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Impact of Age and Sex on Left Ventricular Remodeling in Patients With Aortic Regurgitation

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ABSTRACT

BACKGROUND Current guidelines for aortic regurgitation (AR) recommend the same linear left ventricular (LV) dimension for intervention regardless of age and sex.

OBJECTIVES The purpose of this study was to evaluate the impact of age and sex on the degree of LV remodeling and outcomes.

METHODS We included consecutive patients with severe AR who were serially monitored by echocardiogram between 2010 and 2016. The 2 main endpoints were as follows: 1) LV end-systolic volume indexed to body surface area (LVESVi) and LV end-diastolic volume indexed to body surface area; and 2) adverse events (AE). We evaluated the longitudinal rate of LV remodeling and determined the association between LV volume and AE by age and sex.

RESULTS A total of 525 adult patients (26% women) with a median echocardiogram follow-up of 2.0 years (IQR: 1.0-3.6 years) were included. At baseline, older patients (age ≥60 years) had smaller LV volumes compared with younger patients (age <60 years), eg, the mean LVESVi was 27.3 mL/m^2 vs 32.3 mL/m^2, respectively. Similarly, women had smaller LV volumes compared with men (mean LVESVi was 23.3 mL/m^2 vs 32.4 mL/m^2). On serial evaluation, older patients and women maintained smaller LV volumes compared with younger patients and men, respectively. There were 210 (40%) AE during follow-up. The optimal discriminatory threshold for AE varies by age and sex, eg, the LVESVi threshold was highest for young men (50 mL/m^2), intermediate for older men (35 mL/m^2), and lowest for women (27 mL/m^2).

CONCLUSIONS On serial evaluation, older patients and women with chronic AR maintained smaller LV volumes than younger patients and men, respectively, and develop AE at lower LV volumes. (J Am Coll Cardiol 2023;81:1474–1487)

Aortic regurgitation (AR) is characterized by combined left ventricular (LV) volume and pressure overload.[1] These overload conditions lead to LV cellular and chamber remodeling and increased LV volumes and mass to accommodate the regurgitant volume. Experimental animal models indicate that the degree and pattern of LV remodeling varies by age and sex.[2-4] In humans, the degree of LV remodeling is associated with outcomes and constitutes one of the cardinal parameters used to inform timing of intervention.[5-7] The American College of Cardiology/American Heart Association guidelines for the surgical management of AR have not substantially changed since their original publication in

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1998.[7,8] Yet, there has been an interval expansion of observational studies that question the validity of the guidelines' recommendations of a single cutoff value for LV dimensions to suggest valve intervention. The guideline recommends aortic valve (AV) surgery for asymptomatic severe AR patients based on linear dimensions of LV end-systolic diameter >50 mm (or 25 mm/m^2 when indexed to body surface area [BSA]), or LV end-diastolic diameter >65 mm. However, these recommendations were based on relatively old studies with small sample sizes and little female representation.[9-13] Two contemporary studies have shown that most deaths occurred while patients were below the guideline-recommended LV dimension cutoff values.[5,6] The discrepancy in reported thresholds between studies may be explained, at least in part, by unreliability of linear dimensions as well as differences in LV remodeling by age and/or sex. To circumvent the limitations of linear dimensions, recent reports have proposed a left ventricular end-systolic volume index (LVESVi) threshold of 40 to 45 mL/m^2 as the optimal threshold for intervention.[14-16] However, one threshold may not be the optimal for everyone and may lead to disparity in outcomes. LV volumes decrease as aging progresses; thus, older people have a smaller LV cavity size than younger ones.[17,18] Age, besides being a risk factor, is an important modulating factor in the LV response to overload. Similarly, compared with men, women generally have smaller LV volume per BSA and may exhibit a different response to chronic volume overload.[19,20]

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These findings provided us with a hypothesis that the capacity for LV adaptation in response to overload differs by age and sex in patients with AR. Consequently, we sought to evaluate the impact of age and sex on the following: 1) the degree of LV remodeling in response to AR; 2) the difference in LV remodeling over time; and 3) the association between LV remodeling and outcomes.

METHODS

STUDY POPULATION. The study cohort consisted of patients on routine surveillance for chronic AR with serial echocardiograms at the Cleveland Clinic (Supplemental Figure 1). We included consecutive patients of at least 21 years of age with moderate to severe AR or severe AR and LV ejection fraction ≥50% who underwent echocardiographic studies between 2010 and 2016 at baseline and at least 1 follow-up study that is ≥6 months from the baseline. Patients aged <21 years were excluded to limit the inclusion of patients with other congenital diseases or syndromic conditions that may affect outcomes. We additionally excluded patients with the following: 1) other left-sided valve disease (aortic stenosis, mitral regurgitation, or mitral stenosis) of at least moderate severity; 2) prior AV surgery; 3) congenital heart disease other than dysplastic AV; 4) no repeat study at or after 6 months from the baseline study; and 5) limited or suboptimal echocardiographic studies for which volume quantification could not be reliably performed. For patients who had AV surgery during follow-up, we additionally excluded all echocardiograms performed after the surgery. Ethics approval was obtained from the Cleveland Clinic Institutional Review Board.

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AV = aortic valve

BSA = body surface area

LV = left ventricle/ventricular

LVEDDi = left ventricular end-diastolic diameter indexed to body surface area

LVEDVi = left ventricular end-diastolic volume index

LVESDi = left ventricular end-systolic diameter indexed to body surface area

LVESVi = left ventricular end-systolic volume index

CLINICAL CHARACTERISTICS. Patients' clinical characteristics, including baseline demographics, comorbidities, laboratory measurements, and follow-up data, were determined through detailed review of electronic health records. Baseline age was defined as the chronological age at the time of first echocardiography study.

ECHOCARDIOGRAPHY ASSESSMENT. Echocardiography was performed based on our standard institutional protocol using Vivid 7 or E9 (GE Healthcare) or EPIQ 7C (Philips Medical Systems) machines, and AR grading was performed based on combination of qualitative and quantitative parameters.[21] LV volumes were determined using the biplane disk summation methods in accordance with the guidelines.[22] Briefly, using nonforeshortened apical 4- and 2-chamber views, the endocardial-blood interface was traced from the apex to the mitral valve level to conform to the shape of the ventricle. The length (L) of the LV cavity is defined as the distance from the LV apex to the mitral valve level. The traced inner cavity is then divided into 20 disks, and the volume of each disk was determined by its 2 radii in the 4-chamber (r1) and 2-chamber view (r2) and its height: volume = $\pi(r1 \times r2) \times (L/20)$. The total LV volume was then calculated as the sum of the 20 disks. Other echocardiographic dimensions were assessed per guidelines.[22]

ENDPOINTS. We assessed both echocardiographic and clinical endpoints. The echocardiographic endpoints were measures of LV volumes indexed to BSA. These included LVESVi and left ventricular end-diastolic volume index (LVEDVi). In addition, we evaluated LV linear dimensions (left ventricular end-systolic diameter index [LVESDi] and left ventricular

TABLE 1 Baseline Characteristics of Patients With Severe Aortic Regurgitation, Stratified by Age

