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

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Impact of Left Ventricular Ejection Fraction on Clinical Outcomes in Bicuspid Aortic Valve Disease

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ABSTRACT

Background

The prognostic impact of left ventricular ejection fraction (LVEF) in patients with bicuspid aortic valve (BAV) disease has not been previously studied.

Objectives

The objective of this study was to determine the prognostic impact of LVEF in BAV patients according to the type of aortic valve dysfunction.

Methods

We retrospectively analyzed the data collected in 2,672 patients included in an international registry of patients with BAV. Patients were classified according to the type of aortic valve dysfunction: isolated aortic stenosis (AS) (n=749), isolated aortic regurgitation (AR) (n=554), mixed aortic valve disease (MAVD) (n=190), or no significant aortic valve dysfunction (n=1179; excluded from this analysis). The study population was divided according to LVEF strata to investigate its impact on clinical outcomes.

Results

The risk of all-cause mortality and the composite endpoint of aortic valve replacement or repair (AVR) and all-cause mortality increased when LVEF was <60% in the whole cohort as well as in the AS and AR groups, and <55% in MAVD group. In multivariable analysis, LVEF strata were significantly associated with increased rate of mortality (LVEF 50-59%: HR [95%CI]: 1.83 [1.09-3.07], p=0.022; LVEF 30-49%: HR [95%CI]: 1.97 [1.13-3.41], p=0.016; LVEF<30%: HR [95%CI]: 4.20 [2.01-8.75], p<0.001; versus LVEF 60-70%, reference group).

Conclusion

In BAV patients, the risk of adverse clinical outcomes increases significantly when the LVEF is <60%. These findings suggest that LVEF cut-off values proposed in the guidelines to indicate intervention should be raised from 50 to 60% in AS or AR and 55% in MAVD.

INTRODUCTION

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease with a prevalence of 1-2% in the general population[1]. This congenital cardiac defect is known as a strong risk factor for the development of aortic valve diseases such as aortic stenosis (AS), aortic regurgitation (AR), and mixed aortic valve disease (MAVD)[2-5]. Patients with BAV often develop AS and AR earlier and more frequently than patients with tricuspid aortic valve (TAV) and they have ~50% risk of requiring aortic valve replacement (AVR) during their lifetime[6].

In patients with asymptomatic severe AS (both in BAV and TAV), left ventricular (LV) systolic dysfunction, defined as left ventricular ejection fraction (LVEF) ≤50%, is a major criterion (Class I) to recommend AVR[7-10]. However, LVEF may underestimate the degree of LV systolic dysfunction and several studies conducted in patients with AS suggested that the cut-off value of LVEF to define LV systolic dysfunction and eventually trigger intervention should be raised to 55% or 60%[11]. Accordingly, the recent editions of the American and European guidelines included new recommendations for AVR in asymptomatic patients with severe AS if LVEF is <60% (American guidelines) or 55% (European guidelines). In asymptomatic patients with chronic severe aortic regurgitation, surgery is recommended when LVEF is < 50% (Class I in ESC guidelines) or <55% (Class I in American guidelines and IIb in European guidelines). The prognostic impact of LVEF however, has not been explored in BAV disease.

The objectives of this study were: i) to determine the prognostic impact (AVR and/or all-cause mortality) of LVEF in patients with BAV disease; ii) to determine the cut-off value of LVEF below which the risk of adverse outcomes (AVR and/or all-cause mortality) becomes significant in BAV patients with AS, AR, or MAVD.

METHODS

Population

We retrospectively analyzed the data of 2,672 patients from an international BAV registry.[12] Patients with complex congenital heart disease, previous endocarditis, or AV surgery, or without significant (<moderate) aortic valve disease, were excluded. First, the study population was divided according to LVEF strata (LVEF>70%, n=269; 60-70%, n=679; 50-59%, n=316; 30-49%, n=182; <30%, n=47) in order to investigate the impact of LVEF on clinical outcomes. Then, to investigate the impact of LVEF on clinical outcomes in each type of aortic valve dysfunction, the BAV cohort was divided in 4 groups: whole cohort (BAV patients with significant aortic valve dysfunction, n=1493), isolated AS (significant AS [≥ moderate] and less than moderate AR, n=749), isolated AR (significant

AR [≥ moderate] and less than moderate AS, n=554), mixed AV disease (both AS and AR ≥ moderate, n=190) (Figure 1). Demographic and clinical data were collected at the time of the first diagnosis of BAV on transthoracic echocardiography. The study was approved by the institutional review board of each center, and because of its retrospective nature, written informed consent was not required.

