Original research

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

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ABSTRACT

Objective To investigate the prognostic value of left atrial volume index (LAVI) in patients with moderate to severe aortic regurgitation (AR) and bicuspid aortic valve (BAV).

Methods 554 individuals (45 (IQR 33–57) years, 80% male) with BAV and moderate or severe AR were selected from an international, multicentre registry. The association between LAVI and the combined endpoint of all-cause mortality or aortic valve surgery was investigated with Cox proportional hazard regression analyses.

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±2.0 mm/m^2, 19.4±3.7 mm/m^2, 16.5±3.8 mm/m^2 and 20.4±4.5 mm/m^2, respectively. After a median follow-up of 23 (4–82) months, 272 patients underwent aortic valve surgery (89%) or died (11%). When compared with 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 to 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, multicentre registry of patients with BAV and moderate to severe AR, left atrial 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%–1.3% of the overall population.[1 2] Compared with the general population, patients with BAV are significantly more likely to be diagnosed with aortic regurgitation (AR) or aortic stenosis, with approximately 13%–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) remodelling and dysfunction, with poor long-term postsurgical 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 with 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: (1) determine the prevalence of LA dilation in patients with significant AR due to BAV and (2) 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 1 June 1991 to 6 February 2017 were selected from a large, international, multicentre registry.[14] Patients with previous aortic valve surgery, infectious endocarditis and incomplete follow-up were excluded. Baseline clinical (dyslipidaemia, 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. As this study involved the retrospective analysis of clinically acquired data, the institutional review board of each centre waived the need for written patient informed consent.

Echocardiography

All echocardiographic images were acquired using commercially available ultrasound systems. Experienced observers from each centre retrospectively analysed the acquired images, with the first echocardiographic study confirming a diagnosis of BAV considered as the index study. Standardised 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 centre 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 two-dimensional approach.[13] LA volume was calculated from apical two-chamber and four-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 this 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±SD, while variables that are non-normally distributed are presented as median and IQR. Continuous variables were compared using the Student's t-test if normally distributed, whereas the Mann-Whitney U test was used for non-normally distributed variables. To investigate the 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 dichotomise the population was defined from the spline curve (ie, 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% CIs 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 V.25.0 (IBM Corporation, Armonk, New York) and R V.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 (IQR 33–57 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 dichotomise 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.

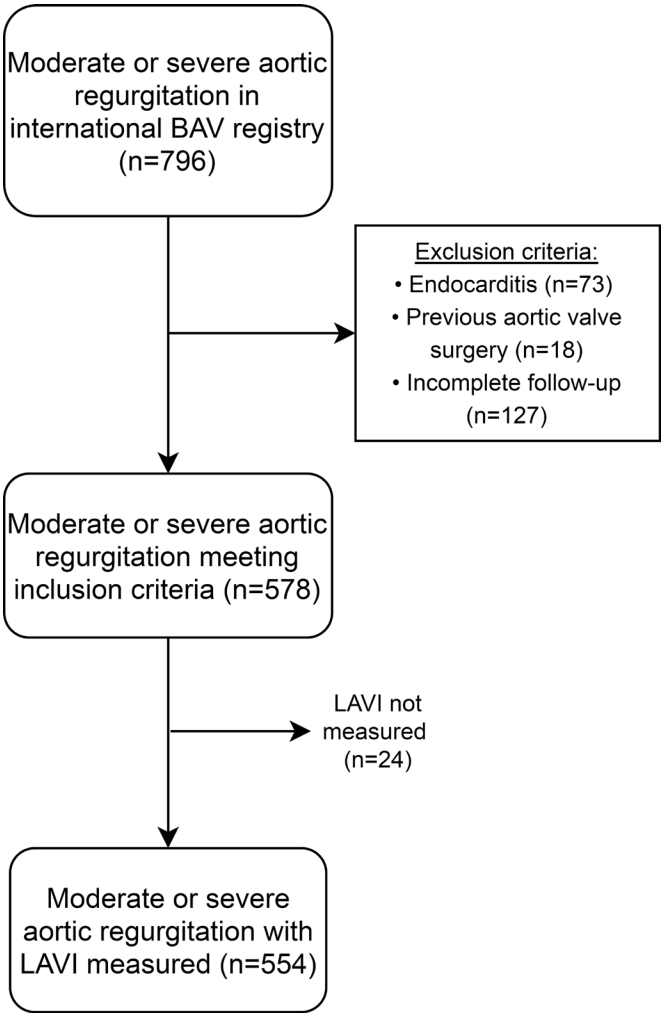

Figure 1 Study flow chart. BAV, bicuspid aortic valve; LAVI, left atrial volume index.