	Total (N = 525)	Age <60 y (n = 289)	Age ≥60 y (n = 236)	*P* Value
Age, y	55.9 ± 15.7	44.4 ± 10.4	69.9 ± 7.8	<0.001
Female	135 (25.7)	63 (21.8)	72 (30.5)	0.02
Race				0.13
White	433 (82.4)	237 (82.0)	196 (83.0)	
Black	54 (10.4)	26 (9.0)	28 (12.1)	
Others	38 (7.2)	26 (9.0)	12 (4.9)	
Symptom status				0.04
Asymptomatic	392 (74.7)	226 (78.2)	166 (70.3)	
Minimal symptoms	133 (25.3)	63 (21.8)	70 (29.6)	
Body surface area, m^2	2.0 ± 0.25	2.0 ± 0.25	1.9 ± 0.23	<0.001
Hypertension	417 (79.4)	214 (74.1)	203 (86.0)	0.001
Diabetes	69 (13.1)	31 (10.7)	38 (16.1)	0.07
Coronary artery disease	200 (38.1)	65 (22.4)	135 (57.2)	<0.001
Atrial fibrillation	53 (10.1)	16 (5.5)	37 (15.6)	<0.001
Prior stroke	36 (6.8)	11 (3.8)	25 (10.5)	0.002
Chronic kidney disease	26 (5.0)	12 (4.1)	14 (5.9)	0.35
Chronic obstructive pulmonary disease	39 (7.4)	18 (6.2)	21 (8.9)	0.24
Prior cardiac surgery				
Other valve surgery	8 (1.5)	6 (2.1)	2 (0.85)	0.24
CABG	5 (0.95)	0 (0.0)	5 (2.1)	0.01
Contributing etiology				
Bicuspid	140 (26.7)	109 (37.7)	31 (13.1)	<0.001
Annular dilatation	123 (23.4)	54 (18.6)	69 (29.2)	0.005
Idiopathic	101 (19.2)	50 (17.3)	51 (21.6)	0.21
Degenerative	69 (13.1)	22 (7.6)	47 (19.9)	<0.001
Endocarditis	20 (3.8)	15 (5.1)	5 (2.1)	0.07
Rheumatic	11 (2.1)	6 (2.1)	5 (2.1)	0.71
Echocardiographic parameters				
AR grade				<0.001
Moderate to severe	339 (64.6)	165 (57.1)	174 (73.7)	
Severe	186 (35.4)	124 (42.9)	62 (26.2)	
LVEF, %	59.2 ± 4.8	59.0 ± 4.8	59.4 ± 4.8	0.79
LA volume index, mL/m^2	32.1 ± 11.1	30.5 ± 11.0	34.2 ± 11.5	<0.001
LVESVi, mL/m^2	30.1 ± 11.1	32.3 ± 11.7	27.3 ± 9.6	<0.001
LVEDVi, mL/m^2	74.5 ± 24.3	80.4 ± 25.3	67.3 ± 21.1	<0.001
LVESDi, mL/m^2	1.8 ± 0.35	1.8 ± 0.37	1.7 ± 0.32	0.001
LVEDDi, mL/m^2	2.7 ± 0.45	2.8 ± 0.44	2.6 ± 0.41	0.001
Medications				
Beta-blocker	52 (9.9)	29 (10.0)	23 (9.7)	0.91
RAASi	247 (47.1)	123 (42.5)	124 (52.5)	0.02
Diuretic agents	152 (28.9)	65 (22.4)	87 (36.8)	<0.001
Laboratory values[a]				
NT-proBNP, pg/mL (n = 113)	183 (81, 894)	123 (49, 335)	297 (105, 1,695)	0.005
Creatinine, mg/dL (n = 417)	0.96 (0.83, 1.10)	0.93 (0.82, 1.10)	0.98 (0.84, 1.20)	0.04

Values are mean ± SD, n (%), or median (Q1, Q3). [a]Number of patients with laboratory values shown in parenthesis.

AR = aortic regurgitation; BNP = B-type natriuretic peptide; CABG = coronary artery bypass graft; LA = left atrium; LVEDDi = left ventricular end-diastolic diameter index; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESDi = left ventricular end-systolic diameter index; LVESVi = left ventricular end-systolic volume index; NT-proBNP = N-terminal pro hormone B-type natriuretic peptide; RAASi = renin-angiotensin-aldosterone system inhibitor.

end-diastolic diameter index [LVEDDi]) for comparison. The clinical endpoint/adverse event was a composite of mortality, incident heart failure hospitalization, or urgent AV surgery (whichever occurred first). Urgent AV surgery was defined as AV surgery because of development of significant symptoms or decrease in LVEF to ≤55%. Clinical endpoints were adjudicated through detailed review of all available health records and obituaries (for mortality).

FOLLOW-UP. Study period was from the time of baseline echocardiogram (2010 to 2016) and clinical data was accrued up to November 2021 or a censoring event. Patients were censored at the time of AV surgery, heart failure hospitalization, death, or last known hospital contact (whichever occurred first).

STATISTICAL ANALYSIS. To compare baseline characteristics by age, patients were categorized into an older (≥60 years) and younger (<60 years) cohort. Age 60 years was chosen for the categorization because it is close to the median age and represents a threshold when LV volume is lower for older patients at baseline examination (Supplemental Figure 2). The baseline characteristics were compared between the categories using Student's *t*-test or Wilcoxon rank sum test (as appropriate) for continuous variables and chi-square test for categorical variables. A similar comparison was performed based on sex.

The impact of age and sex on LV volumes and linear dimensions was assessed in 2 ways. First, we evaluated the cross-sectional association between baseline age and LV volumes/linear dimensions using multivariable-adjusted linear regression. The model was adjusted for important baseline variables, including etiology of AR, grade of AR severity, LV ejection fraction, and other clinical characteristics statistically significant in **Table 1**. The analysis was stratified by sex, and its potential effect as an effect modifier was evaluated by introducing an interaction term between sex and age. Second, we assessed the longitudinal rate of remodeling using serial measurements of LV volumes and linear dimensions for each patient with an interval of 6 months or multiples of 6 months between studies. The longitudinal rate of LV remodeling was determined using a linear mixed model with unstructured matrix and robust variance. The model was stratified by age and sex and was adjusted for important baseline covariates as previously discussed and statistically significant clinical characteristics in **Tables 1 and 2** (as appropriate).

The rate of each component of the adverse events over the follow-up period was compared between categories of age and sex using Cox model. Thereafter, the association between the last LV volume and linear dimension attained before censoring and the first occurrence of any of the adverse events was determined with the Cox model. Analysis time was from the last echocardiogram to the time of censoring, and proportionality assumption was assessed based on scaled Schoenfeld residuals. The models were adjusted for similar covariates as in the previous text, but time-varying covariates were updated for the time of last echocardiogram. Subsequently, we determined the prognostic value of volumetric assessment and linear dimension based on area under the curve (AUC) analysis and compared the 2 methods using jackknife variance estimation and linear combination of estimates.[23] Last, we determined the optimal discriminatory threshold of the last LV volume (by age and sex) above which the risk of adverse events significantly increased at 1 year of follow-up. The optimal discriminatory threshold was based on the receiver-operating characteristic curve and Youden index that maximizes the sum of sensitivity and specificity. Bootstrapping method using 1,000 random sampling with replacement was used to calculate the SEs and 95% confidence limits for the optimal thresholds. The HRs for LV volumes relative to the optimal threshold was displayed for each strata using cubic spline curves.

All analyses were performed using STATA 17 (StataCorp), and a 2-tailed *P* value <0.05 was considered statistically significant.

