Novel imaging insights into cardiac remodeling, myocardial function and risk stratification in cardiovascular disease

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Prognostic implications of left atrial dilation in aortic regurgitation due to bicuspid aortic valve

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ABSTRACT

Aim

The prognostic value of left atrial volume index (LAVI) in patients with moderate to severe aortic regurgitation (AR) and bicuspid aortic valve (BAV) has not been explored. Left atrial (LA) dilation may reflect subclinical left ventricular (LV) fibrosis, chronically impaired LV diastolic function or reduced LV compliance secondary to significant AR.

Methods

A total of 554 individuals (45 [IQR 33-57] years, 80% male) with BAV and moderate or severe AR were selected from an international, multicenter registry of patients with BAV. Cox proportional hazards regression analyses were performed to investigate the association between LAVI and the combined endpoint of all-cause mortality or aortic valve surgery.

Results

Dilated LAVI was observed in 181 (32.7%) patients. The mean indexed aortic annulus, sinus of Valsalva, sinotubular junction and ascending aorta diameters were 13.0 mm/m^2 (±2.0), 19.4 mm/m^2 (±3.7), 16.5 mm/m^2 (±3.8) and 20.4 mm/m^2 (±4.5), respectively. After a median follow-up of 23 (4-82) months, 272 patients underwent aortic valve surgery (89%) or died (11%). When compared to patients with normal LAVI (<35 ml/m^2), those with a dilated LAVI (≥ 35 ml/m^2) had significantly higher rates of aortic valve surgery or mortality (43% and 60% vs 23% and 36%, at 1- and 5-years of follow-up respectively, p<0.001). Dilated LAVI was independently associated with reduced event-free survival (HR=1.450, 95% CI 1.085-1.938, p=0.012) after adjustment for LV ejection fraction, aortic root diameter, LV end-diastolic diameter and LV end-systolic diameter.

Conclusions

In this large, multicenter registry of patients with BAV and moderate to severe AR, LA dilation was independently associated with reduced event-free survival. The role of this parameter for the risk stratification of individuals with significant AR merits further investigation.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common type of congenital heart disease, present in 0.5 to 1.3% of the overall population[1,2]. Compared to the general population, patients with BAV are significantly more likely to be diagnosed with aortic regurgitation (AR) or aortic stenosis, with approximately 13 to 30% demonstrating moderate or severe AR on echocardiography, a complication frequently requiring surgical intervention[3]. Deciding when to intervene is crucial for patients with AR, as inappropriate delays may lead to irreversible left ventricular (LV) remodeling and dysfunction, with poor long-term post-surgical outcome[4-6].

Left atrial (LA) dilation has been demonstrated to be an important marker of prognosis in aortic stenosis [7 8], and may reflect the cumulative effects of subclinical LV fibrosis, chronically impaired LV diastolic function or reduced LV compliance in those with significant AR[9,10]. However, there has been limited investigation of the epidemiology and prognostic significance of LA dilation in the AR population, especially for those with BAV. Although the pathophysiological mechanism has not yet been elucidated, several studies have demonstrated that LV diastolic dysfunction may be more prevalent in those with BAV when compared to those with a tricuspid aortic valve[11,12], and therefore, evaluation of LA size may be particularly pertinent for those with BAV.

LA volume index (LAVI) is the most accurate measurement of the LA size and is recommended by current guidelines[13]. However, most of the previous epidemiological studies on AR have only reported on LA diameter rather than LAVI[7], and did not focus on its prognostic relevance or potential utility for risk stratification. Accordingly, the aim of this study was to (i) determine the prevalence of LA dilation in patients with significant AR due to BAV, and (ii) to investigate the association between LAVI and long-term prognosis.

METHODS

Study population

Patients with BAV and moderate or severe AR referred for echocardiography from June 1, 1991, through February 6, 2017 were selected from a large, international, multicenter registry[14]. Patients with previous aortic valve surgery, infectious endocarditis and incomplete follow-up were excluded. Baseline clinical (dyslipidemia, diabetes, hypertension, and smoking history) and demographic data (including age, sex, height, weight, and body surface area calculated by the Mosteller method[15]) were collected from medical records at the time of transthoracic echocardiography. Data were collected according to regulations approved by the institutional review boards of each center. As this study involved the retrospective analysis of clinically acquired data, the institutional review board of each center waived the need for written patient informed consent. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Echocardiography

All echocardiographic images were acquired using commercially available ultrasound systems. Experienced observers from each center retrospectively analyzed the acquired images, with the first echocardiographic study confirming a diagnosis of BAV considered as the index study. Standardized parasternal, apical, subcostal and suprasternal views were used to evaluate the morphology of the aortic valve. BAV morphology was defined according to the classification system proposed by Sievers and Schmidtke[16]. AR severity was graded according to contemporary recommendations as none, mild, moderate or severe, using a multiparametric integrative approach according to the AR vena contracta width, pressure half-time of the regurgitant jet and AR jet width[17]. Aortic stenosis severity was graded as none, mild, moderate or severe according to peak aortic jet velocity, mean pressure gradient and aortic valve area[18]. The severity of mitral regurgitation was graded as none, mild, moderate or severe using a multiparametric approach, according to contemporary recommendations[17]. The dimensions of the sinus of Valsalva, sinotubular junction and ascending aorta were measured from leading edge to leading edge on the parasternal long-axis view, perpendicular to the center of the aorta in end-diastole, while the aortic annulus was measured from inner edge to inner edge[13]. LV ejection fraction was calculated using the biplane Simpson method, while LV end-diastolic diameter, LV end-systolic diameter and LV mass were calculated using the standard linear 2-dimensional approach[13]. LA volume was calculated from apical 2 and 4 chamber views using the Simpson method, and was indexed for body surface area[13]. LA dilation was defined as a LAVI of 35 ml/m^2 or greater[13]. LA dilation was further classified as mildly dilated (35-41 ml/m^2), moderately dilated (42-48 ml/m^2) or severely dilated (>48 ml/m^2) according to guideline recommendations[13]. LV hypertrophy was defined by a LV mass index >95 g/m^2 in women and >115 g/m^2 in men. All other standard measurements were performed according to the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines[13].

