used to identify determinants of outcomes. Results were summarized by hazard ratio (HR) and 95% confidence interval. Parameters were chosen for multivariable analysis when p was <0.05 in the univariable analysis. AVR was analyzed as a time-dependent covariate in the proportional hazards model. To test for evidence of differential effects of AVR by LVESDi, an interaction was tested within the adjusted proportional hazards regression analysis. A landmark analysis (17) was used to illustrate the time-dependent effect of AVR on survival. After 6 months, surviving subjects were further divided into 2 groups—those with and without AVR within 6 months. Subsequently, the results were plotted according to LVESDi subgroups with adjustment for age, sex, symptoms, and Charlson index. Model-based survival estimates were also plotted by group to illustrate the AVR effect at mean covariate levels. The risk of mortality by LVESDi was illustrated graphically after fitting LVESDi using a spline function. The number of knots was chosen based on chi-square test. Adjusted survival curves were plotted using a method of direct adjustment. All statistical analyses were performed using commercially available software (JMP 11 and SAS 9.4, SAS Institute, Cary, North Carolina). A p value <0.05 was considered to be statistically significant.

RESULTS

The cohort included 748 patients (58 ± 17 years of age; 137 [18%] women) (Figure 1). AVR was performed in 361 (48%) patients: early (within 6 months) in 311

TABLE 1 Baseline Characteristics and Echocardiographic Parameters in All Patients (N = 748)

Age, yrs*	58 ± 17
Women	137 (18)
Systolic blood pressure, mm Hg	130 ± 20
Diastolic blood pressure, mm Hg	64 ± 13
Race/ethnicity	
White	664 (89)
African-American	12 (2)
Asian	11 (1)
Other	61 (8)
Body mass index, kg/m^2	28 ± 5
Body surface area, m^2†	2.01 ± 0.24
Baseline symptoms	339 (46)
NYHA functional class*	
I	431 (58)
II	203 (27)
III + IV	87 (12)
Indeterminate	27 (3)
Medical history	
Hypertension	361 (48)
Diabetes mellitus	31 (4)
Hyperlipidemia	258 (34)
Chronic kidney disease stage >3b	46 (6)
Stroke/transient ischemic attack	49 (7)
Endocarditis	44 (6)
Connective tissue disease	29 (4)
Atrial fibrillation at time of transthoracic echocardiogram	30 (4)
Current/ever smoker	321 (43)
Charlson comorbidity index	1.6 ± 2.1
Lab	
Hemoglobin, g/dl	13.6 ± 1.6
Ln NT-proBNP (n = 244), Ln(pg/ml)	5.6 ± 1.7
Total cholesterol (n = 532), mg/dl	174 ± 37
Low-density lipid protein (n = 533), mg/dl	97 ± 30
High-density lipoprotein (n = 534), mg/dl	54 ± 17
Aortic valve morphology	
Tricuspid	436 (58)
Bicuspid	290 (39)
Unicuspid/quadricuspid	11 (1.5)
Indeterminate	11 (1.5)
Echo parameters	
LVEF, %	59 ± 8
LVEF <50%	72 (10)
LVESD	
Nonindexed, mm‡	40 ± 7
>50 mm	49 (7)
>55 mm	16 (2)
LVESDi, mm/m^2‡	20 ± 4
LVESDi >25 mm/m^2*	74 (10)
LVEDD	
Nonindexed, mm‡	60 ± 7
>65 mm	151 (20)
>75 mm	15 (2)
Indexed, mm/m^2	30 ± 4
AR quantification	
Severity (using integrated approach)	
Moderate-severe	277 (37)
Severe	471 (63)
Regurgitant volume (n = 621), ml	71 ± 26
EROA (n = 584), mm^2	30 ± 12
Vena contracta (n = 652), mm	6.0 ± 1.5
Descending aorta reversal TVI (n = 652), cm/s	15 ± 5
Diastology	
Advanced diastolic dysfunction	187 (25)
Pseudonormalization	165 (22)
Restrictive LV filling pattern	22 (3)
Left atrial volume index (n = 718), ml/m^2	39 ± 14
E velocity (n = 700), m/s	0.7 ± 0.3
Septal e′ (n = 709), cm/s	7.2 ± 2.6
E/e′ (n = 687)	11 ± 6
Right ventricular systolic pressure (n = 557), mm Hg	31 ± 9
Aortic root dimensions	
Annulus, mm	26 ± 4
Sinus of Valsalva (n = 727), mm	40 ± 6
Mid-ascending aorta (n = 692), mm	41 ± 7
>45 mm	169 (23)