RESULTS

The study included 525 patients with 1,687 echocardiograms showing moderate to severe or severe AR over a median follow-up of 2.0 years (IQR: 1.0-3.6 years). At baseline examination, the mean age was 55.9 ± 15.7 years, and 25.7% were women. The patients were either asymptomatic (74.7%) or with only minimal symptoms (25.3%) (stage C valvular heart disease). The most common etiology of AR was bicuspid AV (26.7%), and this occurred predominantly among the younger cohort (37.7%) and men (33.6%). Other baseline characteristics by age and sex are provided in **Tables 1 and 2**. Notably, compared with younger patients (age <60 years), older patients (age ≥60 years) had lower BSA (1.9 m^2 vs 2.0 m^2) and smaller LV volumes even despite indexation to BSA. For example, the mean LVESVi was 27.3 ± 9.6 mL/m^2 for the older cohort compared with 32.3 ± 11.7 mL/m^2 in the younger cohort. Similarly, compared with men, women also had smaller BSA (1.7 m^2 vs 2.0 m^2) and lower indexed LV volumes than men. The mean LVESVi was 23.3 ± 8.3 mL/m^2 for women compared with 32.4 ± 11.0 mL/m^2 for men.

In cross-sectional analysis at the time of first echocardiogram, we found an inverse association

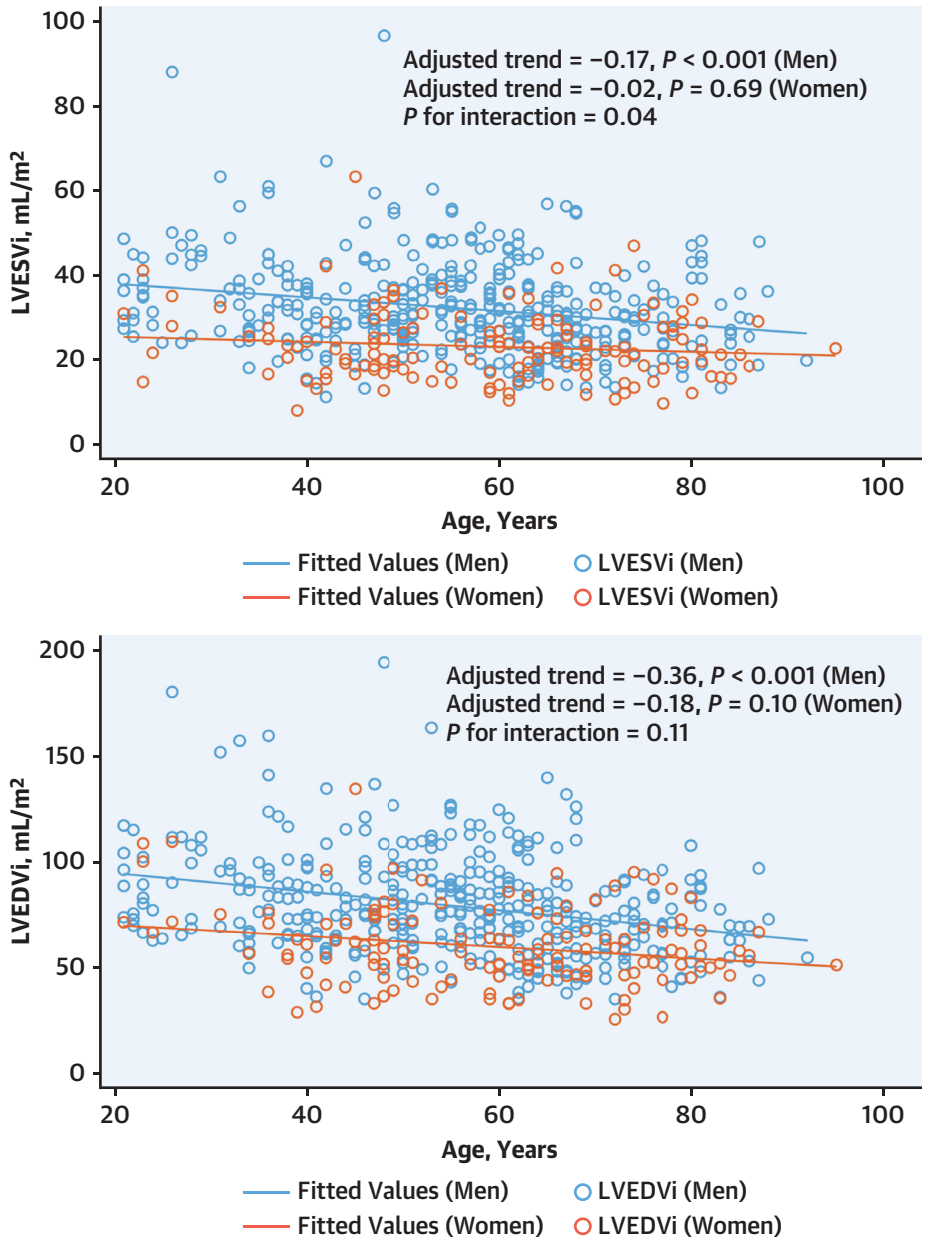
TABLE 2 Baseline Characteristics of Patients With Severe Aortic Regurgitation, Stratified by Sex

	Total (N = 525)	Men (n = 390)	Women (n = 135)	*P* Value
Age, y	55.9 ± 15.7	54.9 ± 15.5	58.9 ± 15.9	0.01
Race				<0.001
White	433 (82.4)	335 (85.8)	98 (72.9)	
Black	54 (10.4)	27 (7.0)	27 (20.1)	
Others	38 (7.2)	28 (7.2)	10 (7.0)	
Symptom status				0.001
Asymptomatic	392 (74.7)	306 (78.5)	86 (63.7)	
Minimal symptoms	133 (25.3)	84 (21.5)	49 (36.3)	
Body surface area, m^2	2.0 ± 0.25	2.0 ± 0.22	1.7 ± 0.20	<0.001
Hypertension	417 (79.4)	311 (79.7)	106 (78.5)	0.76
Diabetes	69 (13.1)	44 (11.3)	25 (18.5)	0.03
Coronary artery disease	200 (38.1)	142 (36.4)	58 (42.9)	0.17
Atrial fibrillation	53 (10.1)	43 (11.0)	10 (7.4)	0.22
Prior stroke	36 (6.8)	21 (5.4)	15 (11.1)	0.02
Chronic kidney disease	26 (5.0)	21 (5.4)	5 (3.7)	0.43
Chronic obstructive pulmonary disease	39 (7.4)	22 (5.6)	17 (12.6)	0.01
Prior cardiac surgery				
Other valve surgery	8 (1.5)	5 (1.3)	3 (2.2)	0.44
CABG	5 (0.95)	4 (1.03)	1 (0.74)	0.76
Contributing etiology				
Bicuspid	140 (26.7)	131 (33.6)	9 (6.7)	<0.001
Annular dilatation	123 (23.4)	95 (24.4)	28 (20.7)	0.39
Idiopathic	101 (19.2)	57 (14.6)	44 (32.6)	<0.001
Degenerative	69 (13.1)	44 (11.3)	25 (18.5)	0.03
Endocarditis	20 (4.7)	15 (3.9)	5 (3.7)	0.94
Rheumatic	11 (2.1)	4 (1.0)	7 (5.2)	0.004
Echocardiographic parameters				
AR grade				0.70
Moderate to severe	339 (64.6)	250 (64.1)	89 (65.9)	
Severe	186 (35.4)	140 (35.9)	46 (34.1)	
LVEF, %	59.2 ± 4.8	58.9 ± 4.7	60.0 ± 5.0	0.01
LA volume index, mL/m^2	32.1 ± 11.1	32.1 ± 11.0	32.0 ± 11.1	0.90
LVESVi, mL/m^2	30.1 ± 11.1	32.4 ± 11.0	23.3 ± 8.3	<0.001
LVEDVi, mL/m^2	74.5 ± 24.3	79.5 ± 24.1	60.1 ± 18.8	<0.001
LVESDi, mL/m^2	1.8 ± 0.35	1.8 ± 0.35	1.8 ± 0.37	0.57
LVEDDi, mL/m^2	2.7 ± 0.45	2.7 ± 0.42	2.7 ± 0.44	0.06
Medications				
Beta-blocker	52 (9.9)	35 (9.0)	17 (12.6)	0.22
RAASi	247 (47.1)	191 (49.0)	56 (41.5)	0.13
Diuretic agents	152 (28.9)	98 (25.1)	54 (40.0)	0.001
Laboratory values[a]				
NT-proBNP, pg/mL (n = 113)	183 (81, 894)	133 (54, 820)	266 (124, 1,252)	0.06
Creatinine, mg/dL (n = 417)	0.96 (0.83, 1.10)	1.01 (0.88, 1.10)	0.82 (0.70, 0.94)	<0.001