Follow-up

The primary endpoint of this study was a composite of aortic valve repair or replacement and all-cause mortality. Aortic valve surgery indications were based on contemporary guidelines[19,20]. Patients with symptomatic severe aortic valve dysfunction or asymptomatic severe aortic valve dysfunction with reduced LV ejection fraction (≤50%) or aortic root/aortic dilation were referred for aortic valve surgery. Follow-up began from the date of the first echocardiogram confirming a diagnosis of BAV and moderate to severe AR, with censoring applied at the time of aortic valve replacement or death (whichever came first). Data of all patients were included up to the last date of follow-up.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical analysis

Categorical variables are expressed as numbers and percentages and were compared using the Pearson χ^2 test. Adherence to a normal distribution was verified using visual assessment of histograms. Normally distributed continuous variables are presented as mean ± standard deviation while variables that are non-normally distributed are presented as median and interquartile range. Continuous variables were compared using the Student *t*-test if normally distributed, whereas the Mann-Whitney *U*-test was utilized for non-normally distributed variables. To investigate the hazard ratio (HR) change for the combined endpoint of aortic valve surgery and all-cause mortality across a range of LAVI values (as a continuous variable), a spline curve was fitted. A threshold of LAVI to dichotomize the population was defined from the spline curve (i.e. when the predicted HR was ≥ 1) and existing literature[13]. Cumulative survival rates were estimated by the Kaplan-Meier method for the combined endpoint, and the log-rank test was used to compare groups. Univariable and multivariable Cox proportional hazards regression analyses were performed to investigate the association between clinical and echocardiographic parameters and the combined endpoint of all-cause mortality or aortic valve repair/replacement. Variables with a univariable value of $p < 0.05$ were incorporated into the multivariable models. Two additional sensitivity analyses were performed, to evaluate the relationship between LAVI and the combined endpoint with the exclusion of patients who underwent surgery within 90 days of the index echocardiogram, and to investigate the association between LAVI and all-cause mortality. Finally, to account for missing data, separate sensitivity analyses were conducted using multiple imputations by predictive mean matching (using a chained-equation approach), generating 100 imputed datasets. The HR and 95% confidence intervals (CI) were calculated and reported. The proportional hazards assumption was verified through the evaluation of scaled Schoenfeld residuals. All tests were two-sided and p-values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, New York) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Clinical characteristics

A total of 554 patients (80% male) of a median age of 45 years (interquartile range 33 to 57 years) fulfilled the inclusion criteria (Figure 1). Severe AR was present in 196 (35%) patients, while 358 (65%) had moderate AR. Spline curve analysis was performed to evaluate the relationship between LAVI and the combined endpoint of all-cause mortality and aortic valve surgery (Figure 2). Following a plateau and minimal increase in HR, the HR increased markedly with higher values of LAVI (≥35 ml/m^2). Therefore, based on the spline curve analysis and the American Society of Echocardiography recommendations [13], a cut-off value of 35 ml/m^2 for LAVI was used to define a dilated LA and to dichotomize the population. By this definition, a total of 181 patients (32.7%) had a dilated LA, with 79 (43.6%) classified as mildly dilated, 36 (19.9%) classified as moderately dilated, and 66 (36.5%) classified as severely dilated, according to guideline definitions[13]. Those with a dilated LA were older, more likely to be male and more frequently had coronary artery disease. There was no significant difference between BAV morphology when comparing those with a dilated LA to those with a normal LA size. The clinical and demographic characteristics of the overall population and according to LAVI are presented in Table 1.

Table 1: Clinical and demographic characteristics

Variable	Total Population (n=554)	LAVI <35 ml/m^2 (n=373)	LAVI ≥35 ml/m^2 (n=181)	p value
Age, years	45 (33-57)	43 (31-56)	51 (41-61)	<0.001
Male sex (%)	445 (80.3)	286 (76.7)	159 (87.8)	0.002
Hypertension (%)	171 (31.7)	118 (32.3)	53 (30.5)	0.663
Dyslipidemia (%)	118 (21.3)	82 (22.0)	36 (19.9)	0.572
DM (%)	36 (6.5)	24 (6.4)	12 (6.6)	0.930
CAD (%)	45 (8.5)	22 (6.2)	23 (13.2)	0.007
Current smoker (%)	100 (18.1)	72 (19.3)	28 (15.5)	0.271
Atrial fibrillation (%)	25 (4.5)	9 (2.4)	16 (8.9)	0.001
BAV morphology				0.708
No raphe (%)	55 (9.9)	35 (9.4)	20 (11.0)	
Type 1 raphe (L-R), (%)	383 (69.1)	258 (69.2)	125 (69.1)	
Type 1 raphe (R-N), (%)	94 (17.0)	63 (16.9)	31 (17.1)	
Type 1 raphe (L-N), (%)	19 (3.4)	14 (3.8)	5 (2.8)	
Type 2 raphe, (%)	3 (0.5)	3 (0.8)	0 (0.0)	

Values are presented as mean ± SD, median (IQR) or n (%).
CAD = coronary artery disease; DM = diabetes mellitus; LAVI = left atrial volume index; L-N = left – non-coronary; L-R = left – right; R-N = right – non-coronary.

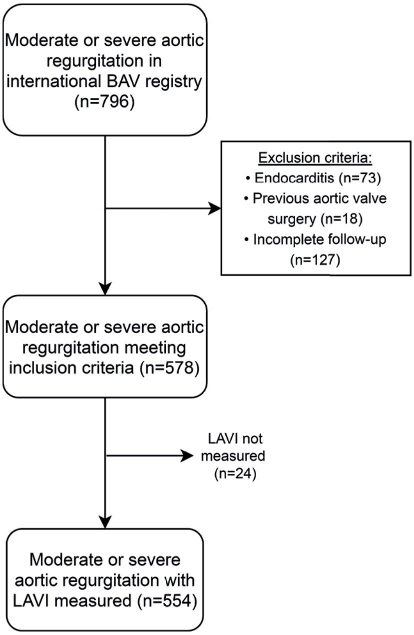

Figure 1: Study flow chart. BAV = bicuspid aortic valve; LAVI = left atrial volume index

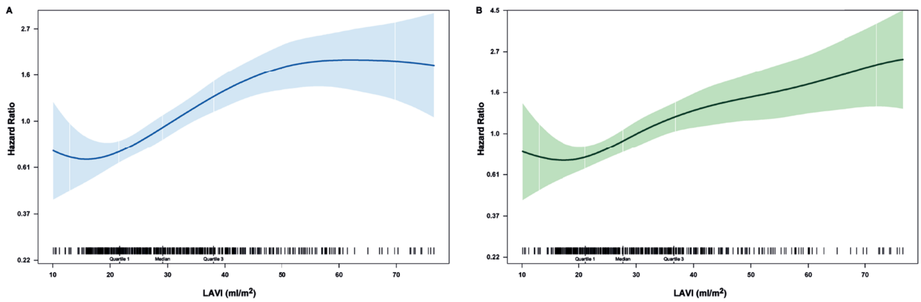

Figure 2: Spline curves for event-free survival according to LAVI for the total population (A, blue) and with those undergoing surgery in the first 90 days excluded (B, green). The curves represent the hazard ratio change for all-cause mortality with overlaid 95% confidence intervals (shaded areas) across a range of LAVI at the time of first echocardiogram. The ticks beneath the curves demonstrate the distribution of the study population according to values of LAVI.
LAVI = left atrial volume index

Echocardiographic characteristics

Patients with a dilated LA had significantly larger LV dimensions and LV mass, lower LV ejection fraction, and more frequently had significant mitral regurgitation when compared to those with normal LAVI. Additionally, those with dilated LA more frequently had concomitant moderate to severe aortic stenosis and a larger AR vena contracta width when compared to the group with normal LAVI. Table 2 summarizes the echocardiographic characteristics of the study population. The variables independently associated with LA dilation are presented in supplemental table S1.