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 with 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 with the group with normal LAVI. Table 2 summarises the echocardiographic characteristics of the study population. The variables independently associated with LA dilation are presented in online supplemental table S1.

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
Dyslipidaemia	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 (%).
BAV, bicuspid aortic valve; 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.

Survival analysis

After a median follow-up of 23 months (IQR 4–82 months), 272 (49%) patients 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-year 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

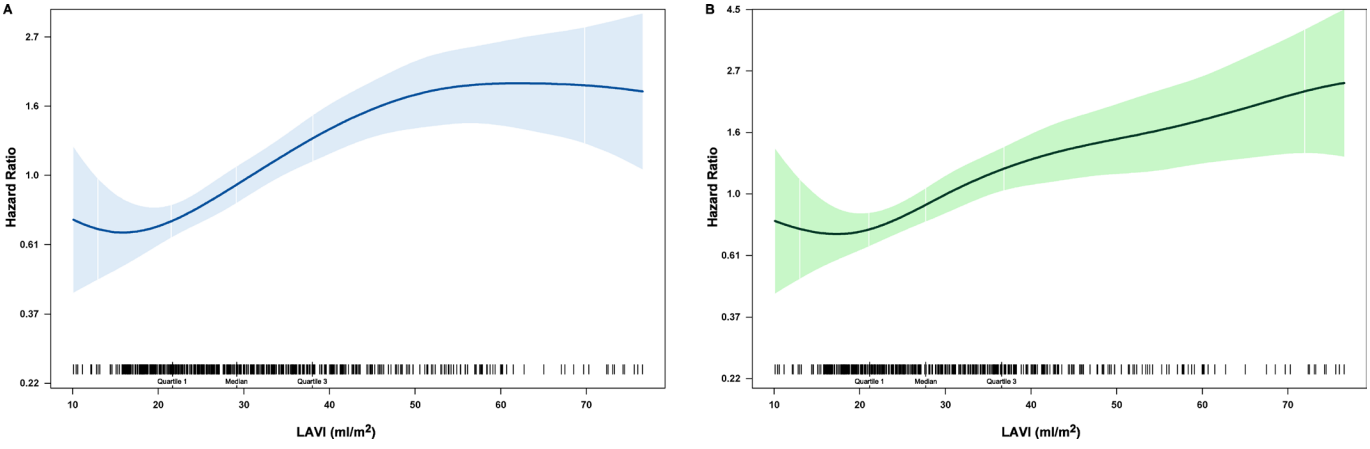

Figure 2 Spline curves for event-free survival according to LAVI for the total population (A, blue) and with those undergoing surgery in the first 90 days excluded (B, green). The curves represent the HR change for all-cause mortality with overlaid 95% CIs (shaded areas) across a range of LAVI at the 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.

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 to 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; LAVI, left atrial volume index; LV, left ventricular; MR, mitral regurgitation; SOV, sinus of Valsalva; STJ, sinotubular junction.

surgery or mortality when compared with patients with normal LAVI (43% and 60% vs 23% and 36%, at 1 year and 5 years of follow-up respectively, p<0.001) (figure 3A,B). 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, using 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.

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 reanalysed 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 with patients with normal LAVI (30% and 51% vs 15% and 30%, at 1 year and 5 years of follow-up, respectively, p<0.001) over a median follow-up period of 36 months (IQR 7–96 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). Furthermore, in patients not meeting contemporary criteria for surgical intervention, the Kaplan-Meier curves showed higher event-free survival rates and survival rates of patients with normal LAVI (<35 mL/m^2, blue line) compared with those with LA dilation (≥35 mL/m^2, red line) (online supplemental figure 1).

Sensitivity analyses were performed to include significant mitral regurgitation (online supplemental table S2) and LVEF as dichotomous variable (<50% vs ≥50%; online supplemental table S3) as covariates in both multivariable models, demonstrating similar results to the primary analyses. Furthermore, LA dilation was independently associated with the combined endpoint of aortic valve surgery and mortality after multiple imputation of missing data (online supplemental 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 (online supplemental table S5).