Values are mean ± SD, n (%), or median (Q1, Q3). [a]Number of patients with laboratory values shown in parenthesis.

Abbreviations as in Table 1.

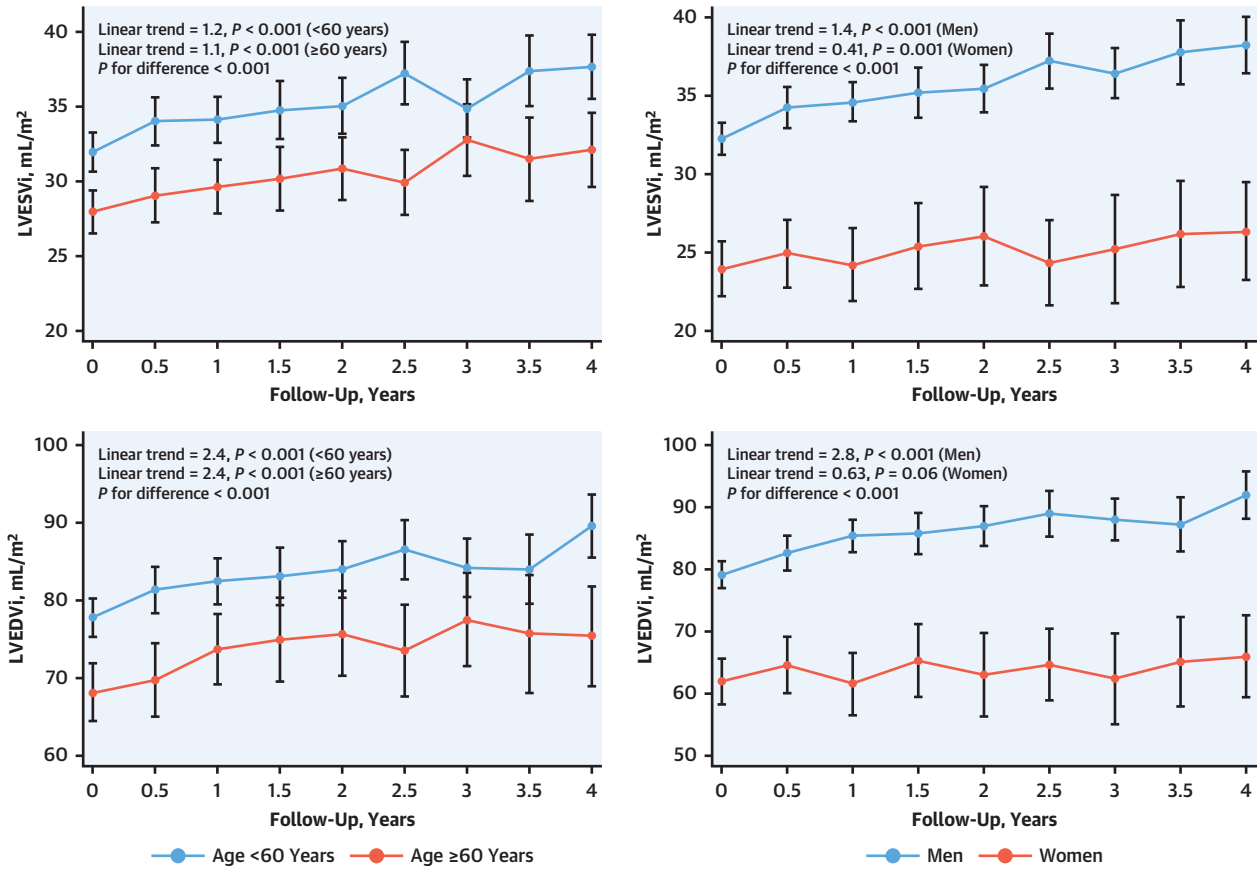
FIGURE 1 Cross-Sectional Association Between Age and Left Ventricle Volume



The figure shows cross-sectional association between age and indexed left ventricular volume at baseline examination, stratified by sex. **(Top)** Association for left ventricular end-systolic volume index (LVESVi), and **(bottom)** association for left ventricular end-diastolic volume index (LVEDVi). Adjusted trend displayed represents the difference in left ventricular volume per 1-year increase in age.

between LV volumes and age (Figure 1). In other words, older patients tend to have smaller LV volumes than younger patients at the time of first diagnosis. The LV volume starts to appear lower for older patients around the age of 60 years (Supplemental Figure 2). The magnitude of the difference was higher for LVEDVi than LVESVi. However, the association between age and LV volume was stronger in men compared with women: the LVESVi was lower by 1.7 mL/m^2 for each 10-year increase in age for men but no significant difference for women (P for interaction = 0.04). A similar difference, albeit without a statistically significant interaction, was found for LVEDVi (3.6 mL/m^2 vs 1.8 mL/m^2 per

