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

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PART II

NEW INSIGHTS INTO RISK STRATIFICATION OF PATIENTS WITH VALVULAR HEART DISEASE

4

Left ventricular remodelling in Bicuspid Aortic Valve Disease

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ABSTRACT

Background

Characterization of left ventricular (LV) geometric pattern and LV mass could provide an important insight into the pathophysiological adaptations of the left ventricle to pressure and/or volume overload in patients with bicuspid aortic valve (BAV) and significant (≥moderate) aortic valve (AV) disease. This study aimed to characterize LV remodelling and its prognostic impact in patients with BAV according to the predominant type of valvular dysfunction.

Methods

In this international, multicenter BAV registry, 1,345 patients (51.0 [37.0 to 63.0] years, 71% male) with significant AV disease were identified. Patients were classified as having isolated aortic stenosis (AS) (n=669), isolated aortic regurgitation (AR) (n=499) or mixed aortic valve disease (MAVD) (n=177). LV hypertrophy was defined as a LV mass index >115 g/m^2 in males and >95 g/m^2 in females. LV geometric pattern was classified as (i) normal geometry: no LV hypertrophy, relative wall thickness (RWT) ≤0.42, (ii) concentric remodelling: no LV hypertrophy, RWT >0.42, (iii) concentric hypertrophy: LV hypertrophy, RWT >0.42, and (iv) eccentric hypertrophy: LV hypertrophy, RWT ≤0.42. Patients were followed-up for the endpoints of event-free survival (defined as a composite of aortic valve repair/replacement and all-cause mortality) and all-cause mortality.

Results

Type of AV dysfunction was related to significant variations in LV remodelling. Higher LV mass index, i.e. LV hypertrophy, was independently associated with the composite endpoint for patients with isolated AS (HR 1.08 per 25g/m^2, 95% CI 1.00 to 1.17, p=0.046) and AR (HR 1.19 per 25g/m^2, 95% CI 1.11 to 1.29, p<0.001), but not for those with MAVD. The presence of concentric remodeling, concentric hypertrophy and eccentric hypertrophy were independently related to the composite endpoint in patients with isolated AS (HR 1.54, 95% CI 1.06 to 2.23, p=0.024; HR 1.68, 95% CI 1.17 to 2.42, p=0.005; HR 1.59, 95% CI 1.03 to 2.45, p=0.038, respectively), while concentric hypertrophy and eccentric hypertrophy were independently associated with the combined endpoint for those with isolated AR (HR 2.49, 95% CI 1.35 to 4.60, p=0.004 and HR 3.05, 95% CI 1.71 to 5.45, p<0.001, respectively). There was no independent association observed between LV remodelling and the combined endpoint for patients with MAVD.

Conclusions

LV hypertrophy or remodelling were independently associated with the composite endpoint of aortic valve repair/replacement and all-cause mortality for patients with isolated AS and isolated AR, although not for patients with MAVD.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most frequent type of congenital heart disease[1], and is a common cause of aortic stenosis (AS) and aortic regurgitation (AR)[2, 3]. Patients with BAV may have a higher prevalence of left ventricular (LV) diastolic dysfunction and reduced LV deformation compared to those with a tricuspid aortic valve (AV)[4, 5]. In addition, individuals with BAV typically develop moderate or severe (significant) AV disease at a considerably younger age[2]. These differences suggest that there could be important differences in LV remodeling in patients with BAV compared to those with a tricuspid AV.

Characterization of LV geometric pattern and LV mass could provide an important insight into the pathophysiological adaptations of the left ventricle to pressure and/or volume overload in patients with BAV and significant AV disease. Although changes in LV mass and geometry may represent a physiological response to altered loading, they may also imply a greater hemodynamic burden on the left ventricle and a higher likelihood of future symptom development[6-8]. In addition, increasing LV mass and changes in LV geometric pattern have been associated with the development of myocardial fibrosis, irreversible LV dysfunction and poor long-term prognosis in patients with significant AV disease[9-12]. Identifying the extent and phenotype of LV remodeling could potentially allow for the identification of patients with BAV and significant AV disease who may benefit from earlier AV surgery or intervention. However, until now, there has only been limited investigation of LV remodeling in patients with BAV and significant AV disease.

Therefore, this study aimed to (i) characterize LV remodelling in patients with BAV and significant AR, AS or mixed AV disease (MAVD), and (ii) investigate the prognostic implications of LV hypertrophy and remodelling according to the type of aortic valve dysfunction for individuals with BAV.

METHODS

Study population

Individuals with BAV and at least moderate AS and/or AR were selected from an international multicenter BAV registry[13]. Patients with previous or current endocarditis, complex congenital heart disease, previous AV surgery, or without moderate or severe (significant) AV disease were excluded. Demographic and clinical data were obtained from medical records corresponding to the time of first diagnosis of BAV by transthoracic echocardiography. Body surface area was calculated using the Mosteller method[14]. Data were obtained according to regulations specified by the institutional review board of each center, and were retrospectively analysed. Due to the retrospective nature of the study design, the ethical committee of each participating center waived the require-

ment for written informed consent. The data that support these findings are available on reasonable request to the corresponding author.

Echocardiography

Echocardiographic studies were performed with commercially available ultrasound systems, with the first transthoracic echocardiogram confirming a diagnosis of BAV considered the index study. Images were retrospectively analyzed by experienced investigators from each center, with BAV morphology classified according to the system proposed by Sievers and Schmidtke[15]. AS severity was classified as none, mild, moderate or severe based on aortic valve area, peak aortic velocity and mean pressure gradient, as per contemporary guideline recommendations[16]. The severity of AR was graded as none, mild, moderate or severe according to AR jet size, pressure half-time and vena-contracta width, according to guideline recommendations[17]. Individuals with significant AS and AR were considered to have MAVD, while patients with significant AS and less than moderate AR were classified as isolated AS. Individuals with significant AR and less than moderate AS were classified as isolated AR. The diameters of the sinus of Valsalva, sinotubular junction and ascending aorta were measured on a parasternal long-axis view from leading-edge to leading-edge, perpendicular to the centerline of the aorta in end-diastole[18]. The aortic annulus was conventionally measured from inner-edge to inner-edge on a parasternal long-axis view[18]. LV ejection fraction (LVEF) was estimated using the biplane Simpson method. LV end-diastolic diameter (LVEDD), posterior wall thickness (PWT) and interventricular septal thickness (IVST) were measured using the 2D linear method, as per guideline recommendations[18]. Relative wall thickness (RWT) was calculated as: (2 X PWT) / LVEDD (18). LV mass was calculated by the following formula: LV mass = 0.8 X 1.04 X [(IVST + LVEDD + PWT)^3 - LVEDD^3] + 0.6 [18]. LV mass was subsequently indexed to body surface area. LV hypertrophy was defined as a LV mass index >115 g/m^2 in males and >95 g/m^2 in females. LV geometric pattern was classified according to guideline recommendations as[18] (i) normal geometry: no LV hypertrophy, RWT ≤0.42, (ii) concentric remodelling: no LV hypertrophy, RWT >0.42, (iii) concentric hypertrophy: LV hypertrophy, RWT >0.42, and (iv) eccentric hypertrophy: LV hypertrophy, RWT ≤0.42. All other measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines[18].