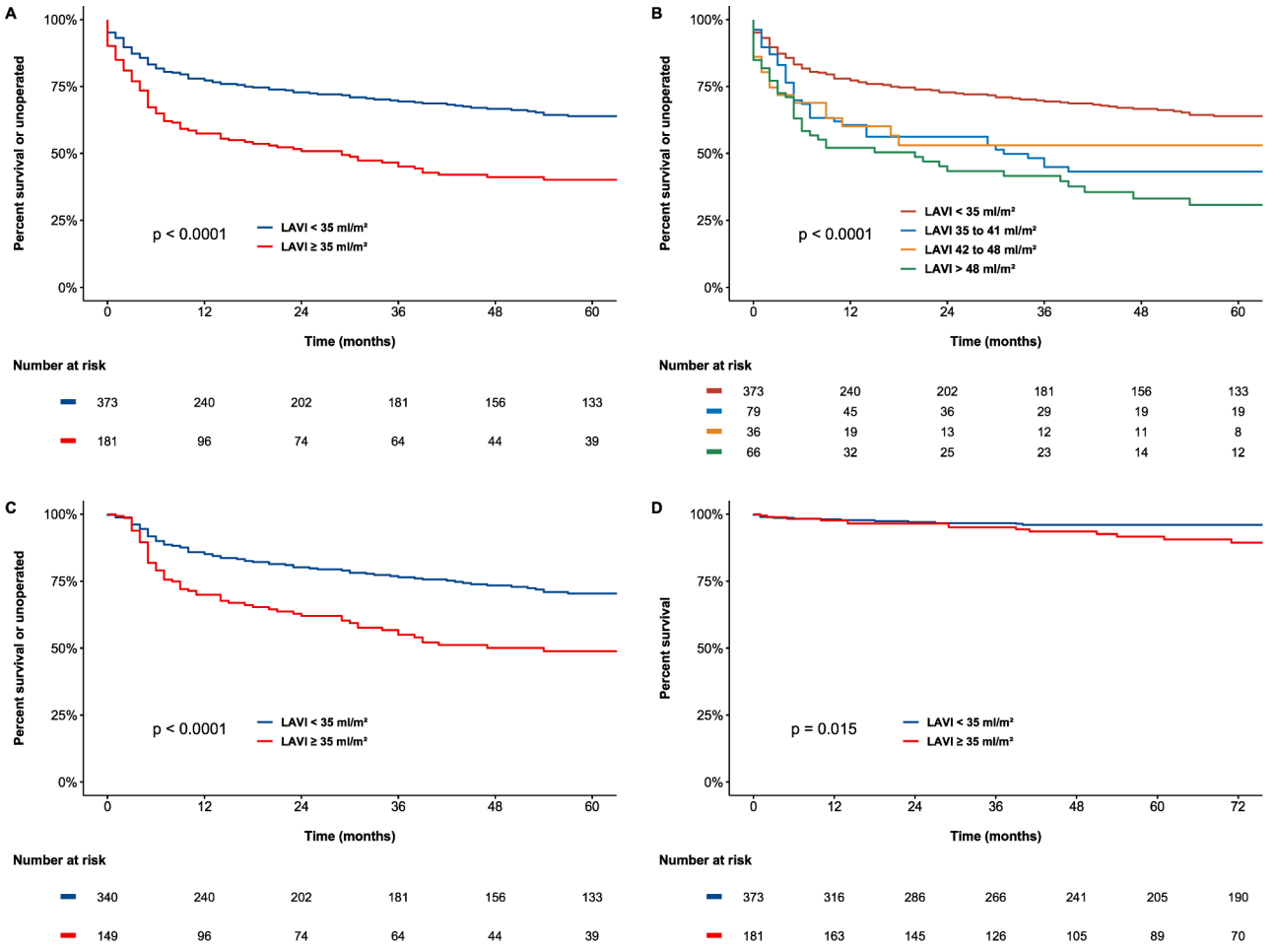

Figure 3 Kaplan-Meier curves for the combined endpoint of event-free survival and for all-cause mortality. Panel A demonstrates the Kaplan-Meier curve for the combined endpoint of event-free survival for the total population at a cut-off of LAVI of 35 mL/m^2. Panel B shows the Kaplan-Meier curve for 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.

After a median follow-up of 65 months (IQR 29–128 months), 41 patients died. Patients with LAVI ≥35 mL/m^2 experienced significantly higher rates of mortality compared with those with normal LAVI at 5 years of follow-up (8.3% vs 4.1%, p=0.015) (figure 3D).

DISCUSSION

In this large, international multicentre 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 AR of a variety of aetiologies, 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 ischaemia and, potentially, myocardial fibrosis.[23 24] In addition, progressive LV remodelling 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 with 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 postoperative LA dilation was independently associated with persistent LV systolic dysfunction at 1 year following surgery in individuals with early postoperative LV