FIGURE 2 **Trend in Left Ventricular Volume Over Time**



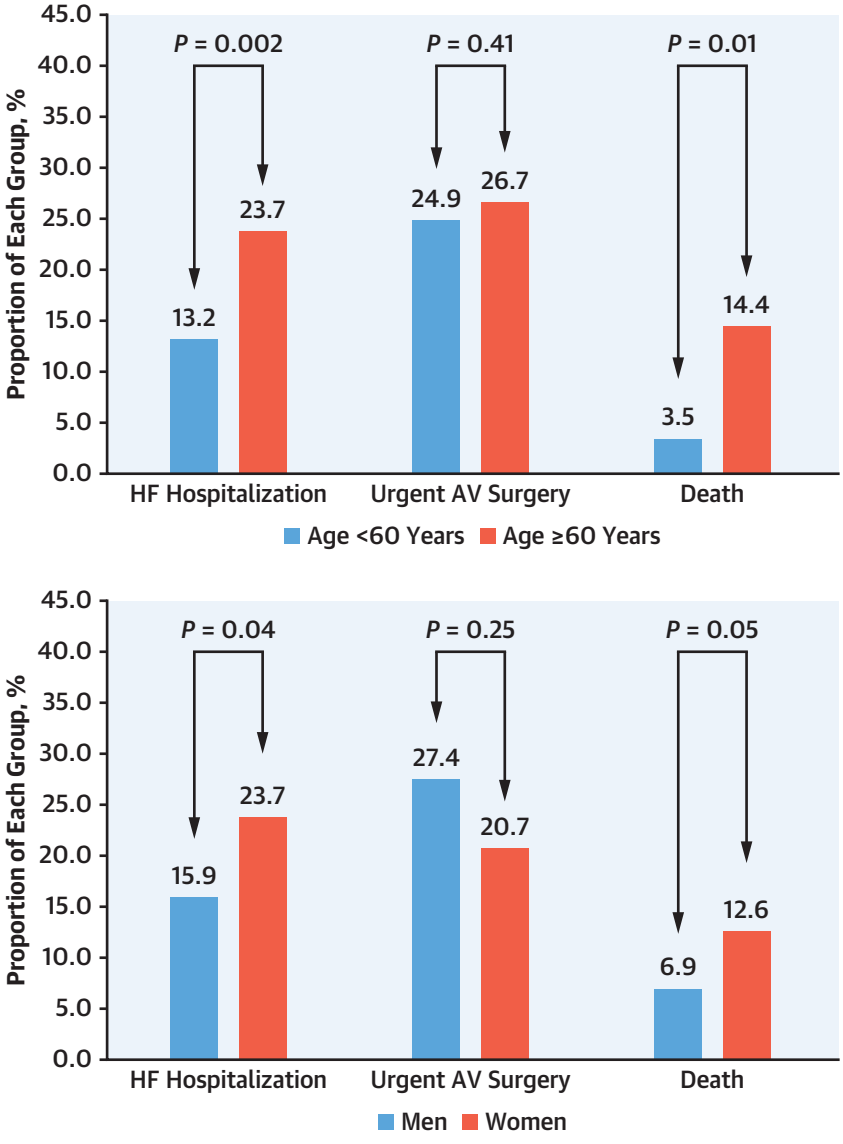
Longitudinal trend in LVESVi **(top)** and LVEDVi **(bottom)**, stratified by baseline age **(left)** and sex **(right)**. Point estimates and 95% CI are shown for each time interval. Linear trends displayed represent average change in the indexed left ventricular volume per year of follow-up. Abbreviations as in Figure 1.

10-year increase in age for men vs women, respectively). Similar associations were observed for linear dimensions (Supplemental Figure 3).

In longitudinal analysis, LV volumes increased over time but older patients and women consistently maintained smaller LV volumes compared with younger patients and men, respectively (**Figure 2**). The magnitude of increase in LVESVi was higher for younger patients (1.2 mL/m^2/y; $P < 0.001$) and men (1.4 mL/m^2/y; $P < 0.001$), and less for the older patients (1.1 mL/m^2/y; $P < 0.001$) and women (0.41 mL/m^2/y). The per-year increase in LVEDVi was 2.4 mL/m^2 for the younger cohort, 2.4 mL/m^2 for the older cohort, and 2.8 mL/m^2 for men ($P < 0.001$ for all). On the other hand, the magnitude of increase in LVEDVi for women was 0.63 mL/m^2/y ($P = 0.06$). In comparison, the change in linear dimensions was minimal over time (Supplemental Figure 4)

Over the study period, there were 94 (17.9%) cases of first heart failure hospitalization, 135 (25.7%) urgent surgeries, and 44 (8.4%) deaths. A total of 210 patients (40%) had at least 1 adverse event. Overall, the rate of at least 1 adverse event was higher for older patients and women compared with younger patients and men, respectively, mostly because of significantly higher rate of heart failure hospitalization and death (**Figure 3**). When we evaluated the association between the last LV volume attained and the first occurrence of adverse event, both LVESVi and LVEDVi were independent predictors of adverse events in multivariable analysis. The HR per SD increase in volume was 1.52 (95% CI: 1.31-1.76; $P < 0.001$) for LVESVi and 1.46 (95% CI: 1.24-1.71; $P < 0.001$) for LVEDVi. In comparison, HR per SD increase in linear dimensions was 1.08 (95% CI: 1.01-1.17; $P = 0.03$) for LVESDi and 1.21 (95% CI: 1.06-1.39;

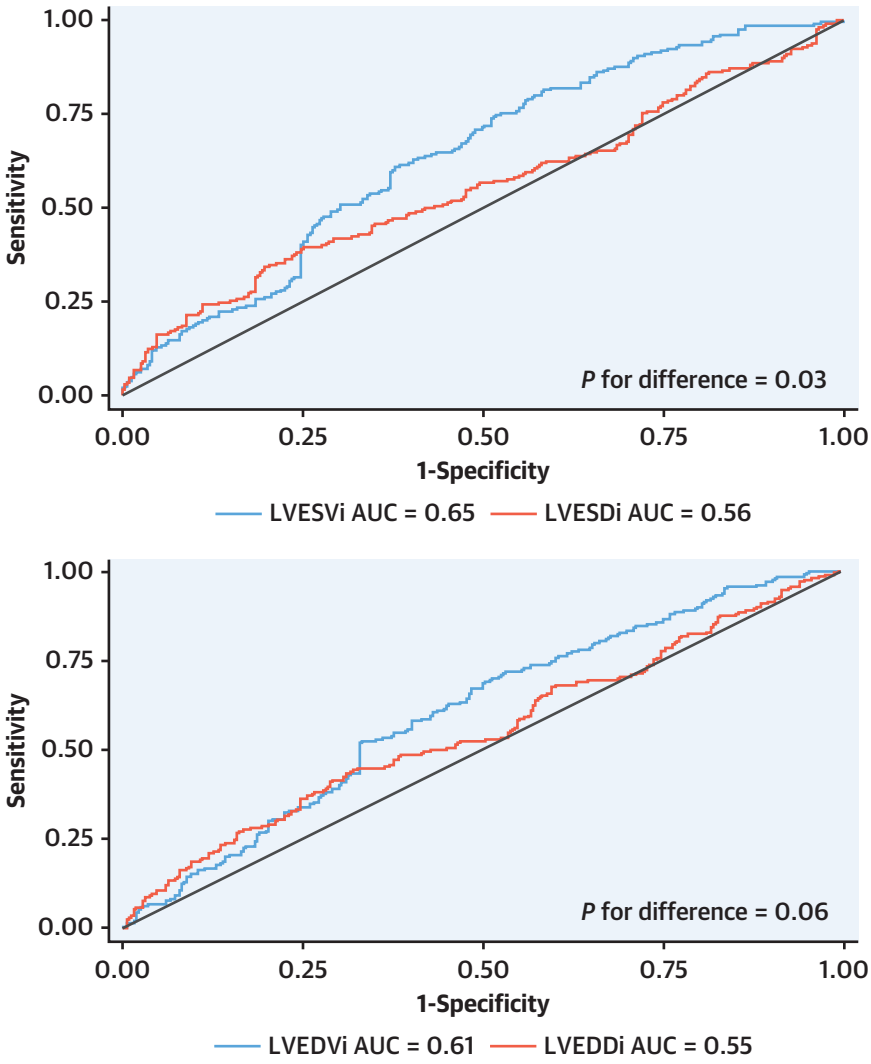
FIGURE 3 Distribution of Adverse Events by Age and Sex



The figure shows proportion of each endpoint—heart failure (HF) hospitalization, urgent aortic valve (AV) surgery, and death—by age **(top)** and sex **(bottom)** as well as *P* value for pairwise comparison.