Continued in the next column

Values are mean ± SD or n (%). *Women with surgery more often had New York Heart Association (NYHA) functional class III or IV (34% vs. 16%), left ventricular end-systolic dimension index (LVESDi) >25 mm/m^2 (34% vs. 9%) (both p ≤ 0.001), and similar age (57 ± 17 years vs. 53 ± 16 years; p = 0.08) as compared with men. †Body surface area in patients older than 65 years of age was smaller in both men (<65 years of age vs. ≥65 years of age: 2.1 ± 0.2 m^2 vs. 2.0 ± 0.2 m^2; p < 0.001) and women (<65 years of age vs. ≥65 years of age: 1.8 ± 0.2 m^2 vs. 1.7 ± 0.2 m^2; p < 0.0001). Body surface area was smaller in women (1.7 ± 0.2 m^2) as compared with men (2.1 ± 0.2 m^2) (p < 0.0001). ‡Women versus men had smaller left ventricular end-systolic dimension (LVESD) (37 ± 7 mm vs. 41 ± 6 mm) and left ventricular end-diastolic dimension (LVEDD) (55 ± 6 mm vs. 61 ± 7 mm), but larger LVESDi (22 ± 4 mm/m^2 vs. 20 ± 4 mm/m^2) (all p < 0.001 adjusted for age). Patients ≥65 years of age versus <65 years of age had smaller LVEDD (60 ± 7 mm vs. 62 ± 6 mm in men; 53 ± 7 mm vs. 58 ± 5 mm in women) and smaller LVESD (40 ± 7 mm vs. 41 ± 6 mm in men; 36 ± 7 mm vs. 39 ± 6 mm in women) (all p ≤ 0.02), but similar LVESDi (20 ± 4 mm/m^2 vs. 20 ± 3 mm/m^2 in men; 22 ± 4 mm/m^2 vs. 22 ± 3 mm/m^2 in women; both p > 0.5).

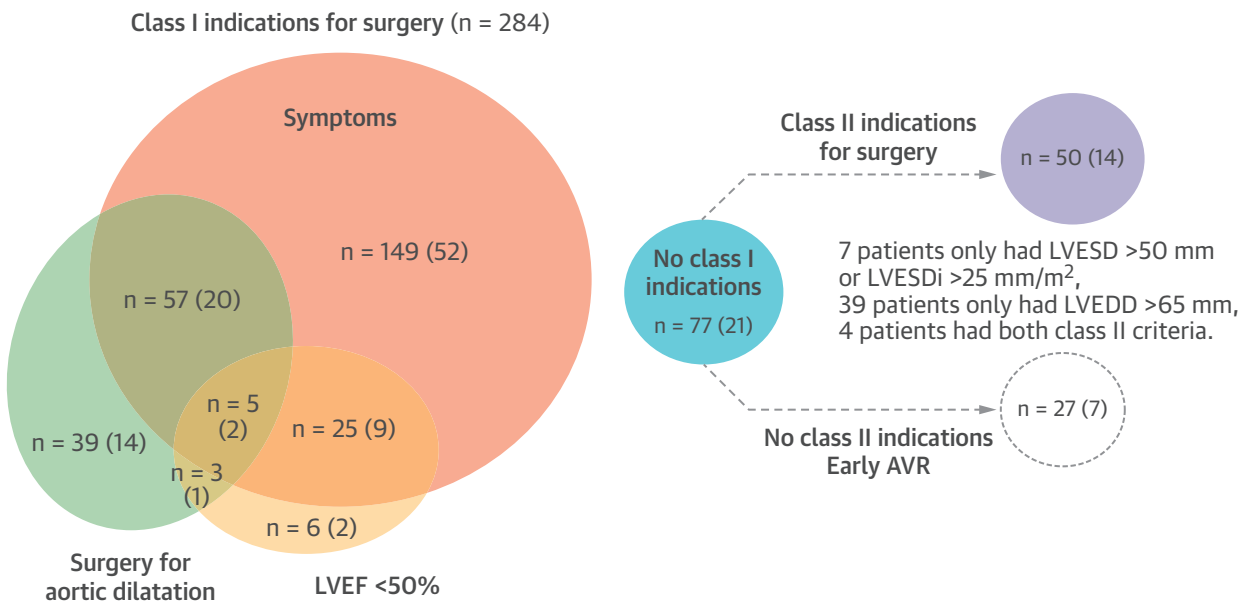
AR = aortic valve regurgitation; E = peak mitral early filling velocity; E/e′ = ratio between tissue Doppler-derived early mitral inflow velocity and mitral annular early diastolic velocity; EROA = effective regurgitant orifice area; Ln = natural log; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TVI = time-velocity integral.

(86%) and >6 months in 50 (14%) patients. The median time between the TTE to AVR was 34 (interquartile range [IQR]: 6 to 86) days. In 387 (52%) patients, no AVR was performed.

BASELINE CHARACTERISTICS. Table 1 shows baseline characteristics of patients. In this cohort without overt CAD, only 10% of patients had LVEF <50%.