Table 2: Echocardiographic characteristics

Variable	Total Population (n=554)	LAVI <35 ml/m^2 (n=373)	LAVI ≥35 ml/m^2 (n=181)	p value
Left ventricle and atrium				
LV EDD, mm	57 (±9)	56 (±9)	60 (±10)	<0.001
LV ESD, mm	39 (±10)	37 (±9)	42 (± 11)	<0.001
LV EDV, ml	156 (126-199)	148 (120-187)	167 (135-222)	<0.001
LV EF, %	58.9 (±12.9)	60.3 (±11.6)	56.1 (±15.0)	0.001
LV mass indexed, g/m^2	132 (105-170)	124 (99-160)	154 (119-195)	<0.001
LA volume indexed, ml/m^2	29.1 (21.5-38.0)	23.8 (19.6-29.3)	44.5 (38.2-55.0)	<0.001
Mitral inflow E velocity, m/s	0.78 (±0.25)	0.66 (±0.24)	0.80 (±0.29)	0.362
Mitral inflow E/A ratio	1.18 (0.86-1.60)	1.28 (0.88-1.60)	1.33 (±0.72)	0.357
Moderate or severe MR, %	46 (8.3)	17 (4.6)	29 (16.0)	<0.001
Aortic valve and aortic root				
Aortic annulus diameter indexed, mm /m^2	13.0 (±2.0)	13.1 (±2.0)	12.7 (±1.9)	0.031
SOV diameter indexed, mm / m^2	19.4 (±3.7)	19.6 (±3.8)	18.9 (±3.5)	0.293
STJ diameter indexed, mm / m^2	16.5 (±3.8)	16.5 (±3.9)	16.4 (±3.6)	0.853
Ascending aorta diameter indexed, mm / m^2	20.4 (±4.5)	20.6 (±4.5)	20.0 (±4.4)	0.230
Presence of raphe	499 (90.1)	338 (90.6)	161 (89.0)	0.538
No AS (%)	306 (55.2)	209 (56.0)	97 (53.6)	0.084
Mild AS (%)	91 (16.4)	69 (18.5)	22 (12.2)	
Moderate AS (%)	87 (15.7)	54 (14.5)	33 (18.2)	
Severe AS (%)	70 (12.6)	41 (11.0)	29 (16.0)	
Moderate-severe AS (%)	157 (28.3)	95 (25.5)	62 (34.4)	0.031
Pressure-half time, ms	425 (±170)	434 (±170)	407 (±167)	0.100
Vena-contracta width, mm	6.0 (4.6-7.0)	5.5 (4.0-7.0)	6.0 (5.0-8.0)	0.006

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; EDD = end-diastolic diameter; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic diameter; LA = left atrial; LV = left ventricular; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction

Survival Analysis

After a median follow-up of 23 months (interquartile range, 4 to 82 months), 272 (49%) had died or undergone aortic valve surgery. Of the 272 events that were recorded during patient follow-up, 243 (89%) were due to aortic valve surgery, while 29 (11%) were due to all-cause mortality. A total of 138 patients underwent concomitant aortic root surgery. The cumulative 1- and 5- year surgery-free survival rates were 70% and 56% respectively. Patients with a dilated LA (≥35 ml/m^2) had significantly higher rates of aortic valve surgery or mortality when compared to patients with normal LAVI (43% and 60% vs 23% and 36%, at 1- and 5-years of follow-up respectively, p<0.001) (Figure 3A, Figure 3B).

To further evaluate the relationship between LAVI and the combined endpoint of aortic valve surgery and mortality, a multivariable Cox proportional hazards model was constructed (Table 3). LV end-systolic diameter ≥50 mm, LV end-diastolic diameter ≥70 mm and aortic root/ascending aorta diameter ≥50 mm were introduced as categorical variables, reflecting current guideline indications for surgical intervention in AR [20 21]. Additionally, LAVI was introduced as a categorical variable, utilizing the threshold derived from spline curve analysis (≥35 ml/m^2). Univariable analysis demonstrated that age, hypertension, LV ejection fraction, LV hypertrophy, LV end-systolic diameter, LV end-diastolic diameter, aortic root/ascending aorta diameter, moderate or severe aortic stenosis, mitral inflow E/A ratio, AR pressure half-time, AR vena contracta width and LAVI were significantly associated with the endpoint of aortic valve surgery or mortality. On multivariable Cox regression analysis, LA dilation (≥35 ml/m^2) remained independently associated with the combined endpoint despite adjustment for important confounders and contemporary indications for aortic valve surgery. Furthermore, the following variables also retained an independent association with the combined endpoint: age, LV hypertrophy, aortic root/ascending aorta diameter, moderate or severe aortic stenosis and AR vena contracta width.