$P = 0.005$) for LVEDDi. On pairwise comparison, LV volumetric assessment had higher prognostic value than linear dimensions (AUC: LVESVi 0.65 vs LVESDi 0.56; $P = 0.03$; LVEDVi 0.61 vs LVEDDi 0.55; $P = 0.06$) (Figure 4). The optimal discriminatory volume thresholds above which the rate of adverse events significantly increase varies by sex, and the effect of age was more evident among men only. Notably, the magnitude of the threshold was highest for young men, intermediate for older men, and lowest for women (Figure 5). The optimal LVESVi threshold was 50 mL/m^2 (95% CI: 43-57 mL/m^2) for young men, 35 mL/m^2 (95% CI: 31-39 mL/m^2) for older men, and 27 mL/m^2 (95% CI: 24-30 mL/m^2) for women. The optimal LVEDVi threshold was 94 mL/m^2 (95% CI: 84-104 mL/m^2) for young men, 75 mL/m^2 (95% CI: 69-81 mL/m^2) for older men, 69 mL/m^2 (95% CI: 63-75 mL/m^2) for young women, and 68 mL/m^2 (95% CI:

FIGURE 4 Discriminatory Ability of Volumetric Assessment Compared With Linear Dimensions



The figure shows the area under the curve (AUC) of volumetric assessment compared with linear dimensions in predicting adverse events—a composite of heart failure hospitalization, urgent aortic valve surgery, and death. Notably, the prognostic utility of volumetric assessment is superior to linear dimension. The **black line** corresponds to a nondiscriminatory AUC of 0.5. LVEDDi = left ventricular end-diastolic diameter index; LVESDi = left ventricular end-systolic diameter index; other abbreviations as in Figure 1.

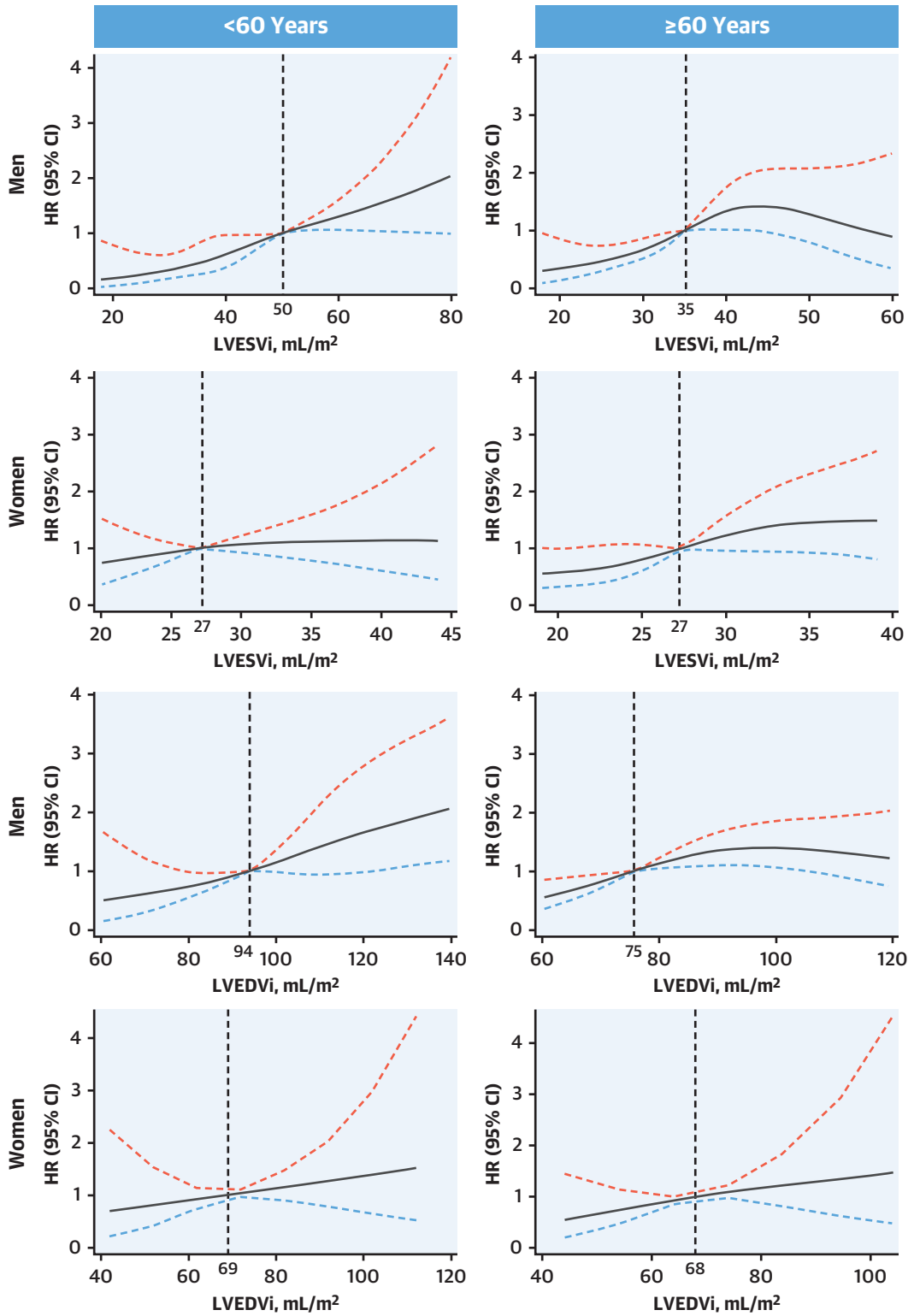
62-74 mL/m^2) for older women. For each stratum of age and sex, patients above the threshold were at higher risk of adverse events compared with those below the threshold (Figure 6).

DISCUSSION

In this cohort of patients with moderate to severe or severe AR and preserved LV systolic function, we showed that despite indexing to BSA, LV volumes were smaller in older compared with younger patients, and in women compared with men. These differences in LV volumes persist on serial assessment over time. In addition, LV volumetric assessment was a better prognostic parameter than linear dimension. The optimal discriminatory volume thresholds above which the rate of adverse events significantly increase was lower in older patients and women (Central Illustration).