SURGICAL INDICATIONS IN PATIENTS HAVING AVR. Figure 2 shows the distribution of surgical indications in 361 patients with AVR according to class of recommendations. Overall 334 (93%) had at least 1 criterion (Class I, IIa, or IIb) for aortic valve repair or replacement; 284 (79%) patients had Class I surgical indications, of which symptoms (83% of 284) were the most common; only 50 (14%) patients had only Class II surgical indications. Patients who had operation due to Class I indications (79%) were older than were those without Class I indications (21%) (55 ± 16

FIGURE 2 **Surgical Indications for 361 Patients With Aortic Valve Surgery**



Patients in the **overlapping area** had at least 2 surgical indications. Class II indications for surgery included left ventricular end-systolic dimension (LVESD) >50 mm, LVESD index (LVESDi) >25 mm/m^2, or left ventricular end-diastolic dimension (LVEDD) >65 mm. Percentages are presented in the **parentheses**. AVR = aortic valve repair or replacement; LVEF = left ventricular ejection fraction.

years of age vs. 51 ± 16 years of age; p = 0.033). In 39 (14%) patients, presence of an ascending aortic aneurysm was the main indication for operation. Among 27 (7%) patients not meeting 2014 AHA/ACC criteria, 20 had LVEDD 60 to 65 mm and the remainder (n = 7; LVEDD 54 to 59 mm) had low surgical risks, and opted for AVR earlier in the natural history of AR. Regarding LV dimensions at time of surgery, only 5% of 361 patients had LVEDD >75 mm or LVESD >55 mm (2006 guideline criteria), suggesting that AVR was performed relatively early. Cox proportional hazards modeling for determinants of AVR is shown in Online Table 1. The presence of symptoms, larger effective regurgitant orifice area (EROA), higher LVESDi, higher LVEDD, and lower LVEF (the current indications for intervention in 2014 AHA/ACC guideline) were associated with performance of AVR.

PERIOPERATIVE EVENTS IN PATIENTS HAVING AVR. The aortic valve was repaired in 96 (27%) and replaced in 265 (73%) of the 361 patients; bioprosthetic valves were used in 138 (38%) patients. Concomitant procedures included repair of the thoracic aorta in 113 (31%) patients (root or ascending aorta in 110 and proximal descending aorta in 3), single-vessel CABG in 21 (6%), maze or pulmonary vein isolation in 23 (6%), closure of patent foramen ovale or atrial septal defect in 23 (6%), and left atrial appendage ligation in 18 (5%). Average duration of hospitalization was 6 ± 3 days. Thirty-day complications included death in 1 (<1%) patient, which occurred out of hospital at 10 days, post-operative atrial fibrillation in 82 (23%), prolonged ventilation (>48 h) in 6 (1.6%), and stroke in 3 (<1%).

ALL-CAUSE MORTALITY AND LVESDi. In follow-up extended to 12.1 years (median 4.9 years [IQR: 2.3 to 8.3 years]), 369 (49%) patients had at least 5 years of follow-up (52% 5-year follow-up in survivors). The follow-up rate was 100% as of May 2018. Death occurred in 125 (17%) patients (**Figure 1**).

Table 2 shows multivariable analysis models in 748 patients. LVEF <50% was a univariable predictor but not a multivariable predictor. Of the Class II indications for AVR, LVESD (absolute value or >50 mm) was not a univariable predictor; LVEDD was paradoxically associated with better outcome univariably due to the effect of AVR. We tested the prognostic utility of LVESDi. Determinants of all-cause death after adjustment for age, comorbidities, and sex were symptoms

TABLE 2 Multivariable Predictors of All-Cause Mortality (N = 748; 125 Deaths)

Model 1, 2, 3, 4 Adjusted for Age, Sex, CCI	HR (95% CI)	p Value
Model 1: LVESDi as a continuous variable		
Symptoms	3.16 (2.10–4.75)	<0.0001
LVESDi per 1 mm/m^2 increase	1.05 (1.04–1.07)	0.01
Time-dependent AVR	0.39 (0.25–0.61)	<0.0001
Model 2: LVESDi as a categorical variable		
Symptoms	3.08 (2.03–4.66)	<0.0001
LVESDi <20 mm/m^2	Reference	
20–25 mm/m^2	1.53 (1.01–2.31)	0.04
≥25 mm/m^2	2.23 (1.32–3.77)	0.003
Time-dependent AVR	0.39 (0.25–0.62)	<0.0001
Model 3: LVESDi as a continuous variable and EROA		
Symptoms	3.06 (2.03–4.61)	<0.0001
LVESDi per 1-mm/m^2 increase	1.05 (1.01–1.09)	0.02
EROA per 10-mm^2 increase*	1.16 (0.96–1.40)	0.11
Time-dependent AVR	0.36 (0.23–0.56)	<0.0001
Model 4: LVESDi as a categorical variable and EROA		
Symptoms	2.97 (1.96–4.50)	<0.0001
LVESDi <20 mm/m^2	Reference	
20–25 mm/m^2	1.48 (0.98–2.24)	0.06
≥25 mm/m^2	2.25 (1.33–3.81)	0.003
EROA per 10-mm^2 increase*	1.16 (1.04–2.54)	0.12
Time-dependent AVR	0.35 (0.22–0.56)	<0.0001
Model 5: Impact of AVR in LVESDi subgroups		
Time-dependent AVR (unadjusted)	0.36 (0.24–0.53)	<0.0001
Time-dependent AVR (adjusted for age, sex, CCI, and symptoms)		
LVESDi <20 mm/m^2	0.46 (0.25–0.86)	0.02
LVESDi 20–25 mm/m^2	0.28 (0.12–0.63)	0.002
LVESDi ≥25 mm/m^2	0.33 (0.10–1.12)	0.08

Mortality count was 96 after adjustment for EROA. *EROA is available in 584 (78%) patients.