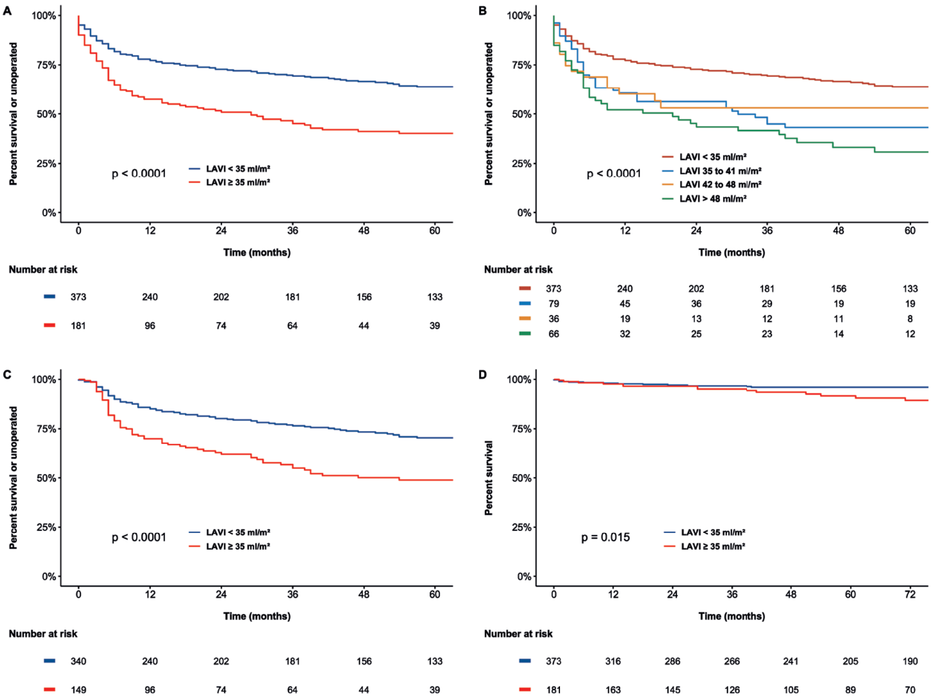

Figure 3: Kaplan-Meier curves for the combined endpoint of event-free survival and for all-cause mortality. Panel A demonstrates the Kaplan Meier curve for the combined endpoint of event-free survival for the total population at a cut-off of LAVI of 35 ml/m^2. Panel B shows the Kaplan Meier curve for the combined endpoint of event-free survival with the population stratified according to normal, mildly, moderately and severely dilated LAVI, while panel C shows the survival curves with those undergoing surgery in the first 90 days excluded. Panel D demonstrates a Kaplan Meier curve for the endpoint of all-cause mortality for the total population at a cut-off of 35 ml/m^2 (D).
LAVI = left atrial volume index

Table 3: Univariable and multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality

	Univariate analysis		Multivariable analysis*	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.029 (1.021-1.037)	<0.001	1.029 (1.017-1.040)	<0.001
Male sex	1.140 (0.844-1.541)	0.386		
Current smoker	1.292 (0.959-1.742)	0.093		
Hypertension	1.315 (1.024-1.688)	0.032	0.889 (0.650-1.217)	0.464
Dyslipidemia	1.233 (0.930-1.633)	0.145		
DM	1.119 (0.760-1.892)	0.436		
CAD	1.696 (1.120-2.569)	0.013	1.373 (0.791-2.380)	0.260
Atrial fibrillation	1.375 (0.829-2.280)	0.216		
Echocardiographic characteristics				
LVEF, %	0.977 (0.968-0.987)	<0.001	0.991 (0.978-1.005)	0.214
LVESD > 50 mm	2.502 (1.758-3.560)	<0.001	1.513 (0.793-2.888)	0.209
LVEDD > 70 mm	2.510 (1.716-3.671)	<0.001	1.353 (0.734-2.496)	0.333
Aortic root or ascending aorta > 50 mm	3.567 (2.445-5.203)	<0.001	3.834 (2.422-6.071)	<0.001
LV hypertrophy	2.378 (1.694-3.339)	<0.001	1.499 (1.017-2.208)	0.041
Moderate or severe MR	1.321 (0.897-1.946)	0.159		
Moderate or severe AS	1.771 (1.386-2.262)	<0.001	2.232 (1.650-3.018)	<0.001
Mitral inflow E/A ratio	0.744 (0.585-0.948)	0.017	1.119 (0.853-1.468)	0.415
VC width, mm	1.127 (1.085-1.171)	<0.001	1.113 (1.063-1.165)	<0.001
LAVI ≥ 35 ml / m^2	1.927 (1.514-2.454)	<0.001	1.450 (1.085-1.938)	0.012

*Due to missing data, 450 patients were included in the multivariable analysis. A sensitivity analysis with imputed data can be found in the supplementary material.
AS = aortic stenosis; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

In addition, to reduce the impact of referral bias and to account for the presence of symptoms and LV ejection fraction <50% at the time of first echocardiogram on the decision to perform surgery, all data were reanalyzed following the exclusion of 65 patients who had surgery within 90 days of the index echocardiogram. A spline curve demonstrated a similar relationship between LAVI and the study endpoint in this cohort (Figure 2B). In accordance with the prior analysis, patients with a LAVI ≥35 ml/m^2 had significantly higher rates of aortic valve surgery or mortality when compared to patients with normal LAVI (30% and 51% vs 15% and 30%, at 1- and 5-years of follow-up respectively, p<0.001) over a median follow-up period of 36 months (interquartile range, 7 to 96 months) (Figure 3C). Furthermore, on multivariable Cox regression analysis, LA dilation remained independently associated with the combined endpoint of aortic valve surgery and mortality, in addition to age, aortic root/ascending aorta diameter, moderate or severe aortic stenosis and AR vena contracta width (Table 4).

Sensitivity analyses were performed to include significant mitral regurgitation (Table S2) and LVEF as dichotomous variable (<50% vs ≥50%; Table S3) as covariates in both multivariable models, demonstrating similar results to the primary analyses. Furthermore, LA dilation was independently associated with mortality after multiple imputation of missing data (Table S4), consistent with the main analyses. In addition, a sensitivity analysis considering only all-cause mortality as the endpoint was performed, and confirmed the prognostic significance of LA dilation (Table S5). After a median follow-up of 65 months (interquartile range, 29 to 128 months), 41 patients died. Patients with LAVI ≥35 ml/m^2 experienced significantly higher rates of mortality compared to those with normal LAVI at 5 years of follow-up (8.3% vs 4.1%, p=0.015) (Figure 3D).

Table 4: Univariable and multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality with exclusion of those undergoing surgery in the first 90 days

	Univariate analysis		**Multivariable analysis***	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Patient demographics and comorbidities				
Age	1.031 (1.022-1.040)	<0.001	1.031 (1.018-1.044)	<0.001
Male sex	1.164 (0.826-1.640)	0.385		
Current smoker	1.185 (0.829-1.692)	0.352		
Hypertension	1.504 (1.133-1.995)	0.005	1.046 (0.736-1.487)	0.804
Dyslipidemia	1.314 (0.954-1.810)	0.095		
DM	1.479 (0.911-2.403)	0.114		
CAD	1.380 (0.798-2.384)	0.249		
Atrial fibrillation	1.550 (0.883-2.723)	0.127		
LVEF, %	0.978 (0.968-0.989)	<0.001	0.995 (0.979-1.011)	0.525
LVESD > 50 mm	2.527 (1.653-3.862)	<0.001	1.657 (0.796-3.450)	0.177
LVEDD > 70 mm	2.717 (1.735-4.257)	<0.001	1.596 (0.802-3.176)	0.183
Aortic root or ascending aorta > 50 mm	2.406 (1.395-4.419)	0.002	2.134 (1.069-4.258)	0.032
LV hypertrophy	2.283 (1.559-3.344)	<0.001	1.277 (0.832-1.961)	0.263
Moderate or severe MR	1.313 (0.841-2.050)	0.231		
Moderate or severe AS	1.646 (1.238-2.188)	0.001	2.128 (1.507-3.005)	<0.001
Mitral inflow E/A ratio	0.597 (0.443-0.804)	0.001	1.007 (0.720-1.408)	0.967
VC width, mm	1.142 (1.090-1.196)	<0.001	1.138 (1.080-1.201)	<0.001
LAVI ≥ 35 ml / ^{m}2	1.901 (1.439-2.512)	<0.001	1.534 (1.104-2.131)	0.011

*Due to missing data, 404 patients were included in the multivariable analysis. A sensitivity analysis with imputed data can be found in the supplementary material.