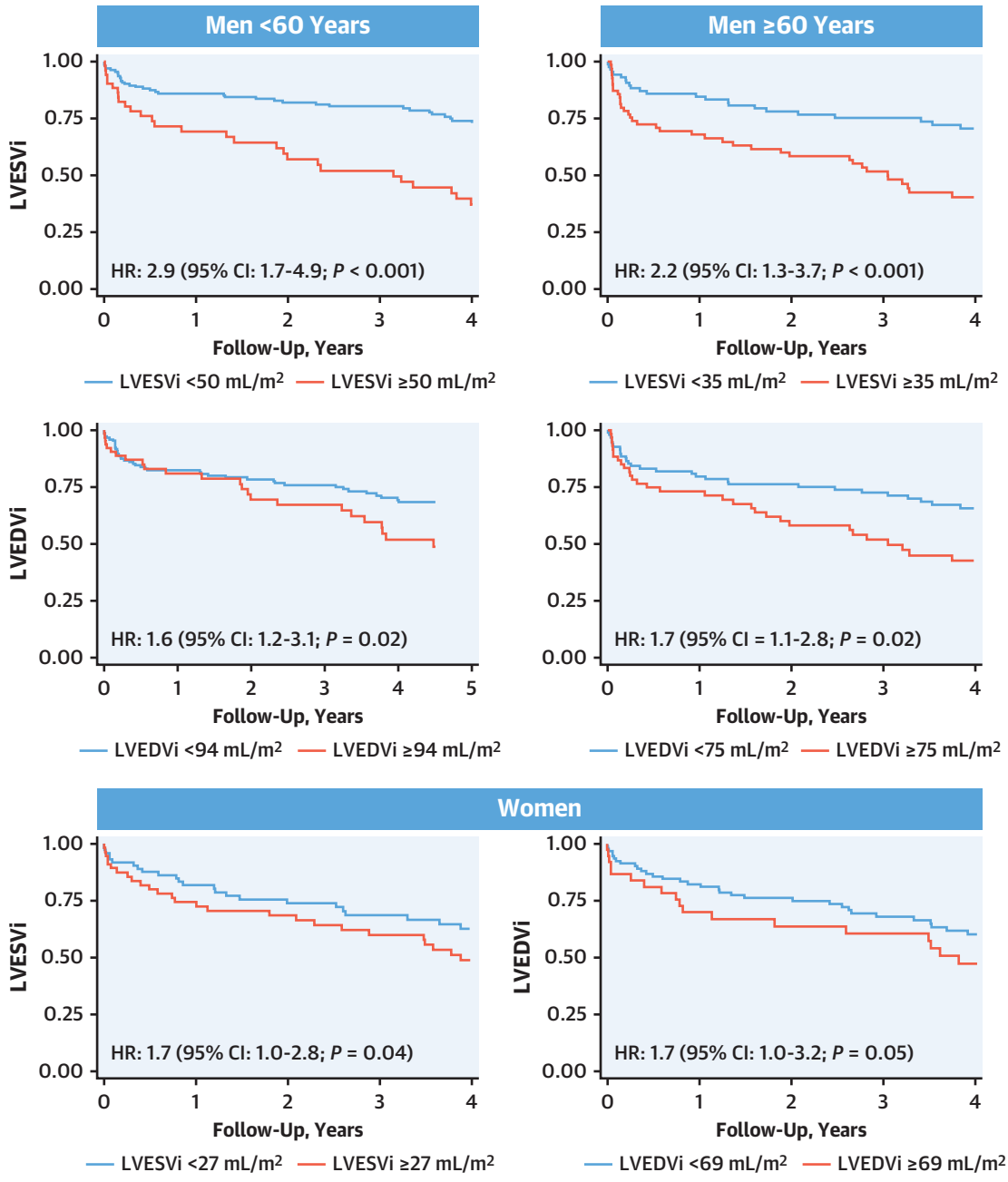
The aging process is characterized by progressive myocyte loss and alteration in myocardial signaling at the subcellular level.[2-4] These characteristic changes

FIGURE 5 **Association Between Left Ventricular Volume and Adverse Events**



Spline curves showing HR (95% CI) of adverse event—a composite of mortality, incident heart failure hospitalization, or urgent aortic valve surgery—for range of volumes with analysis stratified by age and sex. For each figure, **black dashed lines** indicate optimal discriminatory threshold. The **solid black line** represent the spline curve and the **dotted red and blue lines** represent the upper and lower limits, respectively. Abbreviations as in Figure 1.

FIGURE 6 Event-Free Survival According to Proposed Discriminatory Volume Thresholds

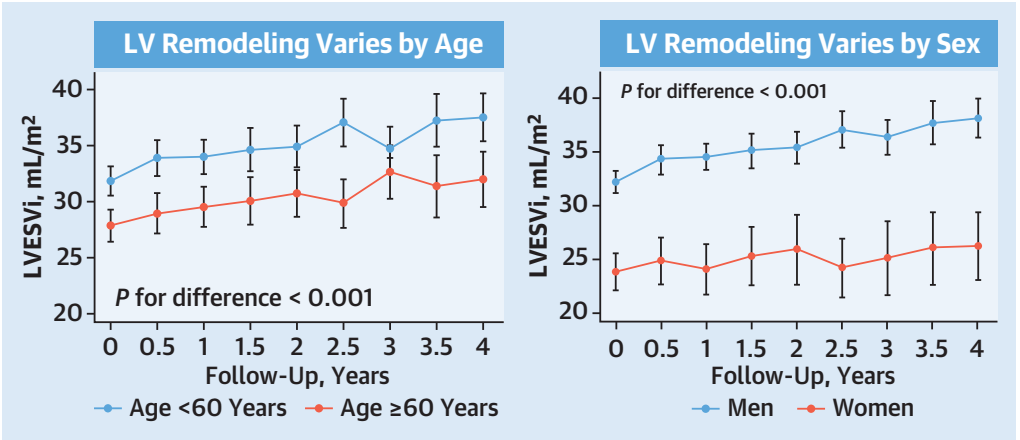


The figure depicts Kaplan-Meier curves of adverse events comparing patients above and below the optimal discriminatory volume thresholds, stratified by age and sex. These underscore that the proposed thresholds can reliably stratify patients into low- and high-risk groups. Abbreviations as in Figure 1.

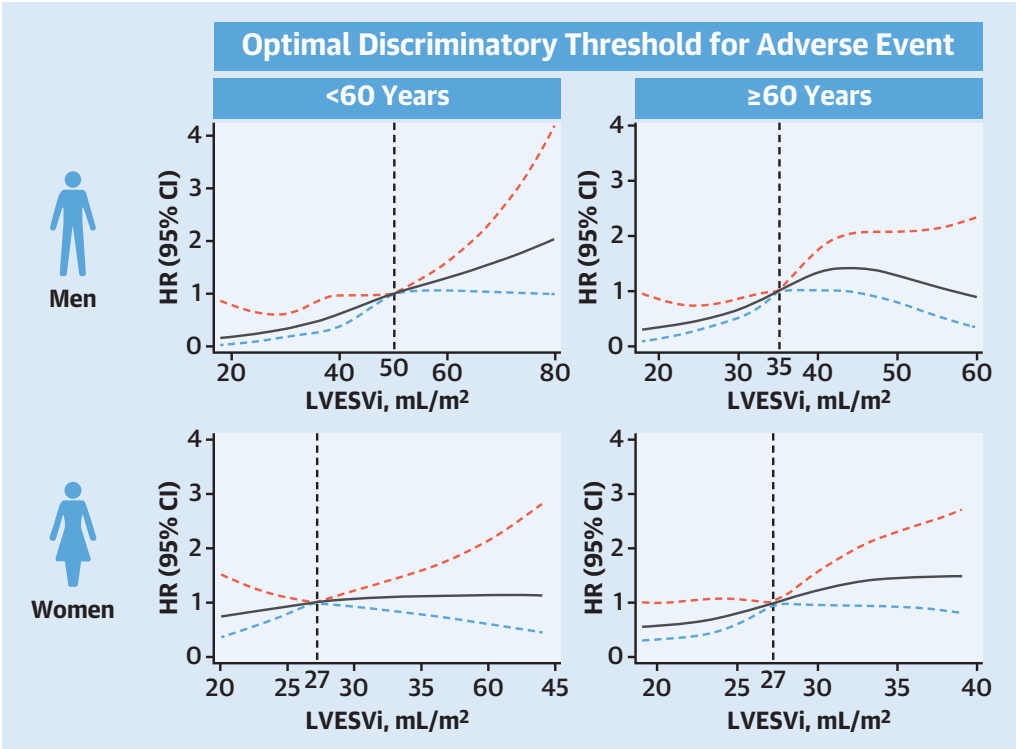
invariably lead to decreasing LV volume with age and,[18] subsequently, a reduced ability of the LV to adapt to change in loading conditions. With respect to sex differences, women generally have smaller LV volumes than men despite indexing to BSA.[22] Also, with increasing age, there is progressive myocyte loss in men but less so in women.[4,24] This, in addition to the differences in cardiac workload, may explain why