AVR = aortic valve repair or replacement; CI = confidence interval; CCI = Charlson comorbidity index; HR = hazard ratio; other abbreviations as in Table 1.

and higher LVESDi (model 1, Table 2). Of 3 strata of LVESDi, risk of death was increased in patients with LVESDi 20 to 25 mm/m^2, and LVESDi ≥25 mm/m^2 as compared with LVESDi <20 mm/m^2 (model 2, Table 2). Higher EROA, representative of the severity of AR, was independently associated with all-cause mortality; after adding EROA in the models, similar HR was noted for LVESDi, LVESDi 20 to 25 mm/m^2, and LVESDi ≥25 mm/m^2, confirming the association between LVESDi and increased risk of death (models 3 and 4, Table 2). In a restricted cubic spline modeling, a nonlinear relationship between LVESDi and predicted probability of mortality was estimated and the 5-year survival started to worsen in patients with LVESDi >20 mm/m^2 (Central Illustration). After excluding 21 patients having CABG (n = 21, 3 died), the results were similar (Online Table 2).

ALL-CAUSE MORTALITY AND AVR. We also tested the benefits of AVR as a time-dependent variable in the entire cohort. AVR was associated with better overall survival (models 1 to 5) (Table 2). There was no evidence that the effect of AVR was different by LVESDi subgroups (interaction p = 0.32). In the landmark analysis, patients with AVR within 6 months had better survival in 3 LVESDi subgroups than did those without AVR within 6 months (88% of whom never had AVR) (Figure 3). Survival estimated at mean covariate levels, illustrating the time dependent AVR effect, was similar to the landmark analysis (Online Figure 1).

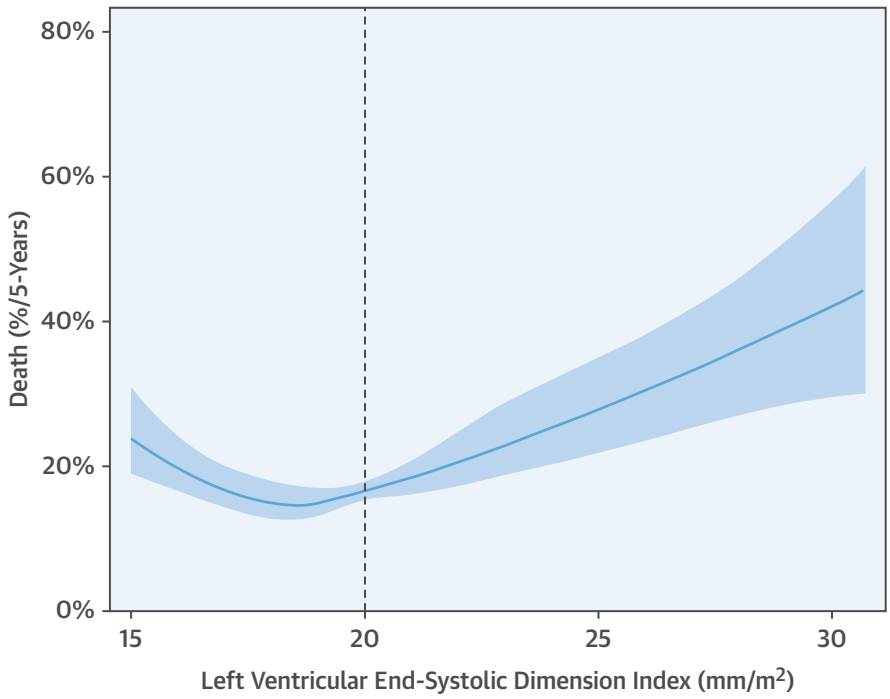
Determinants of post-AVR overall mortality (n = 35) were baseline symptoms, New York Heart Association (NYHA) functional class III or IV, and lower LVEF. When patients with AVR were dichotomized according to the presence of Class I surgical indications, those with Class I indications had poorer survival (Table 3, Figure 4).

Interestingly, although women had more NYHA functional class III or IV and LVESDi >25 mm/m^2 (p ≤ 0.001) when referred for AVR (Table 1), their post-AVR survival was similar to men (p = 0.38). Post-AVR survival according to NYHA functional class is shown in Online Figure 2.