AS = aortic stenosis; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

DISCUSSION

In this large, international multicenter registry of 554 patients with BAV and moderate or severe AR, the prevalence of LA dilation (LAVI ≥35 ml/m^2) was 33%. LA dilation at the time of index echocardiogram was associated with reduced event-free survival following adjustment for contemporary indications for aortic valve surgery and other important confounders. Importantly, this independent association remained after excluding patients who underwent surgery within the first 90 days to avoid referral bias.

Prevalence and pathogenesis of LA dilation in significant AR

This study reveals that LA dilation is common in patients with significant AR and BAV, with one-third demonstrating a LAVI ≥35 ml/m^2. In a study including 372 patients undergoing surgery for aortic regurgitation of a variety of etiologies, LA dilation (defined as an indexed LA diameter ≥23 mm/m^2) was present in 28% of individuals[7], similar to the findings of the present study.

In significant AR, the pathogenesis of LA dilation is highly complex. Initially, the aortic regurgitant jet results in a combination of pressure and volume overload, with higher LV diastolic and systolic wall stress, and dramatic increases in LV volumes and mass[22]. With progressive increases in LV afterload and disturbed coronary flow dynamics, supply-demand mismatch may result, leading to LV myocardial ischemia and potentially, myocardial fibrosis[23,24]. In addition, progressive LV remodeling may result in papillary muscle displacement, tethering of the mitral valve leaflets and a reduction in mitral valve closing forces, leading to secondary mitral regurgitation[25]. Therefore, LA dilation in AR may be the common consequence of several mechanisms, including any one or combination of: secondary mitral regurgitation, chronically impaired LV diastolic function or LV fibrosis and reduced LV compliance[26]. Moreover, compared to other parameters of LV diastolic function (such as mitral inflow E wave velocity and tricuspid regurgitant jet velocity), LA volume may more accurately reflect the cumulative effects of chronically elevated LV filling pressures and LV diastolic dysfunction[9], providing further insight into the pathophysiological status of the LV in individuals with AR. For example, in a study of 54 patients with severe AR, only post-operative LA dilation was independently associated with persistent LV systolic dysfunction at 1 year following surgery in individuals with early postoperative LV systolic dysfunction[27], reflecting the important insight that LA size provides into LV function.

LA dilation as a correlate of event-free survival in significant AR

In the present study, LA dilation was significantly associated with a reduction in event-free survival following adjustment for contemporary indications for aortic valve surgery and clinically important covariates. While previous studies have not investigated the association of LA dilation and the need for future aortic valve surgery in patients with significant AR, inferences can be made from several studies that have identified an association between LA dilation and the development of symptoms (a class I indication for aortic valve surgery)[19, 28, 29]. The presence of LA dilation may identify individuals who have worse subclinical LV diastolic function and are more likely to develop symptoms, thus requiring surgical intervention. However, this study was not designed to investigate the relationship between LA dilatation and diastolic dysfunction.

Consistent with previous literature, the present study also demonstrated a significant increase in all-cause mortality for those with LA dilation compared to those without LA dilation. Previously, in an unadjusted sub-group analysis of 372 patients with significant AR, Mosquera et al. demonstrated that increasing indexed LA diameter on pre-surgical echocardiography was significantly associated with future cardiovascular mortality[7]. Likewise, in another smaller study, a sub-group analysis of 41 patients with AR demonstrated that a LAVI ≥35 ml/m^2 on pre-surgical echocardiography was associated with long-term adverse cardiovascular outcome[30]. However, thus far, no study has demonstrated the independent prognostic impact of LA dilation. Therefore, the potential usefulness of this parameter for risk stratification in AR has remained unclear. The current study demonstrates that LA dilation is independently associated with reduced event-free survival in patients with significant AR and BAV, likely reflecting subclinical LV dysfunction and an increased propensity for the development of symptoms in the future.

Clinical implications and future directions

The present study has demonstrated that LA dilation is common and is independently associated with event-free survival in those with significant AR and BAV. Indeed, LA dilation probably anticipates the onset of symptoms, which currently represents the main indication for surgery in patients with severe AR[19]. However, symptoms or the reduction of LV ejection fraction may represent late markers of LV damage secondary to AR, and the optimal timing for surgical intervention may have passed[22]. The presence of LA dilation in significant AR may also identify patients at increased risk of persistent LV dysfunction and poorer long-term outcome following surgery[7, 27]. For example, a LAVI ≥35 ml/m^2 may be present in patients prior to significant changes in LV dimensions, and may be used to identify those who would benefit from surgery earlier than current guideline recommendations [20, 21]. Additionally, it is possible that LAVI could be integrated into a scoring system with LV ejection fraction, LV end-systolic diameter and LV end-diastolic diameter to identify patients who would benefit from earlier surgical intervention than contemporary guideline recommendations. Furthermore, because LAVI is simple to measure and is widely reported as a standard parameter, integration into clinical workflow would be effortless.

Limitations

This study is subject to all of the limitations associated with a retrospective, observational design. Consequently, the findings of this study are hypothesis generating only, with randomized clinical trials required to determine if earlier surgery is justified in patients with severe AR and LA dilation. Additionally, guideline indications for surgery have changed over the period of the registry, with more contemporary guidelines incorporating LV dimensions into their recommendations, possibly influencing the results of this study. LA strain was not performed which may have provided additional prognostic information through the evaluation of LA function. Although only present in a small percentage of the population, atrial fibrillation rather than AR may have been the primary cause of a dilated LAVI in some patients. Likewise, the presence of concomitant aortic stenosis may also be a primary cause of LA dilation. Furthermore, despite additional analysis excluding patients who underwent surgery within three months of index echocardiography, it is still possible that referral bias and the presence of symptoms at baseline may have influenced the decision to perform surgery after this time period. In addition, remodeling of the LA and LV frequently occur following aortic valve surgery, and the prognostic significance of baseline values of LAVI may depend on an individual patient's response to future surgery.