Follow-up

Follow-up started at the time of the first echocardiogram that confirmed a diagnosis of BAV. The primary endpoint of the study was a composite of aortic valve repair/replacement and all-cause mortality. Indications for aortic valve repair/replacement were according to recommendations of contemporary guidelines, including patients with symptomatic severe aortic valve dysfunction or asymptomatic severe aortic valve

dysfunction with a reduced LVEF (≤50%)[19, 20]. The secondary endpoint was all-cause mortality. Follow-up data were available for 613 (92%) patients with isolated AS, 163 (92%) patients with MAVD and 415 (83%) patients with isolated AR. Data for all patients were included up to the last date of follow-up.

Statistical analysis

Continuous data are expressed as mean ± standard deviation if normally distributed and median and interquartile range (IQR) if non-normally distributed. Data were evaluated for normality by comparing histograms to superimposed normal probability curves. Normally distributed variables were compared using one-way ANOVA, while non-normally distributed variables were compared with the Kruskal-Wallis test. Multiple comparisons for continuous variables were tested using the Bonferroni correction. Categorical data are expressed as counts and percentages and were compared using the Pearson χ^2 test. The association between presence of a dilated aortic root or aorta (≥ 50mm) and LV geometric pattern was evaluated with binary logistic regression.

Cumulative 1- and 5- year event-free survival for the composite endpoint of all-cause mortality and aortic valve repair/replacement were calculated using the Kaplan Meier method and compared using the log-rank test. Univariable Cox proportional hazards regression analysis was used to evaluate the associations between LV mass index and LV geometric pattern with the composite endpoint of all-cause mortality and aortic valve repair/replacement. In addition, to further investigate the relationship between LV mass index and the hazard ratio (HR) change for the combined endpoint of aortic valve repair/replacement and all-cause mortality, a spline curve was fitted for each type of AV disease (isolated AS, MAVD and isolated AR). Multivariable Cox proportional hazards regression analyses were performed adjusting for pre-specified clinical and echocardiographic variables associated with event-free survival specific to each patient group (isolated AS, MAVD, isolated AR). HR and 95% confidence intervals (CI) were reported for each model. The proportional hazards assumption was confirmed through the evaluation of scaled Schoenfeld residuals.

In a sensitivity analysis, univariable Cox regression was used to evaluate the association between LV geometric pattern, LV mass index and the secondary endpoint of all-cause mortality. Multivariable models were constructed adjusting for age and LV ejection fraction only, to avoid overfitting. All tests were two-sided and *P* values <0.05 were regarded as 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

Patient population

Of the 1345 patients with significant AV disease and BAV (median age 51 [37-63] years, 71% male), 669 had isolated AS, 177 MAVD and 499 isolated AR (Figure 1). Individuals with isolated AS were older, more frequently had hypertension, diabetes mellitus and dyslipidemia compared to patients with MAVD or isolated AR. In addition, patients with MAVD more frequently had a type 1 R-N raphe BAV compared to those with isolated AR or AS. A summary of the clinical characteristics of the population is presented in Table 1.

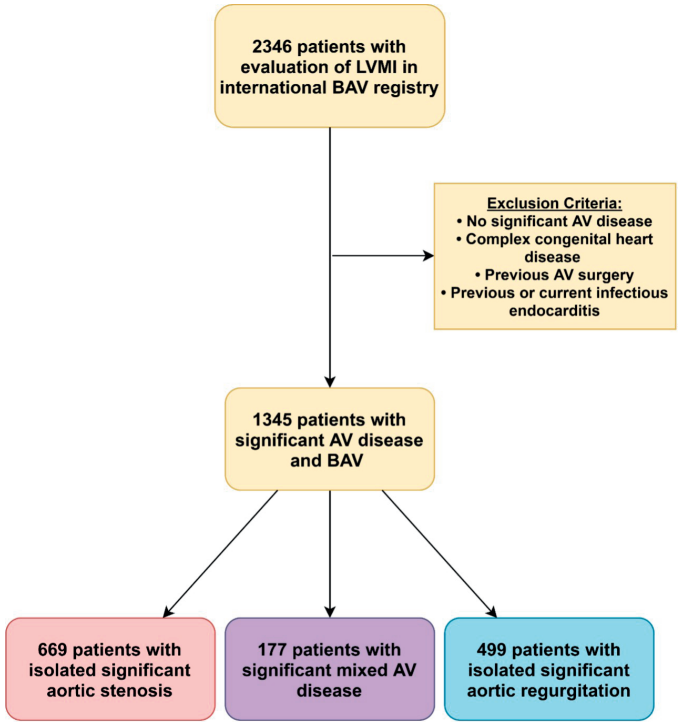

Figure 1: Study flow chart. AV = aortic valve; BAV = bicuspid aortic valve; LVMI = LV mass index.

Echocardiographic characteristics

The echocardiographic characteristics of the study population are displayed in Table 2. Individuals with isolated AR had larger LV dimensions, aortic annulus and sinus of Valsalva diameters compared to the other groups, whereas those with MAVD had larger LV dimensions, aortic annulus and sinus of Valsalva diameters compared to those with isolated AS. In addition, although patients with isolated AR had larger sinotubular junction diameters than those with isolated AS or MAVD, there was no difference observed between ascending aorta diameters.

Table 1: Clinical and BAV characteristics according to AV dysfunction type

	Total Population (n=1345)	Isolated significant AS (n=669)	Significant mixed AV disease (n=177)	Isolated significant AR (n=499)	*P* value
Clinical characteristics					
Age (years)	51.0 (37.0 to 63.0)	57.0 (45 to 67)	51.0 (38.5 to 63.0)*	41.0 (31.0 to 54.0)*†	<0.001
Male (%)	951 (70.7%)	417 (62.3%)	123 (69.5%)	411 (82.4%)*	<0.001
Hypertension (%)	470 (37.5%)	277 (43.7%)	57 (33.7%)*	136 (30.3%)*	<0.001
Current smoker (%)	202 (16.5%)	92 (15.5%)	30 (17.8%)	80 (17.4%)	0.645
Dyslipidemia (%)	385 (29.7%)	249 (38.1%)	40 (23.1%)*	96 (20.5%)*	<0.001
Prior CAD (%)	111 (9.1%)	62 (10.0%)	18 (11.0%)	31 (7.1%)	0.172
Diabetes mellitus (%)	143 (11.7%)	107 (18.0%)	15 (8.9%)*	21 (4.6%)*†	<0.001
BAV characteristics					
No raphe (%)	102 (8.3%)	45 (7.6%)	10 (5.9%)	47 (10.2%)	0.002
Type 1 raphe (L-R), (%)	852 (69.6%)	410 (68.9%)	107 (63.3%)	335 (72.7%)†	
Type 1 raphe (R-N), (%)	207 (16.9%)	104 (17.5%)	42 (24.9%)*	61 (13.2%)†	
Type 1 raphe (L-N), (%)	52 (4.2%)	28 (4.7%)	6 (3.6%)	18 (3.9%)	
Type 2 raphe (%)	12 (1.0%)	8 (1.3%)	4 (2.4%)	0 (0.0%)*†	

Values are median (IQR) and n (%).
AV = aortic valve; AR = aortic regurgitation; AS = aortic stenosis; CAD = coronary artery disease; L-N = left – non-coronary; L-R = left – right; R-N = right – non-coronary.
*p<0.05 vs Group I;†p<0.05 vs Group II

LV remodelling characteristics

Patients with isolated AS had a higher RWT and lower LV mass index compared to those with MAVD or isolated AR (Table 2). However, individuals with MAVD also had a higher RWT than patients with isolated AR. In addition, the distribution of LV geometric patterns differed significantly between groups (Figure 2). Patients with MAVD were less likely to exhibit normal geometry compared to patients with isolated AR. Individuals with isolated AS more frequently had concentric remodelling compared to those with MAVD or isolated AR. Patients with isolated AR more frequently had eccentric hypertrophy than those with MAVD, who in turn, demonstrated this pattern more often than individuals with isolated AS. The patient groups with MAVD and isolated AS had a higher prevalence of concentric hypertrophy when compared to individuals with isolated AR.