LV CHAMBER CRITERIA: AGE AND SEX DIFFERENCES. In this cohort, women had smaller LVEDD, LVESD, and body surface area, but larger LVESDi (footnotes, Table 1). Patients older than 65 years of age had smaller body surface area, LVEDD, and LVESD, but LVESDi was similar in both men and women (see footnotes in Table 1). After adjusting for symptomatic status, independent factors associated with LV chamber criteria were as follows: 1) LVEDD >65 mm: younger age (odds ratio [OR] per 5-year decrease: 1.08; p = 0.005), reduced LVEF (OR per 5% decrease: 1.32; p < 0.0001), and male sex (OR: 11.6; p < 0.0001); 2) LVESD >50 mm: younger age (OR per 5-year decrease: 1.15; p = 0.02), reduced LVEF (OR per 5% decrease: 3.35; p < 0.0001), and male sex (OR: 19.2; p < 0.0001); 3) LVESDi >25 mm/m^2: female sex (OR: 4.2; p < 0.0001) and reduced LVEF (OR per 5% decrease: 2.69; p < 0.0001), but not age.

CHARACTERISTICS OF SYMPTOMATIC VERSUS ASYMPTOMATIC PATIENTS. Overall, 339 (45%) patients had at least 1 baseline symptom, of whom 227 (67%) met none of the LV criteria (i.e., LVEF, LVESDi, and LVEDD) for intervention. Symptomatic patients without guideline-defined LV enlargement included 289 (85%), 307 (91%), and 270 (80%) patients having LVESDi ≤25 mm/m^2, LVESD ≤50 mm, and LVEDD ≤65 mm, respectively. Symptoms included dyspnea on exertion or congestive heart failure in 266 (78%), fatigue in 116 (34%), chest discomfort in 62 (18%), presyncope or syncope in 38 (11%), and palpitations in 23 (6%); information about symptom duration was not available.

CENTRAL ILLUSTRATION **Overall Survival by Left Ventricular End-Systolic Dimension Indexed for Body Surface Area in the Whole Cohort (Operated and Nonoperated Patients)**



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The spline model shows that 5-year survival started to deteriorate in patients with left ventricular end-systolic dimension index >20 mm/m^2.

Symptomatic patients were older than asymptomatic patients (60 ± 17 vs. 56 ± 17 years of age), had higher Charlson comorbidity index (1.9 ± 2.2 vs. 1.4 ± 1.9), more advanced diastolic dysfunction (33% vs. 21%), larger indexed left atrial volume (40 ± 15 vs. 37 ± 12), higher ratio between tissue Doppler-derived early mitral inflow velocity and mitral annular early diastolic velocity (12 ± 6 vs. 10 ± 6), and higher right ventricular systolic pressure (33 ± 11 mm Hg vs. 29 ± 8 mm Hg) (all $p \leq 0.021$). Further, symptomatic patients had lower LVEF (58 ± 10% vs. 60 ± 7%), more LVESDi >25 mm/m^2 (15% vs. 6%), more LVESD >50 mm (10% vs. 4%), and smaller regurgitant volume (68 ± 21 ml vs. 74 ± 30 ml); also, diastolic blood pressure was lower in this group (62 ± 13 mm Hg vs. 65 ± 13 mm Hg) (all $p \leq 0.004$).