CONCLUSION

In this large, multicenter registry of patients with BAV and significant AR, LA dilation was independently associated with reduced event-free survival following adjustment for contemporary indications for aortic valve surgery and other significant confounders. The role of this parameter for the risk stratification of individuals with significant AR merits further investigation.

REFERENCES

1. Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. Heart 2016;102(1):75-85. doi: 10.1136/heartjnl-2014-307020 [published Online First: 2015/11/07]
2. Michelena HI, Khanna AD, Mahoney D, et al. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA 2011;306(10):1104-12. doi: 10.1001/jama.2011.1286 [published Online First: 2011/09/16]
3. Masri A, Svensson LG, Griffin BP, et al. Contemporary natural history of bicuspid aortic valve disease: a systematic review. Heart 2017;103(17):1323-30. doi: 10.1136/heartjnl-2016-309916 [published Online First: 2017/05/12]
4. Bonow RO, Picone AL, McIntosh CL, et al. Survival and functional results after valve replacement for aortic regurgitation from 1976 to 1983: impact of preoperative left ventricular function. Circulation 1985;72(6):1244-56. doi: 10.1161/01.cir.72.6.1244 [published Online First: 1985/12/01]
5. Mentias A, Feng K, Alashi A, et al. Long-Term Outcomes in Patients With Aortic Regurgitation and Preserved Left Ventricular Ejection Fraction. J Am Coll Cardiol 2016;68(20):2144-53. doi: 10.1016/j.jacc.2016.08.045 [published Online First: 2016/11/20]
6. Tornos P, Sambola A, Permanyer-Miralda G, et al. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. J Am Coll Cardiol 2006;47(5):1012-7. doi: 10.1016/j.jacc.2005.10.049 [published Online First: 2006/03/07]
7. Mosquera VX, Bouzas-Mosquera A, Gonzalez-Barbeito M, et al. Indexed left atrial size predicts all-cause and cardiovascular mortality in patients undergoing aortic valve surgery. J Thorac Cardiovasc Surg 2017;153(6):1275-84 e7. doi: 10.1016/j.jtcvs.2017.01.054 [published Online First: 2017/03/16]
8. Beach JM, Mihaljevic T, Rajeswaran J, et al. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. J Thorac Cardiovasc Surg 2014;147(1):362-69 e8. doi: 10.1016/j.jtcvs.2012.12.016 [published Online First: 2013/01/15]
9. Pritchett AM, Mahoney DW, Jacobsen SJ, et al. Diastolic dysfunction and left atrial volume: a population-based study. J Am Coll Cardiol 2005;45(1):87-92. doi: 10.1016/j.jacc.2004.09.054 [published Online First: 2005/01/05]
10. Cayli M, Kanadasi M, Akpinar O, et al. Diastolic function predicts outcome after aortic valve replacement in patients with chronic severe aortic regurgitation. Clin Cardiol 2009;32(8):E19-23. doi: 10.1002/clc.20437 [published Online First: 2009/05/21]
11. Lee SY, Shim CY, Hong GR, et al. Association of aortic phenotypes and mechanical function with left ventricular diastolic function in subjects with normally functioning bicuspid aortic valves and comparison to subjects with tricuspid aortic valves. Am J Cardiol 2015;116(10):1547-54. doi: 10.1016/j.amjcard.2015.08.017 [published Online First: 2015/09/28]
12. Weismann CG, Lombardi KC, Grell BS, et al. Aortic stiffness and left ventricular diastolic function in children with well-functioning bicuspid aortic valves. Eur Heart J Cardiovasc Imaging 2016;17(2):225-30. doi: 10.1093/ehjci/jev151 [published Online First: 2015/06/16]
13. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003

14. Kong WK, Delgado V, Poh KK, et al. Prognostic Implications of Raphe in Bicuspid Aortic Valve Anatomy. JAMA Cardiol 2017;2(3):285-92. doi: 10.1001/jamacardio.2016.5228 [published Online First: 2017/01/05]
15. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317(17):1098. doi: 10.1056/NEJM198710223171717 [published Online First: 1987/10/22]
16. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133(5):1226-33. doi: 10.1016/j.jtcvs.2007.01.039 [published Online First: 2007/05/01]
17. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14(7):611-44. doi: 10.1093/ehjci/jet105 [published Online First: 2013/06/05]
18. Baumgartner HC, Hung JC-C, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2017;18(3):254-75. doi: 10.1093/ehjci/jew335 [published Online First: 2017/04/01]
19. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(22):2438-88. doi: 10.1016/j.jacc.2014.02.537 [published Online First: 2014/03/08]
20. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36):2739-91. doi: 10.1093/eurheartj/ehx391
21. Borger MA, Fedak PWM, Stephens EH, et al. The American Association for Thoracic Surgery consensus guidelines on bicuspid aortic valve-related aortopathy: Full online-only version. J Thorac Cardiovasc Surg 2018;156(2):e41-e74. doi: 10.1016/j.jtcvs.2018.02.115 [published Online First: 2018/07/18]
22. Popovic ZB, Desai MY, Griffin BP. Decision Making With Imaging in Asymptomatic Aortic Regurgitation. JACC Cardiovasc Imaging 2018;11(10):1499-513. doi: 10.1016/j.jcmg.2018.05.027 [published Online First: 2018/10/06]
23. Aksoy S, Cam N, Guney MR, et al. Myocardial Ischemia in Severe Aortic Regurgitation Despite Angiographically Normal Coronary Arteries. Tohoku J Exp Med 2012;226(1):69-73. doi: 10.1620/tjem.226.69
24. zevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010;56(4):278-87. doi: 10.1016/j.jacc.2009.12.074 [published Online First: 2010/07/17]
25. Regeer MV, Al Amri I, Versteegh MI, et al. Mitral valve geometry changes in patients with aortic regurgitation. J Am Soc Echocardiogr 2015;28(4):455-62. doi: 10.1016/j.echo.2015.01.009 [published Online First: 2015/02/14]
26. Tsang TSM, Barnes ME, Gersh BJ, et al. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. Am J Cardiol 2002;90(12):1284-89. doi: Pii S0002-9149(02)02864-3 [published Online First: 2002/12/14]
27. Cho IJ, Chang HJ, Hong GR, et al. Left atrial volume index as a predictor for persistent left ventricular dysfunction after aortic valve surgery in patients with chronic aortic regurgitation: the role of early postoperative echocardiography. Echocardiography 2015;32(6):896-903. doi: 10.1111/echo.12756 [published Online First: 2014/09/25]