There was no significant association between BAV morphology and LV geometric pattern observed in patients with isolated AS, MAVD or isolated AR. However, a significant association between the presence of a dilated aortic root or aorta (≥ 50mm) and LV geometric pattern was observed in patients with isolated AS (concentric remodelling versus normal geometry, OR 0.61, 95% CI 0.10 to 3.70, p=0.59; concentric hypertrophy versus normal geometry, OR 4.13, 95% CI 1.18 to 14.42, p=0.026; eccentric hypertrophy versus normal geometry, OR 5.79, 95% CI 1.49 to 22.43, p=0.011), although not in patients with MAVD or isolated AR.

Table 2: Echocardiographic characteristics

	Total population (n=1345)	Isolated significant AS (n=669)	Significant mixed AV disease (n=177)	Isolated significant AR (n=499)	*P* value
Left ventricle and atrium					
LV EDD, mm	52.6 (±9.6)	48.0 (±7.2)	54.6 (±8.7)*	58.2 (±9.4)*†	<0.001
LV ESD, mm	35.4 (±10.0)	31.7 (±8.4)	36.6 (±10.2)*	39.4 (±10.2)*†	<0.001
LV EDVi, ml/m^2	67.9 (54.2 to 88.5)	57 (47 to 70)	76 (61 to 94)*	83 (67 to 104)*†	<0.001
LV EF, %	63 (55 to 69)	65 (57 to 70)	61 (52 to 71)	61 (54 to 67)*	<0.001
LV EF <50%	205 (15.3%)	86 (12.9%)	34 (19.2%)	85 (17.1%)	0.045
LAVI, ml/m^2	27 (20 to 36)	27 (21 to 36)	30 (21 to 42)	25 (19 to 35)†	0.002
Mitral inflow E velocity, m/s	0.80 (±0.25)	0.81 (±0.26)	0.84 (±0.29)	0.77 (±0.23)*†	0.003
Mitral inflow E/A ratio	1.14 (0.83 to 1.56)	1.00 (0.78 to 1.49)	1.14 (0.82 to 1.67)	1.25 (0.88 to 1.61)*	<0.001
LV remodelling parameters					
LV mass index, g/m^2	117 (93 to 150)	107 (85 to 134)	132 (101 to 168)*	127 (102 to 169)*	<0.001
RWT	0.43 (±0.12)	0.47 (±0.12)	0.42 (±0.11)*	0.38 (±0.09)*†	<0.001
LV geometric pattern					
Normal geometry	339 (25.2%)	170 (25.4%)	34 (19.2%)	135 (27.1%)†	<0.001
Concentric remodelling	229 (17.0%)	184 (27.5%)	12 (6.8%)*	33 (6.6%)*	
Concentric hypertrophy	408 (30.3%)	231 (34.5%)	72 (40.7%)	105 (21.0%)*†	
Eccentric hypertrophy	369 (27.4%)	84 (12.6%)	59 (33.3%)*	226 (45.3%)*†	
Aortic valve and aortic root					
Aortic annulus diameter, mm	23.1 (±3.6)	21.6 (±2.7)	23.0 (±3.3)*	25.0 (±3.7)*†	<0.001
SOV diameter, mm	34.8 (±6.3)	33.0 (±5.6)	34.6 (±5.9)*	37.2 (±6.6)*†	<0.001
STJ diameter, mm	30.0 (±6.6)	28.7 (±5.4)	29.8 (±6.1)	31.7 (±7.6)*†	<0.001
Ascending aorta diameter, mm	37.6 (±7.4)	37.2 (±6.8)	37.9 (±6.8)	38.0 (±8.2)	0.149
Dilated aortic root or tubular aorta (≥ 50mm), %	75 (5.6%)	29 (4.4%)	8 (4.5%)	38 (7.6%)*	0.046
Severe aortic stenosis, %	444 (33%)	369 (55.2%)	75 (42.4%)*	0 (0%)*†	<0.001
Severe aortic regurgitation, %	241 (17.9%)	0 (0%)	51 (28.8%)*	190 (38.8%)*†	<0.001

Values are presented as mean ± SD, median (IQR) or n (%).
AS = aortic stenosis; AR = aortic regurgitation; EDD = end-diastolic diameter; EDVi = end-diastolic volume index; EF = ejection fraction; ESD = end-systolic diameter; LAVI = left atrial volume index; LV = left ventricle; MR = mitral regurgitation n; RWT = relative wall thickness; SOV = sinus of Valsalva; STJ = sinotubular junction
*p<0.05 vs Group I;†p<0.05 vs Group II

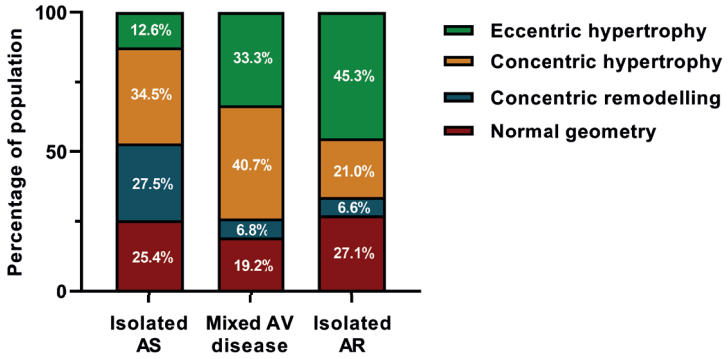

Figure 2: LV geometric pattern according to type of AV dysfunction in patients with BAV. AV = aortic valve; AR = aortic regurgitation; AS = aortic stenosis; BAV = bicuspid aortic valve

Prognostic implications of LV remodelling in isolated AS

Of the individuals with isolated AS, 344 died (n=31, 4.6%) or underwent aortic valve repair/replacement (n=313, 46.8%) over a median follow-up of 20 (IQR 3 to 60) months. The 1- and 5- year cumulative event-free survival rates were 70% and 48% for the composite endpoint of all-cause death and aortic valve repair/replacement, respectively (Figure 3A). Kaplan-Meier analysis demonstrated a significant reduction in event-free survival for the composite endpoint in individuals with concentric remodelling, concentric hypertrophy and eccentric hypertrophy compared to those with normal LV geometry (χ^2=48.44, p<0.001)(Figure 3B). On multivariable Cox regression analysis, following adjustment for possible confounding variables (age, smoking, coronary artery disease, aortic root or ascending aorta dilation, aortic valve area, left atrial volume index (LAVI) and LVEF), concentric remodelling (HR 1.54, 95% CI 1.06 to 2.23, p=0.024), concentric hypertrophy (HR 1.68, 95% CI 1.17 to 2.42, p=0.005) and eccentric hypertrophy (HR 1.59, 95% CI 1.03 to 2.45, p=0.038), remained independently associated with the composite endpoint (Figure 4, Figure 5, C, panel 1, Table S1). To examine the relationship between LV mass index and the combined endpoint for each patient group (isolated AS, MAVD and isolated AR), spline curves were fitted, demonstrating a continuous increase in HR across a range of values of LV mass index for all groups (Figure 5, B). Multivariable Cox regression analysis demonstrated that LV mass index remained independently associated with the combined endpoint for patients with isolated AS and BAV (HR 1.08 per 25g/m^2, 95% CI 1.00 to 1.17, p=0.046) (Figure 4, Table S1).