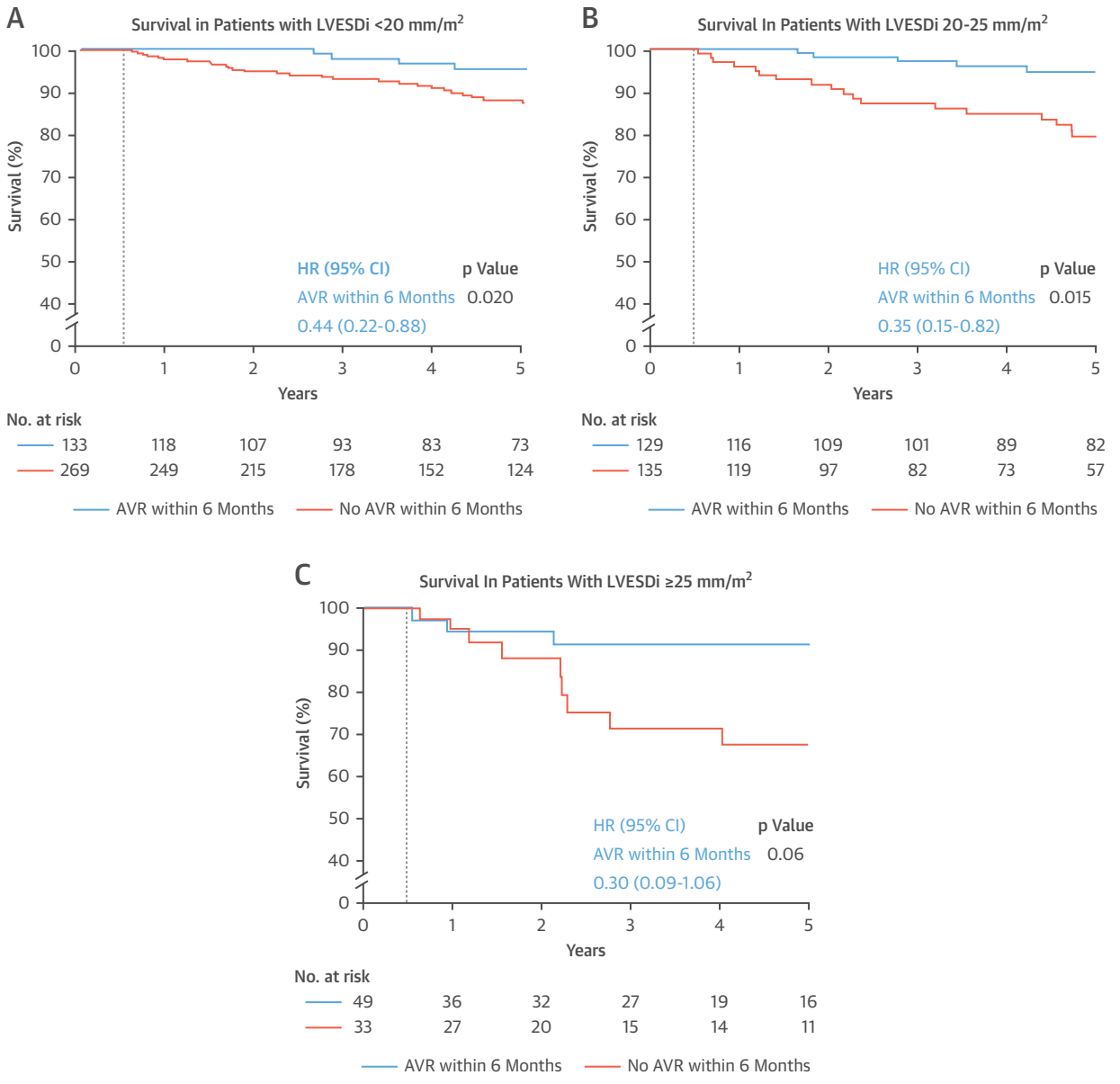
Factors independently associated with symptoms in multivariable models were: older age (OR per 5-year increase: 1.07), higher ratio between tissue Doppler-derived early mitral inflow velocity and mitral annular early diastolic velocity (OR per 1-unit increase: 1.03), and LVESDi >25 mm/m^2 (OR: 2.16) or lower LVEF (OR per 5% decrease: 1.14) (all $p \leq 0.014$).

DISCUSSION

This study provides a reappraisal of risk factors for mortality in contemporary patients with significant AR without overt CAD. The principle findings were: 1) referral for AVR was driven largely by Class I indications for surgery, mainly symptoms, and Class II indications for surgery were the only criteria in 14% with AVR; 2) AVR was associated with low risk and better survival, especially in patients having Class II surgical triggers; 3) LVESDi was the only LV criterion linked to all-cause mortality; and 4) the risk of death increased gradually when LVESDi reaches 20 mm/m^2, a cutoff lower than endorsed by current guidelines.

CHANGING PROFILES OF SURGICAL AR IN THE CONTEMPORARY ERA. Before the introduction of 2006 VHD guidelines, patients with severe AR were referred for AVR with advanced symptoms (18). As numerous studies had found an association between a large LV and poorer outcome (prediction of symptoms, increased peri-operative or post-operative mortality, and unsatisfactory post-operative LV function recovery) (1), the 2014 AHA/ACC VHD

FIGURE 3 Kaplan-Meier Survival Curves Adjusted for Age, Sex, Charlson Comorbidity Index, and Symptoms in 3 Strata of LVESDi



In this landmark analysis, follow-up spans from 6 months through 5 years (15 patients who died and 14 that were lost to follow-up within 6 months were not included). At 6 months, 300 alive subjects had received AVR and 419 patients had not received AVR (50 of them received AVR >6 months). AVR was associated with better survival in patients with **(A)** LVESDi <20 mm/m², **(B)** 20 to 25 mm/m², and **(C)** ≥25 mm/m². CI = confidence interval; HR = hazard ratio; other abbreviations as in Figures 1 and 2.

guidelines proposed a lower cutoff for LVESD (from 55 to 50 mm) and LVEDD (from 75 to 65 mm) for surgery (2). In the current study spanning more than a decade, only 5% and 39% surgical patients met the LV size cutoffs in 2006 and 2014 recommendations, respectively, suggesting that contemporary patients with pure AR were referred for AVR relatively early. Indeed, compared with previous reports, our patients had greater pre-operative LVEF, smaller LV dimensions, and less advanced NYHA functional class (4,19-21). Finally, in surgical patients, the prevalence of LVEDD >65 mm was over 3 times that of LVESD >50 mm in the present study. Given that greater LVESD reflects intrinsic myocardial decompensation

(22,23), these observations again suggest that patients in the current surgical era were in the relatively early stage of hemodynamically significant AR.