Echocardiographic Data

All echocardiographic exams were conducted using commercially available ultrasound systems. Measurements were retrospectively performed by experienced investigators from each center, using the first transthoracic echocardiography that allowed to diagnose BAV according to the system proposed by Sievers and Schmidtke[13]. AS severity was classified according to the actual guideline recommendations[14]. AR severity was assessed using a multiparametric approach as previously described[15]. MAVD was defined as the coexistence of moderate AS and moderate AR. MAVD was considered being severe if AS and / or AS was equal or greater than moderate. 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[16]. The aortic annulus was conventionally measured in mid-systole from inner-edge to inner-edge on a parasternal long-axis view[16]. LVEF was estimated using the biplane Simpson method. LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were measured using the 2D linear method, as per guideline recommendations[16]. LV mass was calculated by the modified American Society of Echocardiography formula and subsequently indexed to body surface area [16]. All other measurements were performed according to the European Association of Cardiovascular Imaging and American Society of Echocardiography guidelines and as previously described[16].

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 all-cause mortality occurring prior or after AVR, and the secondary endpoint was the composite of AVR and all-cause mortality. Indications for AVR were according to recommendations of contemporary guidelines, including patients with symptomatic severe aortic valve dysfunction, asymptomatic severe aortic valve dysfunction with reduced LVEF (≤50%), or patients with aortopathy, irrespective of the severity of aortic valve dysfunction[7,8]. The occurrence of surgical aortic valve repair or replacement was recorded with data collected by medical record review. The end-of-study follow-up date was September 31st, 2019. Follow-up data were available for 1334 (89.3%) patients: 693 (92.5%) of patients with isolated AS, 176 (92.6%)

patients with MAVD and 465 (83.9%) patients with isolated AR. Data for all patients were included up to the last date of follow-up.

Statistical Analyses

Continuous variables were expressed as median and interquartile range (IQR) and Kruskal-Wallis tests were performed to evaluate for differences according to the type of AV dysfunction. Multiple comparisons were tested using Bonferroni's correction. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate, and are expressed in number of patients with percentages. To account for missing data, analyses were conducted using multiple imputations by predictive mean matching using a chained-equation approach and generating 100 imputed datasets[17]. The results of the survival analyses were obtained by averaging the parameter estimates across the multiple datasets using Rubin's rules to combine the standard errors[18]. Cumulative incidence of 1- and 5- year all-cause mortality and the composite endpoint of all-cause mortality and AVR 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 LVEF strata with the endpoint of all-cause mortality and the composite endpoint of all-cause mortality and AVR. 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). Hazard ratio (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 addition, to further investigate the relationship between LVEF strata and the HR change for the primary and secondary endpoints, a spline curve was fitted for each type of AV disease (isolated AS, isolated AR and MAVD). The incremental predictive value on the multivariable models including LVEF versus the baseline model was assessed by the C-index. Likelihood ratio (LR) tests and the rank correlation U-statistic for paired censored data were used to evaluate the prognostic value of LVEF by comparing model fit and the concordance of models with and without LVEF, respectively. 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 and echocardiographic characteristics

Baseline characteristics of the study population according to LVEF are shown in Table 1. Among the 1493 patients with BAV disease, 269 (18.0%) had LVEF >70%, 679 (45.5%) had LVEF between 60-70%, 316 (21.2%) had LVEF between 50-59%, 182 (12.2%) had LVEF between 30-49% and 47 (3.1%) had LVEF <30%. In the total cohort, the median age was 51 (37-63) years and 70% were male. Overall, patients with reduced LVEF (<50%) were older, more frequently male and had worse cardiovascular profiles. Echocardiographic data are presented in Table 2. Patients with LVEF >70% had smaller LV, aorta and sinus of Valsalva dimensions as compared to the other groups ($p<0.05$). On the other hand, patients with LVEF <30% had more extensive cardiac damage. The proportion of AS ≥ moderate was similar across all groups, but moderate aortic and mitral regurgitation were more prevalent in groups with reduced LVEF (<50%) (Table 2). Echocardiographic characteristics of the whole cohort according to aortic valve dysfunction are presented in Table S1.

Prognostic value of LVEF in overall cohort

In the whole cohort, the primary endpoint of all-cause mortality occurred in 117 (8.8%) patients over a median follow-up of 56 (22-102) months. The secondary endpoint occurred in 675 (51%) patients: i.e. 602 (45%) patients underwent AVR and 73 (5.5%) died over a median follow-up of 21 (3-67) months. Of those who underwent AVR, 334 (55%), had a biological AVR, 178 (30%) had a mechanical AVR, 13 (2.2%) had a homograft or autograft, 13 (2.2%) underwent valvulotomy, 18 (3.0%) underwent TAVI, 18 (3.0%) underwent aortic valve repair, while data pertaining to the specifics of the other 28 (4.6%) surgeries were not available. In addition, 268 (44.5%) patients also underwent aortic root repair.