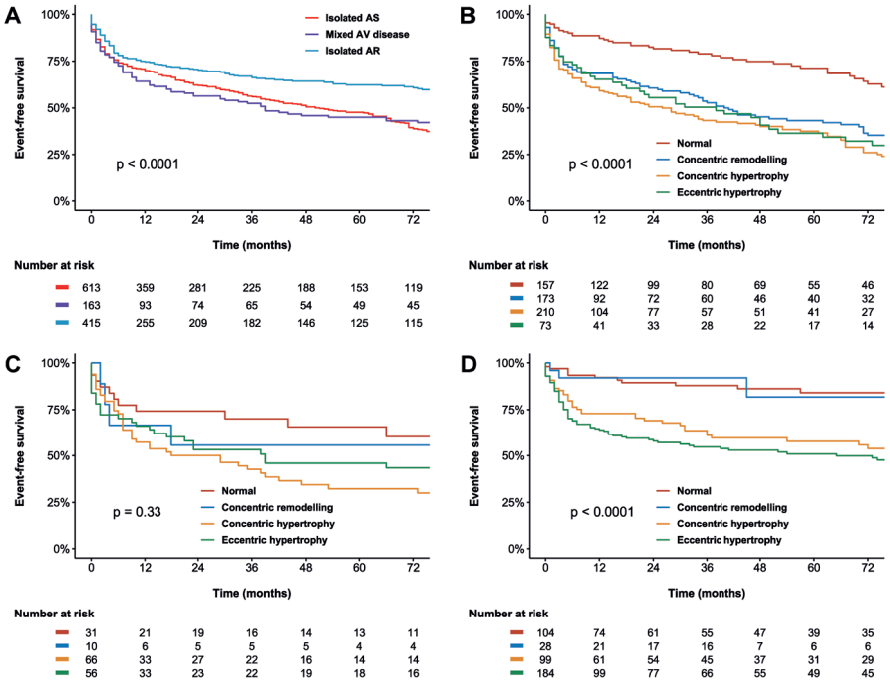

Figure 3: Kaplan-Meier curves demonstrating event-free survival for the composite endpoint of all-cause mortality and aortic valve repair/replacement according to the type of AV dysfunction in patients with BAV, and according to LV geometric pattern within each group. Panel A demonstrates that patients with significant aortic stenosis or mixed AV disease have reduced event-free survival compared to those with significant aortic regurgitation. Panels B, C and D demonstrate Kaplan Meier survival estimates according to LV geometric pattern for aortic stenosis, mixed AV disease and aortic regurgitation, respectively.
AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricular

Prognostic implications of LV remodelling in MAVD

For those with MAVD, after a median follow-up of 18 (IQR 2 to 76) months, 107 (60.4%) patients died (n=12, 6.8%) or underwent aortic valve repair/replacement (n=95, 54.6%). Kaplan-Meier and univariable Cox regression analysis did not demonstrate an association between LV geometric pattern and the composite endpoint of all-cause mortality and aortic valve repair/replacement for patients with MAVD (χ^2=3.44, p=0.33) (Figure 3C), including after adjustment in a multivariable model (Figure 4, Figure 5, C, panel 2). Although on univariable Cox regression analysis, LV mass index was associated with the combined endpoint in patients with MAVD (HR 1.17 per 25g/m^2, 95% CI 1.08 to 1.27, p<0.001), an independent association was not observed following adjustment (HR 0.97 per 25g/m^2, 95% CI 0.85 to 1.10, p=0.62).

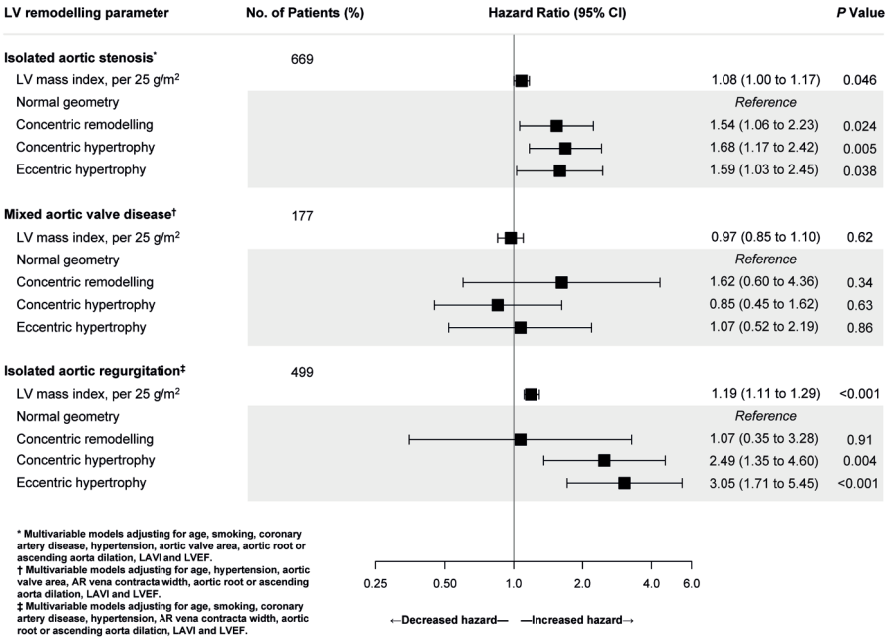

Figure 4: Forest plot of Cox regression models investigating the association between parameters of LV remodelling and event-free survival according to type of aortic valve disease. AR = aortic regurgitation; AV = aortic valve; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction

Prognostic implications of LV remodelling in isolated AR

Over a median follow-up of 24 (4 to 79) months, 170 patients with isolated AR died (n=14, 2.8%) or underwent aortic valve repair/replacement (n=156, 31.3%). Univariable Cox regression and Kaplan-Meier analyses demonstrated reduced event-free survival for the composite endpoint for patients with concentric hypertrophy and eccentric hypertrophy compared to those with normal geometry (χ^2=34.90, p<0.001) (Figure 3D). In a multivariable model, concentric and eccentric hypertrophy (HR 2.49, 95% CI 1.35 to 4.60, p=0.004 and HR 3.05, 95% CI 1.71 to 5.45, p<0.001, respectively) remained independently associated with the combined endpoint (Figure 4, Figure 5, C, panel 3). Likewise, LV mass index remained significantly associated with the composite endpoint in an adjusted model (HR 1.19 per 25g/m^2, 95% CI 1.11 to 1.29, p<0.001).