CHAMBER CRITERIA ARE NOT 1 SIZE FITS ALL. In our cohort, variables associated with larger chamber dimensions were younger age, male sex, and decreased LVEF. Although not consistently mentioned in the 2014 AHA/ACC guideline (2), LVESDi appears to be an important variable in identifying asymptomatic surgical candidates, specifically in women and elderly patients who had smaller body surface area. In our and previous studies, women, whose body surface areas were smaller, were less likely to have nonindexed LV dimensions large enough to meet surgical indications, leading to underestimation of the impact of AR on LV enlargement (24). This may explain why women with AR presented with more advanced NYHA functional class and LVESDi >25 mm/m^2. It is important to note, however, that post-AVR survival of women was comparable to that of men.

Important also is the finding that LVESDi >25 mm/m^2 was age neutral. This was likely because elderly patients (≥65 years of age), like women, had both smaller nonindexed LV dimensions and body surface area (Table 1). The inverse relationship between age and nonindexed LV dimensions could be explained partly by age-related physiological change (11) and that older patients may tolerate the same volume load less than younger patients due to diastolic dysfunction and impaired vascular compliance (25).

RELATIONSHIP OF SYMPTOMS AND PROGNOSIS. Before the introduction of 2006 AHA/ACC VHD guidelines, Class I surgical indications in minimally symptomatic (NYHA functional class II) patients with severe AR included only those with progressive LV enlargement (1,18). It is now well-accepted that AVR should not be delayed even for patients having NYHA functional class II limitation (2). Despite the fact that surgical mortality has been reduced to very low levels encouraging earlier operations (3,8), symptomatic status is still a strong predictor of all-cause mortality in our study and another recent study (26).

Plausible explanations for increased risk of death in symptomatic patients included age-related LV and vascular stiffness (reduced compliance). Symptomatic patients were older, and had more advanced diastolic dysfunction. Further, despite a smaller regurgitant volume, they had lower diastolic blood pressure which further impaired coronary perfusion. This, coupled with decreased elasticity of the circulatory system, increases cardiovascular risks (27,28). Symptomatic patients, who tended to be older, appear not to adapt well to LV volume overload as reflected in the finding that they tended to present with a less dilated LV than asymptomatic patients, who tended to be younger (25). Indeed, we found that 80% to 91% symptomatic patients did not have guideline-defined LV enlargement. This lack of marked LV enlargement could lead to misinterpretation of symptoms to other non-AR related causes and delay timely AVR. Finally, clinicians evaluating patients with AR must carefully consider symptoms however transient, especially in older patients with elevated LV filling pressure (29).

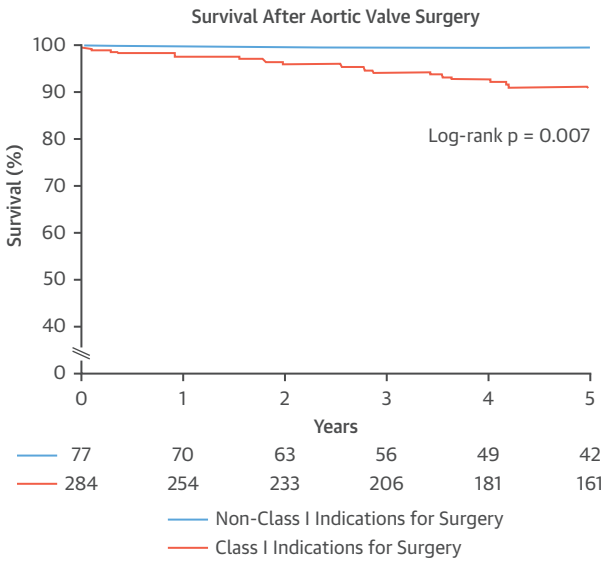
CONTEMPORARY OUTCOME DETERMINANTS: LV AND AR FACTORS. In asymptomatic patients, the indications for AVR in current guidelines were derived from studies conducted more than 1 decade

TABLE 3 Multivariable Predictors of Post-AVR Survival (n = 361; 35 deaths)

	HR (95% CI)	p Value
Symptoms adjusted for age and CCI	2.41 (1.10–6.04)	0.025
NYHA functional class III/IV adjusted for age and CCI	2.55 (1.23–5.07)	0.012
LVEF per 5% increase adjusted for age and CCI	0.81 (0.67–0.99)	0.041
Class I indications for surgery adjusted for age and CCI*	7.98 (1.71–141.90)	0.003
LVESDi >25 mm/m^2 adjusted for age and CCI	2.72 (0.89–6.81)	0.07

*Class I indications included symptoms, LVEF <50%, and surgery for aortic dilatation.
Abbreviations as in Tables 1 and 2.