On Kaplan-Meier analysis, LVEF stratum <50% was significantly associated with higher rates of all-cause mortality (Figure 2A) and the composite endpoint of AVR and mortality (Figure 3A), and there was also a trend toward association with events for patients with a LVEF 50-59%. Using spline curve analysis, a LVEF <60% was found to be associated with increased risk of mortality (Figure S1A) and of the composite endpoint of mortality and AVR (Figure S2A).

In univariate Cox regression analysis, using LVEF 60-70% stratum as a reference group, there was a significant increase in the risk of all-cause mortality and of the composite endpoint for each decrease in LVEF stratum except for the LVEF 50-59% stratum where a strong trend was noted (Table 3). In multivariable analysis, when compared to the LVEF 60-70% stratum as a reference group, each decrease in LVEF strata was significantly associated with incremental increase in the rate of mortality (LVEF 50-59%: HR

Table 1: Patient Characteristics According to LVEF Strata

Variable	Overall N = 1,493	LVEF >70% N = 269	LVEF 60-70% N = 679	LVEF 50-59% N = 316	LVEF 30-49% N = 182	LVEF <30% N = 47	P-value
Age, years	51 (37 – 63)	50 (36 – 63)	50 (35 – 62)	51 (37 – 61)	60 (47 – 69) *†‡	57 (46 – 64)	**<0.001**
Male Sex	1,049 (70%)	178 (66%)	458 (67%)	232 (73%)	145 (80%)*†	36 (77%)	**0.005**
Hypertension	531 (38%)	90 (38%)	237 (37%)	109 (36%)	77 (44%)	18 (41%)	0.47
Dyslipidemia	427 (30%)	58 (24%)	198 (30%)	83 (27%)	75 (42%)*†‡	13 (28%)	**0.002**
Current smoker	226 (16%)	38 (16%)	95 (16%)	52 (17%)	34 (19%)	7 (15%)	0.87
Diabetes mellitus	161 (12%)	27 (11%)	62 (10%)	36 (12%)	26 (15%)	10 (22%)	0.13
Coronary artery disease	119 (8.7%)	19 (8.1%)	49 (7.8%)	24 (8.2%)	19 (11%)	8 (18%)	0.15
BAV morphology							0.07
No raphe	132 (9.6%)	17 (7.1%)	56 (9.3%)	31 (10%)	21 (12%)	7 (15%)	
Type 1 raphe (L-R)	935 (68%)	159 (67%)	404 (67%)	210 (69%)	128 (72%)	34 (74%)	
Type 1 raphe (R-N)	229 (17%)	46 (19%)	115 (19%)	45 (15%)	19 (11%)	4 (8.7%)	
Type 1 raphe (L-N)	63 (4.6%)	14 (5.9%)	19 (3.2%)	18 (5.9%)	11 (6.1%)	1 (2.2%)	
Type 2 raphe	12 (0.9%)	3 (1.3%)	8 (1.3%)	1 (0.3%)	0 (0%)	0 (0%)	

Legends: Continuous data are expressed by median (IQR). Categorical data are expressed by number (percent). P-values refer to comparison between LVEF groups. BAV, bicuspid aortic valve; LVEF, left ventricular ejection fraction.
*p<0.05 vs Group I; †p<0.05 vs Group II; ‡p<0.05 vs Group III; §p<0.05 vs Group IV.