LV remodelling and all-cause mortality

In sensitivity analyses, the association between LV geometric pattern, LV mass and all-cause mortality were evaluated for each type of AV dysfunction (Table S2, Figure S1). A total of 59 (8.8%) patients with isolated AS (median follow-up 53 [IQR 23 to 86] months), 17 (9.6%) with MAVD (median follow-up 69 [IQR 29 to 127] months) and 23 (4.6%) with isolated AR (median follow-up 57 [IQR 21 to 122] months) died during follow-up. LV

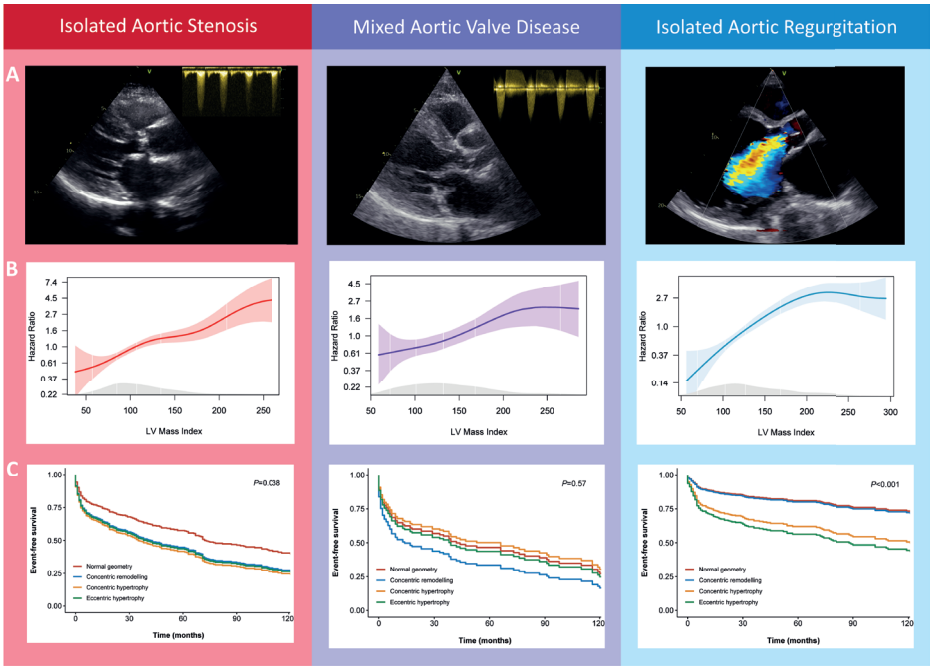

Figure 5: Prognostic implications and differences in LV remodelling according to type of AV dysfunction in BAV. Panel A demonstrates the typical LV geometric patterns according to the type of AV dysfunction. Patients with significant isolated aortic stenosis are more likely to have lower LV mass compared to those with significant isolated aortic regurgitation or mixed AV disease. Individuals with significant isolated aortic stenosis and mixed AV disease typically have a higher relative wall thickness compared to those with significant isolated aortic regurgitation. The spline curves in panel B show the hazard ratio change for event-free survival with 95% confidence intervals (shaded red, purple and blue areas) across a range of values of LV mass index for each patient group. The density plots beneath the curves shows the distribution of the study population according to values of LV mass index. Panel C demonstrates adjusted event-free survival curves according to LV geometric pattern. LV geometric pattern was independently associated with event-free survival in individuals with isolated aortic stenosis and aortic regurgitation, but not for those with mixed AV disease.
AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricular

geometric pattern was associated with all-cause mortality in patients with isolated AS, but not with MAVD or isolated AR on univariable analysis. In a multivariable model adjusting for age and LVEF, concentric hypertrophy remained significantly associated with all-cause mortality for patients with isolated AS (HR 2.87, 95% CI 1.09 to 7.54, p=0.032). Although LV mass index was associated with increased all-cause mortality for each type of AV dysfunction, following adjustment for age and LVEF, an association was only observed for patients with isolated AR (HR 1.19 per 25g/m^2, 95% CI 1.00 to 1.40, p=0.044). For patients with isolated AS and AR, subgroup analyses and interactions for the association between LV remodelling and all-cause mortality and the combined endpoint are displayed in supplementary tables S3-S8.

DISCUSSION

In this large, international, multicenter BAV study, the type of AV dysfunction (isolated AS, isolated AR or MAVD) was related to significant variations in LV mass and geometric pattern. In addition, for patients with isolated AS and AR, increasing LV mass index was independently associated with the composite endpoint of aortic valve repair/replacement and all-cause mortality. The presence of concentric hypertrophy or concentric remodeling was independently related to worse event-free survival in patients with isolated AS, while eccentric hypertrophy and concentric hypertrophy LV geometric patterns were independently associated with the composite endpoint for those with isolated AR. There was no independent association observed between indices of LV remodelling and the composite endpoint for BAV patients with MAVD.

Differences in LV remodelling in patients with BAV according to type of AV disease

BAV is a common congenital valvular disease with different AV, aortic root and ascending aorta phenotypes, leading to valvular dysfunction and/or aortic dilatation at a younger age compared to those with tricuspid AV morphology[21]. This dysfunction imposes varying degrees of pressure and volume overload on the left ventricle according to the predominant valvular lesion/s, which may lead to changes in LV mass and geometric pattern.

In patients with isolated AS, pressure overload triggers cardiomyocyte hypertrophy in order to reduce wall stress and maintain adequate systolic function[22]. The result is myocardial thickening with comparatively smaller changes in LV dimensions, leading to predominantly concentric LV geometry. The predominance of LV concentric hypertrophy observed in those with isolated AS in the present study is in accordance with previous reports, although a lower prevalence was observed in our population[23, 24]. Notably, the majority of preceding reports included mostly patients with degenerative calcific aortic stenosis, who are significantly older and have higher prevalence of clinical comorbidities, important risk factors for LV hypertrophy. Conversely, patients with AR are subject to a combination of volume and pressure overload, typically resulting in considerable LV dilation, myocyte elongation and compensatory increases in LV mass, although without substantial increases in myocardial thickness, translating as eccentric hypertrophy[25]. Our study is consistent with prior literature, demonstrating a prevalence of eccentric hypertrophy of approximately 50% in patients with isolated AR[8, 26]. In patients with MAVD, substantial pressure and volume overload coexist, and the consequent LV remodelling is a result of the additional hemodynamic burden imposed on the myocardium[27, 28]. Consistent with the literature, the present study demonstrates a high prevalence of LV hypertrophy in patients with MAVD[28], with increased relative wall thickness compared to those with isolated AR, and increased LV mass index compared to those with isolated AS.

Prognostic implications of LV remodelling in patients with BAV

LV remodelling can produce diastolic dysfunction and sub-endocardial ischemia due to an imbalance between myocardial oxygen supply and demand, and may be related to myocardial fibrosis and the onset of symptoms[25]. It is possible that changes in LV remodelling may anticipate the onset of symptoms (currently the major indication for surgery in individuals with BAV and significant AV disease) and foreshadow a future need for AV intervention. It is also possible that these findings may be extrapolated to patients with a tricuspid AV, with the caveat that these patients are usually older with greater comorbidity profile, which could somewhat confound the underlying etiology of LV hypertrophy and remodeling.