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 to 1.037)	<0.001	1.029 (1.017 to 1.040)	<0.001
Male sex	1.140 (0.844 to 1.541)	0.386		
Current smoker	1.292 (0.959 to 1.742)	0.093		
Hypertension	1.315 (1.024 to 1.688)	0.032	0.889 (0.650 to 1.217)	0.464
Dyslipidaemia	1.233 (0.930 to 1.633)	0.145		
DM	1.119 (0.760 to 1.892)	0.436		
CAD	1.696 (1.120 to 2.569)	0.013	1.373 (0.791 to 2.380)	0.260
Atrial fibrillation	1.375 (0.829 to 2.280)	0.216		
Echocardiographic characteristics				
LVEF, %	0.977 (0.968 to 0.987)	<0.001	0.991 (0.978 to 1.005)	0.214
LVESD >50 mm	2.502 (1.758 to 3.560)	<0.001	1.513 (0.793 to 2.888)	0.209
LVEDD >70 mm	2.510 (1.716 to 3.671)	<0.001	1.353 (0.734 to 2.496)	0.333
Aortic root or ascending aorta >50 mm	3.567 (2.445 to 5.203)	<0.001	3.834 (2.422 to 6.071)	<0.001
LV hypertrophy	2.378 (1.694 to 3.339)	<0.001	1.499 (1.017 to 2.208)	0.041
Moderate or severe MR	1.321 (0.897 to 1.946)	0.159		
Moderate or severe AS	1.771 (1.386 to 2.262)	<0.001	2.232 (1.650 to 3.018)	<0.001
Mitral inflow E/A ratio	0.744 (0.585 to 0.948)	0.017	1.119 (0.853 to 1.468)	0.415
VC width, mm	1.127 (1.085 to 1.171)	<0.001	1.113 (1.063 to 1.165)	<0.001
LAVI ≥35 mL/m^2	1.927 (1.514 to 2.454)	<0.001	1.450 (1.085 to 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 online supplemental material.
AS, aortic stenosis; CAD, coronary artery disease; DM, diabetes mellitus; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; VC, vena contracta.

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

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 to 1.040)	<0.001	1.031 (1.018 to 1.044)	<0.001
Male sex	1.164 (0.826 to 1.640)	0.385		
Current smoker	1.185 (0.829 to 1.692)	0.352		
Hypertension	1.504 (1.133 to 1.995)	0.005	1.046 (0.736 to 1.487)	0.804
Dyslipidaemia	1.314 (0.954 to 1.810)	0.095		
DM	1.479 (0.911 to 2.403)	0.114		
CAD	1.380 (0.798 to 2.384)	0.249		
Atrial fibrillation	1.550 (0.883 to 2.723)	0.127		
LVEF, %	0.978 (0.968 to 0.989)	<0.001	0.995 (0.979 to 1.011)	0.525
LVESD >50 mm	2.527 (1.653 to 3.862)	<0.001	1.657 (0.796 to 3.450)	0.177
LVEDD >70 mm	2.717 (1.735 to 4.257)	<0.001	1.596 (0.802 to 3.176)	0.183
Aortic root or ascending aorta >50 mm	2.406 (1.395 to 4.419)	0.002	2.134 (1.069 to 4.258)	0.032
LV hypertrophy	2.283 (1.559 to 3.344)	<0.001	1.277 (0.832 to 1.961)	0.263
Moderate or severe MR	1.313 (0.841 to 2.050)	0.231		
Moderate or severe AS	1.646 (1.238 to 2.188)	0.001	2.128 (1.507 to 3.005)	<0.001
Mitral inflow E/A ratio	0.597 (0.443 to 0.804)	0.001	1.007 (0.720 to 1.408)	0.967
VC width, mm	1.142 (1.090 to 1.196)	<0.001	1.138 (1.080 to 1.201)	<0.001
LAVI ≥35 mL/m^2	1.901 (1.439 to 2.512)	<0.001	1.534 (1.104 to 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 online supplemental material.
AS, aortic stenosis; CAD, coronary artery disease; DM, diabetes mellitus; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; VC, vena contracta.

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 dilation 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 with those without LA dilation. Previously, in an unadjusted subgroup analysis of 372 patients with significant AR, Mosquera *et al*[7] demonstrated that increasing indexed LA diameter on presurgical echocardiography was significantly associated with future cardiovascular mortality. Likewise, in another smaller study, a subgroup analysis of 41 patients with AR demonstrated that a LAVI ≥35 mL/m^2 on presurgical 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 randomised 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 3 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, remodelling 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, multicentre 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.

Key messages

What is already known on this subject?

- There has been limited investigation of the prognostic significance of left atrial (LA) dilation in patients with aortic regurgitation (AR) and bicuspid aortic valve (BAV).

What might this study add?

- This study demonstrates that LA dilation is independently associated with reduced event-free survival in a cohort of patients with BAV and moderate to severe AR, after adjustment for contemporary indications for aortic valve surgery and other important confounders.

How might this impact on clinical practice?

- LA dilation in significant AR may anticipate the onset of symptoms and identify patients at an increased risk of requiring future aortic valve surgery. The role of LAVI for the risk stratification of individuals with significant AR merits further investigation.

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