CENTRAL ILLUSTRATION Age and Sex Effect on Remodeling and Outcomes in Aortic Regurgitation

• 525 Patients with severe aortic regurgitation
• Median echocardiogram follow-up of 2.0 years (IQR: 1.0-3.6 years)



• Older patients maintained smaller LV volumes compared to younger patients
• Women maintained smaller LV volumes compared to men



• Rate of adverse events significantly increased at a lower LV volume threshold in older men compared to younger men
• Rate of adverse events significantly increased at a lower LV volume threshold in women compared to men

Akintoye E, et al. J Am Coll Cardiol. 2023;81(15):1474-1487.

Despite indexing to body surface area, older patients and women with aortic regurgitation (AR) consistently maintained smaller left ventricular (LV) volumes than younger patients and men, respectively, and the optimal discriminatory thresholds above which the rate of adverse events significantly increase was lower in older patients and women. LVESVi = left ventricular end-systolic volume index.

men respond to chronic volume overload by significant LV dilatation compared with women, who tend to have blunted progression in LV dilation.[25,26] A plausible contributory mechanism to the sex difference includes the effect of sex hormones. For example, estrogen has a direct effect on myocardial cells and fibroblasts and modulates the expression of some myocardial genes and,[27,28] therefore, may regulate the degree and pattern of LV remodeling and interstitial fibrosis in response to AR.

Although prior reports indicate decreasing LV volume with age,[17,18] there is lack of evidence of the impact of age on longitudinal LV remodeling in the setting of AR. Thus, our study provides the first evidence, to the best of our knowledge, that the apparent difference in LV volume between younger and older patients persists over time in the setting of AR. With respect to sex, a few studies have reported on sex differences in LV remodeling in the setting of AR based on cross-sectional analysis between LV volume and AR severity grade. In 270 patients with chronic AR, Kammerlander et al[20] showed that LV remodeling is common in men but not in women. A similar finding was reported in a recent cardiovascular magnetic resonance (CMR) study of 243 patients by Tower-Rader et al[26] where women were shown to have smaller LV volumes and blunted progression in LV dilation in the setting of AR. Extending on the results of these prior studies, we provide the first longitudinal analysis of the impact of age and sex on the degree of LV remodeling over a relatively long time period in patients with AR. Notably, despite indexing to BSA, women and older patients with AR persistently maintained smaller LV volumes than men and younger patients, respectively, on serial evaluation.

On the other hand, older patients and women under surveillance for chronic AR experience disproportionally higher rates of adverse events compared with younger patients and men, respectively. Prior reports of chronic AR patients under surveillance revealed that the incidence of cardiovascular death significantly increases with increasing age,[29] and women have a significantly higher risk of adverse events,[20] including a 20% to 40% higher risk of mortality, than men.[30,31] These observations are consistent with our findings of higher risk of adverse events in older patients and women despite adjusting for multiple traditional risk factors. Notably, the mortality rate was 14.4% in older patients compared with 3.5% in younger patients, and 12.6% in women compared with 6.9% in men in our cohort. This disparity in outcomes by age and sex may be explained in part by the use of the same criteria to inform intervention for all patients. For example, older adults have impaired myocardial relaxation and are more sensitive to the pressure and volume overload of AR and may develop a higher rate of adverse event with less amount of remodeling compared with younger patients. Currently, in the absence of symptoms or other Class I indications for surgery, treatment guidelines recommend the use of the same linear dimensions to inform intervention in all patients.[7] Not only do these linear dimensions fail to account for the complex LV geometric change caused by remodeling, but the use of the same dimension threshold for all ages and sexes despite differences in the degree of LV remodeling may also lead to late referral for intervention in older patients and women. Prior reports have proposed an LVESVi threshold of 40 to 45 mL/m^2 as the optimal volume threshold for intervention.[14-16] Our analysis extends on the reports of these studies in 2 ways. First, we showed that volumetric assessment is superior to linear dimensions for prognostication. Second, we showed that the optimal discriminatory volume threshold for prognostication varies by sex, and the effect of age was more evident among men only. The magnitude of the threshold was highest for young men, intermediate for older men, and lowest for women. For example, the optimal LVESVi threshold was 50 mL/m^2 (95% CI: 43-57 mL/m^2) for young men, 35 mL/m^2 (95% CI: 31-39 mL/m^2) for older men, and 27 mL/m^2 (95% CI: 24-30 mL/m^2) for women. Our study therefore underscores the need for an age- and sex-specific LV volume threshold for timing of AR intervention.

STUDY LIMITATIONS. First, this is a single-center observational study. However, our results are consistent with prior experimental and other observational studies. In addition, we expand on these prior reports using longitudinal evaluation and providing age-specific and sex-specific LV volume thresholds. There is a need for external validation of our findings in other cohorts. Second, follow-up echocardiography was not available at every time point for each patient. To account for the unbalanced data during analysis, we used an unstructured matrix and robust variance. Third, we included AR caused by multiple etiologies, and some of these etiologies (eg, bicuspid AV) may differ by age and/or sex. To limit the potential bias by etiology, we performed a model-based adjustment for etiology in all of our multivariable analyses. Last, the mean age at presentation was slightly higher (by only 4 years) in women compared with men in our cohort. However, this is unlikely to

explain the difference in adverse events between the 2 groups because women naturally have greater life expectancy than men and we also adjusted for the effect of age in our analyses.

CONCLUSIONS

Independent of BSA, older patients and women with significant AR maintain smaller LV volumes than younger patients and men, respectively, on serial evaluation. In addition, they have lower LV volume thresholds above which the rate of adverse events significantly increases. Our results suggest that the use of a singular LV threshold for intervention may lead to delayed referral and disproportionately worse outcomes in older patients and women. Hence, age-specific and sex-specific LV volume thresholds should be considered for timing of AR intervention to address disparity in outcomes. Future studies to evaluate surgical outcomes based on these newly derived thresholds are warranted.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Older patients and women with chronic AR have smaller LV volumes indexed to BSA than younger patients and men, respectively. The incidence of adverse events rises at lower LV volume thresholds in women than men, and in older men compared with younger men.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to determine whether AV intervention is beneficial at lower LV volume thresholds for women than men and for older men compared with younger men with asymptomatic, chronic, severe AR.

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