High LV mass index has been associated with adverse outcomes in patients with isolated AS[6, 7, 29]. In addition, Debry et al. previously demonstrated that concentric LV remodelling and hypertrophy, compared to normal LV geometry, were independently associated with decreased survival in patients with moderate and severe AS[24]. Likewise, Capoulade et al. analyzed the impact of LV remodelling patterns in patients with AS (peak velocity > 2.0 m/s) and preserved LVEF, demonstrating that concentric hypertrophy was independently associated with all-cause mortality when compared to other LV geometric patterns[23]. However, tricuspid AV morphology was the predominant phenotype in these studies. Our results confirm that patients with concentric geometry, isolated AS and BAV have reduced event-free survival compared to those with normal geometry.

The present study also demonstrates that elevated LV mass index, concentric hypertrophy and eccentric hypertrophy are independently related to a composite endpoint of aortic valve repair/replacement and all-cause mortality in patients with isolated AR. Furthermore, higher LV mass index was associated with all-cause mortality at long-term follow-up. Data investigating the prognostic implications of LV remodelling in significant isolated AR remain scarce. In a study including 130 patients undergoing surgery for significant AR due to a variety of etiologies, post-operative, but not pre-operative LV mass index was associated with all-cause mortality on univariable analysis[30]. Contrarily, in a study of 113 patients with significant AR, no preoperative hemodynamic or echocardiographic variables (including LV mass) were related to long-term outcome, although preoperative echocardiographic data were only available in 44 patients[31]. Providing a possible pathophysiological mechanism linking elevated LV mass index with poorer outcome, Taniguchi et al. demonstrated that substantial increases in LV mass index, but not LV geometric pattern, were associated with a deterioration in LV contractility that persisted post-operatively[32]. Nonetheless, further research is required to confirm the role of LV mass index for the risk stratification of patients with isolated AR.

Interestingly, we did not observe an independent association between LV mass index or LV geometric pattern and the composite endpoint in the patient subgroup with MAVD. However, our findings are consistent with most previous studies. In three studies of

patients with MAVD of a variety of etiologies, increasing LV mass index or LV hypertrophy were not independently associated with event-free survival[27, 33, 34], although one study did observe an independent association[28]. Likewise, in a study of 138 patients with unicuspid or bicuspid aortic valves and MAVD, LV mass index was not related to event-free survival[35]. It is possible that increased LV mass in MAVD is principally an adaptive (rather than maladaptive) physiological response to the combination of extreme volume and pressure overload imposed on the left ventricle, a concept which may provide an explanation for the absence of an association between indices of LV remodelling and the primary endpoint in this study.

Limitations

This study is subject to the limitations of its retrospective, observational design. Furthermore, several centers involved in this international registry act as referral centers for their respective regions, potentially leading to an imperfect estimation of prevalence data and heterogeneity in the time until surgical intervention across centers. Additionally, data analysis for the secondary endpoint of all-cause mortality was limited by a low-event rate. Although this study had a substantial number of participants, further analysis in studies that are adequately powered to evaluate interactions between LV remodelling and sex are needed for each type of BAV disease. Furthermore, additional studies are required to establish validated prediction models that integrate anatomical LV remodelling (including LV geometry and LV mass index, as appropriate for the type of valvular dysfunction), LV function (LV ejection fraction and/or LV global longitudinal strain), valvular disease severity, and other clinical characteristics, to identify BAV patients at the highest risk for requiring future aortic valve surgery.

CONCLUSION

LV hypertrophy and remodelling were independently associated with the composite endpoint of aortic valve repair/replacement and all-cause mortality for patients with a BAV and isolated AS and isolated AR, although not for patients with MAVD.

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SUPPLEMENTARY MATERIAL

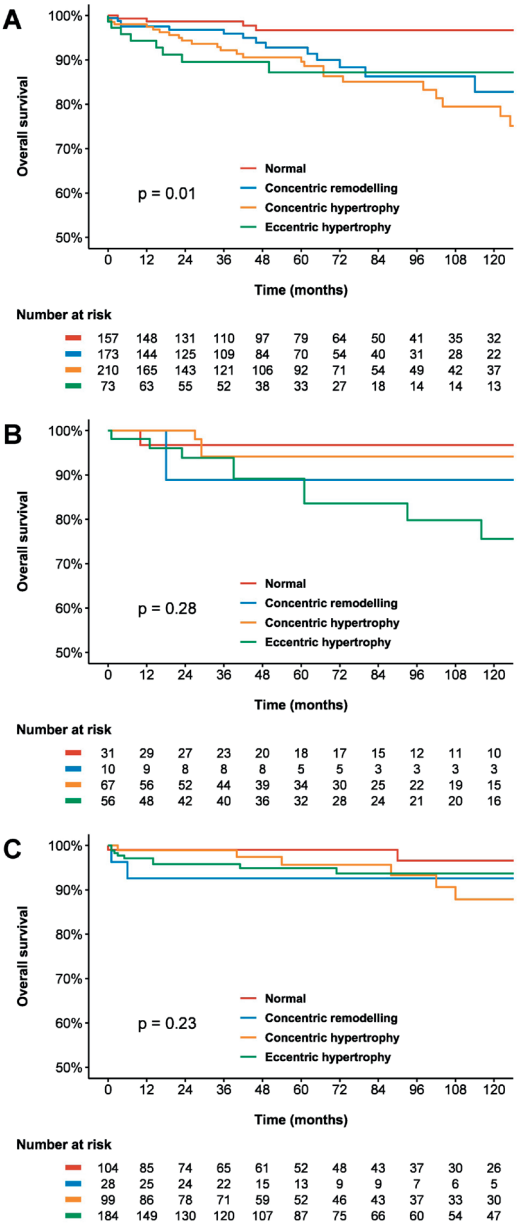

Figure S1: Kaplan-Meier curves for all-cause mortality according LV geometric pattern. Panels A, B and C demonstrate the Kaplan-Meier survival estimates according to LV geometric pattern for aortic stenosis, mixed AV disease and aortic regurgitation, respectively.

AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricular; MR = mitral regurgitation

Table S1: Cox regression models for event-free survival according to AV dysfunction type

	Isolated aortic stenosis[a] (n=669)		Mixed aortic valve disease[b] (n=177)		Isolated aortic regurgitation[c] (n=499)	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Univariable analysis						
LV mass index, per 25g/m^2	1.226 (1.155 to 1.302)	<0.001	1.173 (1.084 to 1.269)	<0.001	1.284 (1.217 to 1.354)	<0.001
LV geometric pattern						
Normal geometry	*Reference*		*Reference*		*Reference*	
Concentric remodelling	2.188 (1.572 to 3.044)	<0.001	1.195 (0.466 to 3.063)	0.711	1.300 (0.476 to 3.551)	0.609
Concentric hypertrophy	2.902 (2.118 to 3.977)	<0.001	1.657 (0.936 to 2.934)	0.083	3.313 (1.878 to 5.843)	<0.001
Eccentric hypertrophy	2.165 (1.453 to 3.226)	<0.001	1.513 (0.842 to 2.718)	0.166	3.952 (2.327 to 6.713)	<0.001
Multivariable models for LV mass index						
LV mass index, per 25g/m^2	1.080 (1.001 to 1.165)	0.046	0.968 (0.849 to 1.102)	0.621	1.194 (1.110 to 1.285)	<0.001
Multivariable models for LV geometric pattern						
LV geometric pattern						
Normal geometry	*Reference*		*Reference*		*Reference*	
Concentric remodelling	1.535 (1.058 to 2.227)	0.024	1.621 (0.603 to 4.360)	0.339	1.066 (0.347 to 3.279)	0.911
Concentric hypertrophy	1.682 (1.168 to 2.423)	0.005	0.854 (0.450 to 1.620)	0.630	2.489 (1.346 to 4.603)	0.004
Eccentric hypertrophy	1.587 (1.026 to 2.454)	0.038	1.067 (0.520 to 2.191)	0.859	3.051 (1.709 to 5.446)	<0.001