28. Ma W, Zhang W, Shi W, et al. Left Ventricular Diastolic Function After Aortic Valve Replacement for Chronic Aortic Regurgitation. Ann Thorac Surg 2018;106(1):24-29. doi: 10.1016/j.athoracsur.2018.03.034 [published Online First: 2018/04/21]
29. Lee SY, Shim CY, Hong GR, et al. Determinants and Prognostic Significance of Symptomatic Status in Patients with Moderately Dysfunctional Bicuspid Aortic Valves. PLoS One 2017;12(1):e0169285. doi: 10.1371/journal.pone.0169285 [published Online First: 2017/01/07]
30. Lazzeroni D, Gaibazzi N, Bini M, et al. Prognostic value of new left atrial volume index severity partition cutoffs after cardiac rehabilitation program in patients undergoing cardiac surgery. Cardiovasc Ultrasound 2016;14(1):35. doi: 10.1186/s12947-016-0077-0 [published Online First: 2016/08/25]

SUPPLEMENTARY MATERIAL

Table S1: Univariable and multivariable logistic regression models evaluating clinical and echocardiographic parameters associated LA dilation (LAVI ≥ 35ml/m^2)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Patient demographics and comorbidities				
Age	1.025 (1.014-1.037)	<0.001	1.009 (0.996-1.023)	0.184
Male sex	2.199 (1.325-3.648)	0.002	1.808 (1.032-3.168)	0.038
Current smoker	0.830 (0.550-0.1252)	0.374		
Hypertension	0.917 (0.621-1.355)	0.663		
Dyslipidemia	0.881 (0.568-1.368)	0.572		
DM	1.033 (0.504-2.115)	0.930		
CAD	2.306 (1.246-4.266)	0.008	1.684 (0.801-3.541)	0.169
Atrial fibrillation	3.915 (1.695-9.046)	0.001	1.990 (0.737-5.376)	0.175
Echocardiographic characteristics				
LVEF, %	0.976 (0.962-0.989)	0.001	0.987 (0.971-1.004)	0.123
Aortic root or ascending aorta > 50 mm	0.720 (0.329-1.576)	0.411		
LV hypertrophy	2.920 (1.835-4.646)	<0.001	2.291 (1.358-3.864)	0.002
Moderate or severe MR	3.995 (2.132-7.487)	<0.001	2.756 (1.281-5.930)	0.009
Moderate or severe AS	1.525 (1.037-2.241)	0.032	1.299 (0.811-2.080)	1.299
Mitral inflow E/A ratio	1.175 (0.865-1.596)	0.303		
VC width, mm	1.124 (1.044-1.210)	0.002	1.087 (1.000-1.182)	0.050
LV stroke volume, ml	1.005 (1.000-1.010)	0.066		

AS = aortic stenosis; CAD = coronary artery disease; DM = diabetes mellitus; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S2: Multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality including significant mitral regurgitation as a covariate

	Total Population		Total population excluding those who underwent surgery in first 90 days	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.029 (1.017-1.040)	<0.001	1.031 (1.018-1.044)	<0.001
Hypertension	0.877 (0.641-1.201)	0.414	1.018 (0.715-1.451)	0.919
CAD	1.458 (0.838-2.537)	0.182		
Echocardiographic characteristics				
LVEF, %	0.989 (0.975-1.003)	0.136	0.993 (0.976-1.009)	0.377
LVESD > 50 mm	1.465 (0.766-2.801)	0.248	1.629 (0.779-3.406)	0.195
LVEDD > 70 mm	1.401 (0.756-2.596)	0.285	1.671 (0.829-3.367)	0.151
Aortic root or ascending aorta > 50 mm	3.729 (2.351-5.915)	<0.001	2.024 (1.008-4.062)	0.047
LV hypertrophy	1.508 (1.023-2.221)	0.038	1.291 (0.841-1.982)	0.243
Moderate or severe MR	0.729 (0.427-1.244)	0.247	0.691 (0.376-1.268)	0.232
Moderate or severe AS	2.257 (1.668-3.053)	<0.001	2.161 (1.528-3.056)	<0.001
Mitral inflow E/A ratio	1.096 (0.834-1.442)	0.511	0.981 (0.699-1.376)	0.911
VC width, mm	1.114 (1.065-1.165)	<0.001	1.140 (1.081-1.201)	<0.001
LAVI ≥ 35 ml / m^2	1.467 (1.098-1.962)	0.010	1.566 (1.125-2.178)	0.008

AS = aortic stenosis; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S3: Multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality including LVEF at a cut-off of 50% as a covariate

	Total Population		Total population excluding those who underwent surgery in first 90 days	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.030 (1.018-1.041)	<0.001	1.031 (1.018-1.044)	<0.001
Hypertension	0.889 (0.649-1.217)	0.462	1.039 (0.730-1.479)	0.832
CAD	1.356 (0.781-2.353)	0.280		
Echocardiographic characteristics				
LVEF < 50%	1.172 (0.762-1.803)	0.469	1.203 (0.728-1.987)	0.471
LVESD > 50 mm	1.659 (0.873-3.155)	0.122	1.633 (0.783-3.407)	0.191
LVEDD > 70 mm	1.334 (0.722-2.463)	0.357	1.601 (0.803-3.190)	0.181
Aortic root or ascending aorta > 50 mm	3.740 (2.347-5.960)	<0.001	2.053 (1.019-4.136)	0.044
LV hypertrophy	1.499 (1.018-2.209)	0.040	1.276 (0.832-1.959)	0.265
Moderate or severe AS	2.183 (1.618-2.946)	<0.001	2.110 (1.498-2.972)	<0.001
Mitral inflow E/A ratio	1.141 (0.871-1.495)	0.338	1.008 (0.722-1.408)	0.962
VC width, mm	1.111 (1.062-1.163)	<0.001	1.139 (1.080-1.201)	<0.001
LAVI ≥ 35 ml / m^2	1.464 (1.096-1.956)	0.010	1.545 (1.112-2.147)	0.010

AS = aortic stenosis; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S4: Multivariable Cox proportional hazard models for combined end-point of surgical intervention and all-cause mortality: sensitivity analysis after multiple imputation of missing data