FIGURE 4 Kaplan-Meier Curves in Survival After Aortic Valve Surgery (n = 361): Separated on the Basis of Class I Indications for Surgery



Patients with non-Class I indications for surgery had better post-operative survival.

ago. Although an early surgical timing has been proposed (20,21,26), most of these studies focused on post-AVR outcome. There have been few recent longitudinal studies of unoperated patients with AR (26). Further, inclusion of patients with overt CAD and prior myocardial infarction in prior studies may have obscured the association between LV chamber criteria and mortality in patients with AR.

In this study of patients with relatively low-risk profiles, only 10% had LVEF <50%; there was little prognostic value of LVEF after adjustment for covariates. Although enlarged LVESD was a harbinger of intrinsic LV dysfunction and poor outcome (1,22,30), LVESDi appears to be a more sensitive prognosticator (24,30). After stratifying patients according to LVESDi, LVESDi 20 to 25 mm/m^2, and LVESDi ≥25 mm/m^2 were associated with 1.5-fold and over 2-fold increase in mortality, respectively, suggesting that AVR should be considered when LVESDi >20 mm/m^2 instead of waiting until LVESDi ≥25 mm/m^2. Similar to our results, Mentias et al. (26) showed that LVESDi was the most robust outcome predictor, and that LVESDi >20 mm/m^2 was associated with increased risk of death. Based on these findings, instead of absolute LV dimensions, it seems reasonable to advocate the use of indexed values, specifically, LVESDi, in the assessment of AR.

TIMING OF SURGERY IN THE CURRENT ERA: HOW TO MOVE THE NEEDLE TOWARD BETTER OUTCOME? In this retrospective study in which we were unable to adjust for the duration of symptoms, we found that the presence of Class I surgical indications (i.e., any symptoms) compromised post-AVR survival and were the major reason for surgery in contrast to few patients having Class II indications. It seems reasonable that referral for AVR should be considered in asymptomatic patients with Class II surgical triggers. To move the needle toward better outcome, our data suggest that AVR might be considered relatively early, before LVESDi >25 mm/m^2 and when LVESDi progressively increases beyond 20 mm/m^2. This management strategy is analogous to recommendations for management of primary mitral regurgitation, where surgery is recommended when LVESD <40 mm with progressive LV enlargement (31), with the caveat that in the case of AR, surgery usually means valve replacement (and not repair) with the subsequent prosthesis-related risks (25).

Finally, our results highlight the importance of LVESDi, as has been previously recommended (32). Because it is age, sex, and body size neutral, it can correctly assess the severity of LV enlargement, and was associated with all-cause death. Importantly, late mortality was increased in patients who had LVESDi 20 to 25 mm/m^2, values below the threshold for surgery in current guidelines.

STUDY LIMITATIONS. In this retrospective study, observation of patients was started at somewhat different stages in the natural history of AR although all had at least moderate-severe AR; our results may differ from a cohort of patients prospectively identified, followed at regular, predetermined time intervals, and assigned to surgery randomly. We did not include patients with overt CAD; their survival would be different. However, even in patients with lower risks of cardiovascular events caused by myocardial ischemia, LVESDi 20 to 25 mm/m^2 was associated with excess risks of mortality. Also, oxygen consumption stress testing and invasive hemodynamics were not routinely performed to confirm symptomatic status. This study was conducted in a tertiary referral center with high surgical volumes thus bias may arise regarding low peri-operative risks and excellent aortic valve repair outcomes. We did not include follow-up changes in LV dimensions, the intensity of medical treatment (e.g., guideline recommended antihypertensive medications), the cumulative incidence of hypertension, and development of adverse cardiovascular comorbidities (e.g., atrial fibrillation), which may have impacted outcomes. Because of varying follow-up, we used baseline data for analysis, which was more complete. Quality of life as an endpoint was not assessed in this study, which could provide valuable information in nonsurgical patients who met guideline criteria. Importantly, we did not have information about the duration of symptoms; new symptoms would be expected to be associated with better outcome compared with longstanding symptoms. Our work should not be interpreted as a reason to deny AVR in the symptomatic patients.

CONCLUSIONS

In contemporary practice, 93% surgical patients fulfilled 2014 AHA/ACC criteria. However, the majority had Class I surgical indications, which were associated with poorer post-operative survival. Baseline symptoms were the hallmark of mortality and were frequently present before the LV markedly dilated, particularly in older patients. LVESDi merits more attention as an indication for surgery and to better assess LV enlargement in patients with small body size. LVESDi was the only LV chamber criteria

associated with all-cause death. As AVR is associated with improved outcome, it should be considered at an earlier stage of chamber enlargement.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with AR, the LVESDi is inversely related to all-cause mortality. AVR should be considered in patients at low surgical risk when the LVESDi reaches 20 mm/m^2 to improve survival, even if conventional Class I indications are present.

TRANSLATIONAL OUTLOOK: Future research should explore relationship of LVESDi to symptom status in patients with AR.

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KEY WORDS aortic regurgitation, echocardiography, guideline, left ventricular dimension, prognosis, surgery

APPENDIX For expanded Methods and Results sections as well as supplemental tables and figures, please see the online version of this paper.