[a] Multivariable model adjusting for age, smoking, coronary artery disease, hypertension, aortic valve area, aortic root or ascending aorta dilation, LAVI and LVEF.
[b] Multivariable model adjusting for age, aortic root or ascending aorta dilation, hypertension, aortic valve area, AR vena contracta width, LAVI and LVEF.
[c] Multivariable model adjusting for age, smoking, coronary artery disease, hypertension, aortic root or ascending aorta dilation, AR vena contracta width, LAVI and LVEF.
AR = aortic regurgitation; AV = aortic valve; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction

Table S2: Cox regression models for all-cause mortality according to AV dysfunction type

	Isolated aortic stenosis[a] (n=669)		Mixed aortic valve disease[a] (n=177)		Isolated aortic regurgitation[a] (n=499)	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Univariable analysis						
LV mass index, per 25g/m^2	1.274 (1.105 to 1.468)	0.002	1.186 (1.012 to 1.390	0.036	1.284 (1.115 to 1.480	0.001
LV geometric pattern						
Normal geometry	*Reference*		*Reference*		*Reference*	
Concentric remodeling	3.049 (1.190 to 7.811)	0.020	3.306 (0.207 to 52.903)	0.398	5.779 (0.964 to 34.650)	0.055
Concentric hypertrophy	4.040 (1.672 to 9.758)	0.002	2.615 (0.306 to 22.386)	0.380	3.280 (0.679 to 15.857)	0.140
Eccentric hypertrophy	3.640 (1.295 to 10.232)	0.014	5.207 (0.659 to 41.122)	0.118	2.709 (0.590 to 12.431)	0.200
Multivariable models for LV mass index						
LV mass index, per 25g/m^2	1.143 (0.982 to 1.329)	0.084	1.057 (0.862 to 1.296)	0.592	1.186 (1.004 to 1.400)	0.044
Multivariable models for LV geometric pattern						
LV geometric pattern						
Normal geometry	*Reference*					
Concentric remodeling	2.711 (0.982 to 7.484)	0.054				
Concentric hypertrophy	2.871 (1.093 to 7.541)	0.032				
Eccentric hypertrophy	2.347 (0.749 to 7.356)	0.143				

[a]Multivariable model adjusting for age and LVEF.

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction

Table S3: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Stenosis

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
Age						0.871
	< 50 years	**197**	**Normal**	*Reference*		
			CR	1.738 (1.001 to 3.017)	0.050	
			CH	2.463 (1.437 to 4.220)	0.001	
			ER	1.566 (0.765 to 3.208)	0.220	
	≥ 50 years	**416**	**Normal**	*Reference*		
			CR	2.065 (1.350 to 3.159)	0.001	
			CH	2.481 (1.655 to 3.720)	<0.001	
			ER	2.164 (1.318 to 3.554)	0.002	
Sex						0.612
	Male	**385**	**Normal**	*Reference*		
			CR	2.539 (1.674 to 3.850)	<0.001	
			CH	3.315 (2.206 to 4.982)	<0.001	
			ER	2.704 (1.618 to 4.519)	<0.001	
	Female	**228**	**Normal**	*Reference*		
			CR	1.711 (0.976 to 3.001)	0.061	
			CH	2.478 (1.497 to 4.102)	<0.001	
			ER	1.665 (0.883 to 3.139)	0.115	
Hypertension						0.844
	Yes	**265**	**Normal**	*Reference*		
			CR	2.166 (1.318 to 3.561)	0.002	
			CH	2.584 (1.611 to 4.144)	<0.001	
			ER	1.941 (1.051 to 3.583)	0.034	
	No	**332**	**Normal**	*Reference*		
			CR	2.166 (1.384 to 3.388)	0.001	
			CH	3.128 (2.040 to 4.797)	<0.001	
			ER	2.305 (1.354 to 3.923)	0.002	
Diabetes						0.347
	Yes	**100**	**Normal**	*Reference*		
			CR	1.137 (0.517 to 2.504)	0.749	
			CH	1.621 (0.766 to 3.430)	0.206	
			ER	1.066 (0.430 to 2.640)	0.890	
	No	**453**	**Normal**	*Reference*		
			CR	2.233 (1.520 to 3.280)	<0.001	
			CH	2.980 (2.086 to 4.257)	<0.001	
			ER	2.222 (1.402 to 3.524)	0.001	
CAD						0.416
	Yes	**62**	**Normal**	*Reference*		

Table S3: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Stenosis (*continued*)

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
			CR	2.464 (0.856 to 7.094)	0.095	
			CH	5.467 (1.956 to 15.276)	0.001	
			ER	6.343 (1.738 to 23.149)	0.005	
	No	**525**	**Normal**	*Reference*		
			CR	2.231 (1.558 to 3.196)	<0.001	
			CH	2.870 (2.037 to 4.043)	<0.001	
			ER	2.123 (1.381 to 3.264)	0.001	

ER = eccentric remodelling; CAD = coronary artery disease; CH = concentric hypertrophy; CR = concentric remodelling; LV = left ventricular; Normal = normal geometry

Table S4: Subgroup analysis and interaction for event-free survival for LV Mass Index (per 25g/m^2) in Isolated Aortic Stenosis

Subgroup		Number	Hazard Ratio (95% CI)	P-value	P-value for interaction
Age					0.231
	< 50 years	**197**	1.290 (1.106 to 1.504)	0.001	
	≥ 50 years	**416**	1.161 (1.084 to 1.243)	<0.001	
Sex					0.698
	Male	**385**	1.245 (1.159 to 1.338)	<0.001	
	Female	**228**	1.211 (1.083 to 1.355)	0.001	
Hypertension					0.142
	Yes	**265**	1.171 (1.073 to 1.278)	<0.001	
	No	**332**	1.278 (1.169 to 1.398)	<0.001	
Diabetes					0.105
	Yes	**100**	1.097 (0.951 to 1.265)	0.203	
	No	**453**	1.256 (1.169 to 1.349)	<0.001	
CAD					0.228
	Yes	**62**	1.166 (1.038 to 1.310)	0.010	
	No	**525**	1.243 (1.156 to 1.338)	<0.001	