	Total Population		Total population excluding those who underwent surgery in first 90 days	
	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities				
Age	1.025 (1.015-1.036)	<0.001	1.027 (1.015-1.039)	<0.001
Hypertension	0.899 (0.683-1.184)	0.450	0.993 (0.727-1.355)	0.964
CAD	0.984 (0.619-1.565)	0.946		
Echocardiographic characteristics				
LVEF	0.994 (0.980-1.007)	0.367	0.998 (0.983-1.013)	0.575
LVESD > 50 mm	1.311 (0.696-2.472)	0.402	1.304 (0.610-2.789)	0.494
LVEDD > 70 mm	1.160 (0.649-2.071)	0.617	1.225 (0.604-2.484)	0.575
Aortic root or ascending aorta > 50 mm	3.003 (1.983-4.548)	<0.001	1.542 (0.834-2.851)	0.168
LV hypertrophy	1.523 (1.066-2.178)	0.021	1.397 (0.937-2.083)	0.101
Moderate or severe AS	1.861 (1.429-2.423)	<0.001	1.791 (1.322-2.427)	<0.001
Mitral inflow E/A ratio	1.096 (0.834-1.441)	0.511	0.975 (0.705-1.350)	0.881
VC width, mm	1.101 (1.052-1.153)	<0.001	1.129 (1.069-1.193)	<0.001
LAVI ≥ 35 ml / m^2	1.449 (1.115-1.884)	0.006	1.519 (1.129-2.045)	0.006

AS = aortic stenosis; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; VC = vena contracta

Table S5: Univariable and multivariable Cox proportional hazard models for all-cause mortality.

	Univariable analysis		Multivariable model 1		Multivariable model 2	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Patient demographics and comorbidities						
Age	1.064 (1.040-1.088)	<0.001	1.054 (1.029-1.079)	<0.001	1.052 (1.027-1.078)	<0.001
Hypertension	2.265 (1.207-4.250)	0.011			1.374 (0.713-2.648)	0.342
DM	3.596 (1.633-7.919)	0.001	2.896 (1.270-6.601)	0.011		
CAD	4.386 (1.994-9.646)	<0.001			2.117 (0.916-4.895)	0.079
LVEF, %	0.952 (0.933-0.973)	<0.001	0.971 (0.950-0.992)	0.007		
Category of LA dilation						
LAVI <35ml/m^2	*Reference group*		*Reference group*		*Reference group*	
LAVI 35 to 48 ml/m^2	1.188 (0.504-2.802)	0.694	1.073 (0.452-2.551)	0.873	0.925 (0.386-2.216)	0.861
LAVI >48 ml/m^2	3.765 (1.854-7.649)	<0.001	2.315 (1.039-5.159)	0.040	2.718 (1.293-5.710)	0.008

*Clinically important, pre-specified variables were included in univariable and multivariable analyses, with a maximum of 4 variables included per model to avoid overfitting.
DM = diabetes mellitus; CAD = coronary artery disease; HR = hazard ratio; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction

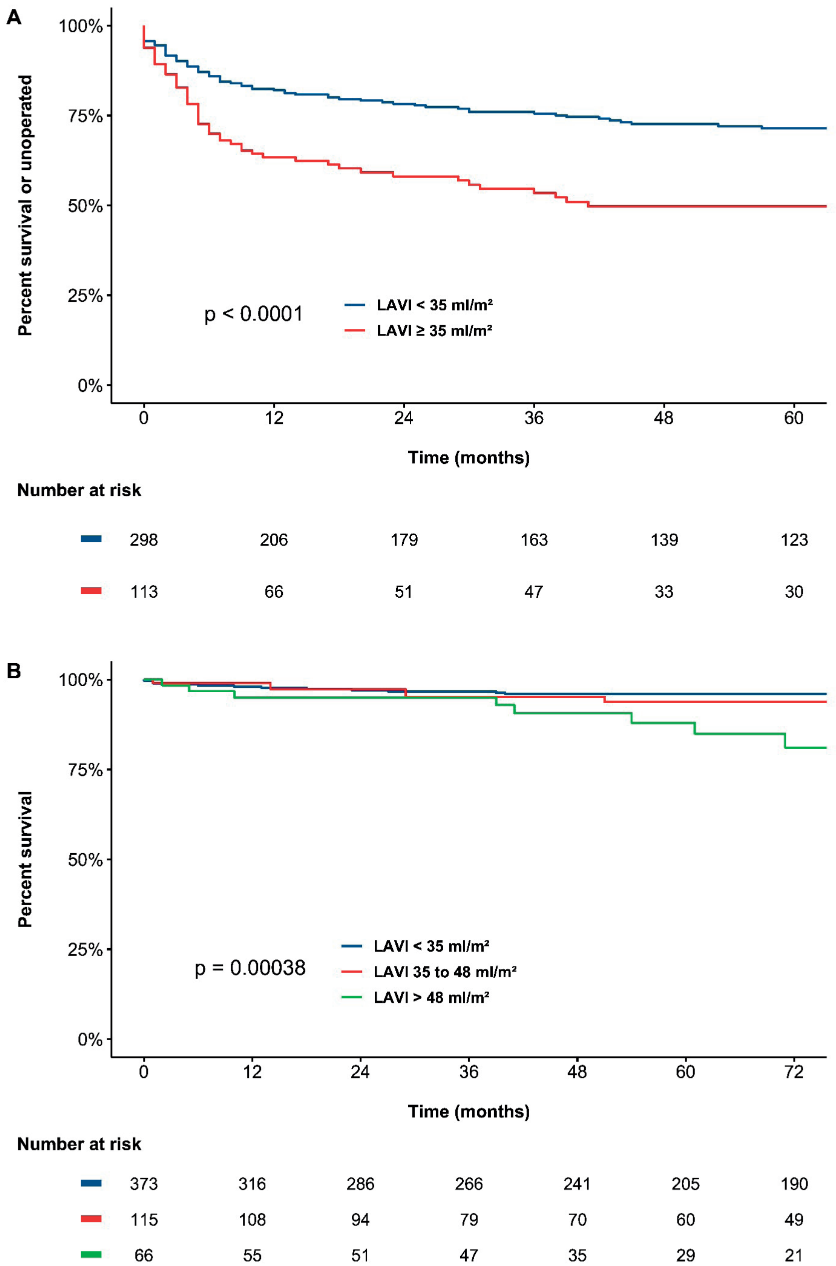

Figure S1: Kaplan-Meier curves for the combined endpoint of event-free survival for patients not meeting contemporary criteria for surgical intervention (A), for all-cause mortality stratified according to normal LAVI, mild to moderately dilated LAVI and severely dilated LAVI (B). The Kaplan-Meier curve in panel A demonstrates the higher event-free survival rates and survival rates of patients with normal LAVI (≥35 ml/m^2, blue line) compared to those with LA dilation (<35 ml/m^2, red line) in the patient subgroup with an LVEF≥50%, LVEDD < 70mm and LVESD < 50mm. The curve in panel B demonstrates the increased rates of all-cause mortality for patients with a LAVI > 48 ml/m^2.
LAVI = left atrial volume index