CAD = coronary artery disease; LV = left ventricular

Table S5: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Regurgitation

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
Age						0.695
	< 50 years	**277**	**Normal**	*Reference*		
			CR	1.201 (0.259 to 5.566)	0.815	
			CH	4.050 (1.904 to 8.615)	<0.001	
			ER	4.433 (2.195 to 8.951)	<0.001	
	≥ 50 years	**138**	**Normal**	*Reference*		
			CR	0.973 (0.249 to 3.792)	0.968	
			CH	2.122 (0.895 to 5.038)	0.088	
			ER	3.012 (1.338 to 6.779)	0.008	
Sex						0.331
	Male	**347**	**Normal**	*Reference*		
			CR	1.409 (0.512 to 3.882)	0.507	
			CH	3.339 (1.855 to 6.012)	<0.001	
			ER	3.497 (2.008 to 6.089)	<0.001	
	Female	**68**	**Normal**	*Reference*		
			CR	-		
			CH	3.936 (0.439 to 35.322)	0.221	
			ER	9.475 (1.269 to 70.731)	0.028	
Hypertension						0.407
	Yes	**126**	**Normal**	*Reference*		
			CR	0.474 (0.057 to 3.941)	0.489	
			CH	1.825 (0.705 to 4.722)	0.215	
			ER	2.446 (1.027 to 5.829)	0.043	
	No	**275**	**Normal**	*Reference*		
			CR	1.726 (0.540 to 5.514)	0.357	
			CH	4.319 (2.122 to 8.790)	<0.001	
			ER	4.221 (2.152 to 8.279)	<0.001	
Diabetes						0.679
	Yes	**19**	**Normal**	*Reference*		
			CR	-		
			CH	1.271 (0.177 to 9.138)	0.812	
			ER	0.775 (0.070 to 8.599)	0.836	
	No	**389**	**Normal**	*Reference*		
			CR	1.463 (0.527 to 4.067)	0.465	
			CH	3.424 (1.876 to 6.249)	<0.001	
			ER	4.262 (2.430 to 7.477)	<0.001	
CAD						0.806
	Yes	**30**	**Normal**	*Reference*		

Table S5: Subgroup analysis and interactions for event-free survival for LV Remodelling in Isolated Aortic Regurgitation (*continued*)

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
			CR	-		
			CH	1.728 (0.323 to 9.248)	0.523	
			ER	1.755 (0.351 to 8.762)	0.493	
	No	**363**	**Normal**	*Reference*		
			CR	1.633 (0.582 to 4.586)	0.352	
			CH	3.598 (1.931 to 6.704)	<0.001	
			ER	4.024 (2.241 to 7.226)	<0.001	

ER = eccentric remodelling; CAD = coronary artery disease; CH = concentric hypertrophy; CR = concentric remodelling; LV = left ventricular; Normal = normal geometry

Table S6: Subgroup analysis and interaction for event-free survival for LV Mass Index (per 25g/m^2) in Isolated Aortic Regurgitation

Subgroup		Number	Hazard Ratio (95% CI)	P-value	P-value for interaction
Age					0.011
	< 50 years	**277**	1.345 (1.252 to 1.446)	<0.001	
	≥ 50 years	**138**	1.187 (1.092 to 1.292)	<0.001	
Sex					0.085
	Male	**347**	1.270 (1.199 to 1.345)	<0.001	
	Female	**68**	1.485 (1.225 to 1.801)	<0.001	
Hypertension					0.639
	Yes	**126**	1.263 (1.133 to 1.407)	<0.001	
	No	**275**	1.279 (1.200 to 1.363)	<0.001	
Diabetes					0.567
	Yes	**19**	1.235 (0.818 to 1.863)	0.315	
	No	**389**	1.286 (1.219 to 1.357)	<0.001	
CAD					0.029
	Yes	**30**	2.225 (1.397 to 3.544)	0.001	
	No	**363**	1.275 (1.205 to 1.348)	<0.001	

CAD = coronary artery disease; LV = left ventricular

Table S7: Subgroup analysis and interactions for all-cause mortality for LV Remodelling in Isolated Aortic Stenosis

Subgroup		Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
Age						0.928
	< 50 years	**197**	**Normal**	*Reference*		
			CR	3.363 (0.304 to 37.195)	0.323	
			CH	3.734 (0.387 to 36.060)	0.255	
			ER	6.014 (0.544 to 66.498)	0.143	
	≥ 50 years	**416**	**Normal**	*Reference*		
			CR	2.184 (0.784 to 6.089)	0.135	
			CH	2.610 (0.995 to 6.850)	0.051	
			ER	2.617 (0.829 to 8.262)	0.101	
Sex						0.580
	Male	**385**	**Normal**	*Reference*		
			CR	2.341 (0.885 to 6.191)	0.086	
			CH	2.528 (0.985 to 6.489)	0.054	
			ER	3.113 (1.044 to 9.279)	0.042	
	Female	**228**	**Normal**	*Reference*		
			CR	-*		
			CH	-		
			ER	-		
Hypertension						0.093
	Yes	**265**	**Normal**	*Reference*		
			CR	1.429 (0.450 to 4.540)	0.545	
			CH	3.356 (1.261 to 8.930)	0.015	
			ER	3.032 (0.922 to 9.968)	0.068	
	No	**332**	**Normal**	*Reference*		
			CR	10.508 (1.330 to 83.050)	0.026	
			CH	5.400 (0.649 to 44.906)	0.119	
			ER	4.947 (0.448 to 54.671)	0.192	
Diabetes						0.087
	Yes	**100**	**Normal**	*Reference*		
			CR	1.852 (0.359 to 9.562)	0.462	
			CH	2.623 (0.565 to 12.174)	0.218	
			ER	2.560 (0.467 to 14.037)	0.279	
	No	**453**	**Normal**	*Reference*		
			CR	3.250 (0.995 to 10.614)	0.051	
			CH	3.661 (1.223 to 10.955)	0.020	
			ER	3.372 (0.905 to 12.570)	0.070	
CAD						0.321
	Yes	**62**	**Normal**	*Reference*		

Table S7: Subgroup analysis and interactions for all-cause mortality for LV Remodelling in Isolated Aortic Stenosis (*continued*)

Subgroup	Number		Hazard Ratio (95% CI)	P-value	P-value for interaction
		CR	-		
		CH	3.028 (0.338 to 27.116)	0.322	
		ER	-		
No	**525**	**Normal**	*Reference*		
		CR	3.650 (1.323 to 10.070)	0.012	
		CH	4.021 (1.528 to 10.578)	0.005	
		ER	3.849 (1.259 to 11.772)	0.018	

*Coefficients did not converge
ER = eccentric remodelling; CAD = coronary artery disease; CH = concentric hypertrophy; CR = concentric remodelling; LV = left ventricular; Normal = normal geometry

Table S8: Subgroup analysis and interactions for all-cause mortality for LV Mass Index (per 25g/m^2) in Isolated Aortic Regurgitation

Subgroup		Number	Hazard Ratio (95% CI)	P-value	P-value for interaction
Age					0.807
	< 50 years	**277**	1.203 (0.916 to 1.579)	0.184	
	≥ 50 years	**138**	1.298 (1.087 to 1.551)	0.004	
Sex					0.726
	Male	**347**	1.298 (1.123 to 1.502)	<0.001	
	Female	**68**	0.970 (0.448 to 2.099)	0.938	
Hypertension					0.794
	Yes	**126**	1.247 (0.908 to 1.713)	0.173	
	No	**275**	1.250 (1.046 to 1.494)	0.014	
Diabetes					0.741
	Yes	**19**	4.027 (0.019 to 856.392)	0.610	
	No	**389**	1.280 (1.107 to 1.480)	0.001	
CAD					0.658
	Yes	**30**	1.425 (0.928 to 2.188)	0.105	
	No	**363**	1.263 (1.051 to 1.517)	0.013	

CAD = coronary artery disease; LV = left ventricular