Table 2: Echocardiographic Characteristics According to LVEF Strata

Variable	Overall N = 1,493	LVEF >70% N = 269	LVEF 60-70% N = 679	LVEF 50-59% N = 316	LVEF 30-49% N = 182	LVEF <30% N = 47	P-value
LV end-diastolic diameter, cm	5.20 (4.60 – 5.80)	4.90 (4.40 – 5.40)	5.04 (4.50 – 5.60)*	5.20 (4.80 – 5.80)*†	5.80 (5.20 – 6.40)*†‡	6.80 (5.60 – 7.60)*†‡	**<0.001**
LV end-systolic diameter, cm	3.40 (2.90 – 4.00)	2.70 (2.40 – 3.00)	3.30 (2.90 – 3.70)*	3.70 (3.30 – 4.10)*†	4.60 (4.00 – 5.20)*†‡	6.20 (5.20 – 6.70)*†‡	**<0.001**
LV end diastolic volume, ml	127 (97 – 166)	108 (86 – 137)	122 (95 – 154)*	129 (103 – 167)*	163 (129 – 211)*†‡	227 (172 – 294)*†‡§	**<0.001**
LV end systolic volume, ml	47 (32 – 69)	27 (20 – 35)	42 (32 – 56)*	58 (47 – 74)*†	97 (71 – 130)*†‡	174 (130 – 228)*†‡§	**<0.001**
LVEF, %	63 (55 – 69)	75 (73 – 79)	65 (62 – 67)*	55 (53 – 58)*†	42 (36 – 46)*†‡	23 (20 – 26)*†‡	-
LV mass index, g/m^2	117 (93 – 150)	111 (90 – 143)	111 (88 – 138)	119 (93 – 150)	145 (116 – 188)*†‡	167 (144 – 221)*†‡	**<0.001**
Left atrial volume index, ml/m^2	28 (21 – 37)	24 (20 – 34)	27 (21 – 36)	27 (20 – 36)	32 (23 – 48)*†‡	37 (26 – 56)*†‡	**<0.001**
Mitral inflow E wave velocity, m/s	0.80 (0.60 – 0.91)	0.80 (0.62 – 0.96)	0.80 (0.63 – 0.90)	0.80 (0.60 – 0.90)	0.78 (0.60 – 0.95)	0.80 (0.65 – 1.00)	0.22
Mitral inflow E/A ratio	1.14 (0.82 – 1.55)	1.11 (0.85 – 1.43)	1.14 (0.83 – 1.50)	1.14 (0.79 – 1.60)	1.00 (0.75 – 1.60)	1.67 (0.99 – 2.02)*†‡§	**0.014**
MR							
Moderate MR	82 (5.5%)	5 (1.9%)	22 (3.2%)	12 (3.8%)	27 (15%)*†‡	15 (32%)*†‡§	**<0.001**
Severe MR	25 (1.7%)	5 (1.9%)	3 (0.4%)	5 (1.6%)	5 (2.7%)*†‡	7 (15%)*†‡§	**<0.001**
AS							
Moderate AS	458 (31%)	87 (32%)	221 (32%)*	95 (30%)*	48 (26%)	7 (15%)‡	**<0.001**
Severe AS	481 (32%)	113 (42%)	208 (31%)*	81 (26%)*	57 (31%)	22 (47%)‡	**<0.001**
AR							
Moderate AR	487 (33%)	87 (32%)	209 (31%)	122 (39%)	56 (31%)*†	13 (28%)*‡	**<0.001**
Severe AR	257 (17%)	31 (12%)	105 (15%)	59 (19%)	48 (26%)*†	14 (30%)*†	**<0.001**
Severe MAVD	190 (13%)	49 (18%)	64 (9%)*	41 (13%)	27 (15%)	9 (19%)	**0.002**
Mean pressure gradient, mmHg	20 (10 – 35)	27 (15 – 41)	20 (10 – 34)*	17 (8 – 30)*†	16 (9 – 29)*	19 (8 – 34)*	**<0.001**
Peak aortic velocity, m/s	2.97 (2.12 – 3.80)	3.48 (2.67 – 4.20)	2.99 (2.20 – 3.80)*	2.68 (2.00 – 3.55)*†	2.66 (2.05 – 3.52)*	2.80 (1.84 – 3.62)*	**<0.001**
Aortic valve area, cm	1.30 (1.00 – 2.10)	1.10 (0.90 – 1.50)	1.30 (1.00 – 2.10)*	1.36 (1.00 – 2.50)*	1.30 (1.00 – 2.20)	1.15 (0.75 – 1.98)	**<0.001**
SOV diameter indexed, mm/m^2	18.3 (16.3 – 20.5)	17.1 (15.3 – 19.3)	18.4 (16.3 – 20.5)*	18.7 (16.6 – 20.7)*	19.4 (17.1 – 21.8)*†	18.8 (16.8 – 20.9)*	**<0.001**
STJ diameter indexed, mm/m^2	15.8 (13.8 – 17.9)	15.3 (13.5 – 17.1)	15.7 (14.0 – 17.6)	16.1 (13.7 – 18.4)*	16.7 (14.6 – 19.0)*†	16.2 (13.7 – 18.5)	**<0.001**
Ascending aorta diameter indexed, mm/m^2	19.7 (17.2 – 22.5)	19.7 (17.0 – 22.5)	19.9 (17.3 – 22.5)*	19.3 (16.9 – 22.3)*†	20.1 (17.5 – 23.5)*†‡	19.8 (17.8 – 22.4)*†‡§	0.41

Legends: As Table 1. AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; BAV, bicuspid aortic valve; LV, left ventricle; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease; MR, mitral regurgitation; SOV, sinus of Valsalva; STJ, sinotubular junction.
*p<0.05 vs Group I; †p<0.05 vs Group II; ‡p<0.05 vs Group III; §p<0.05 vs Group IV.

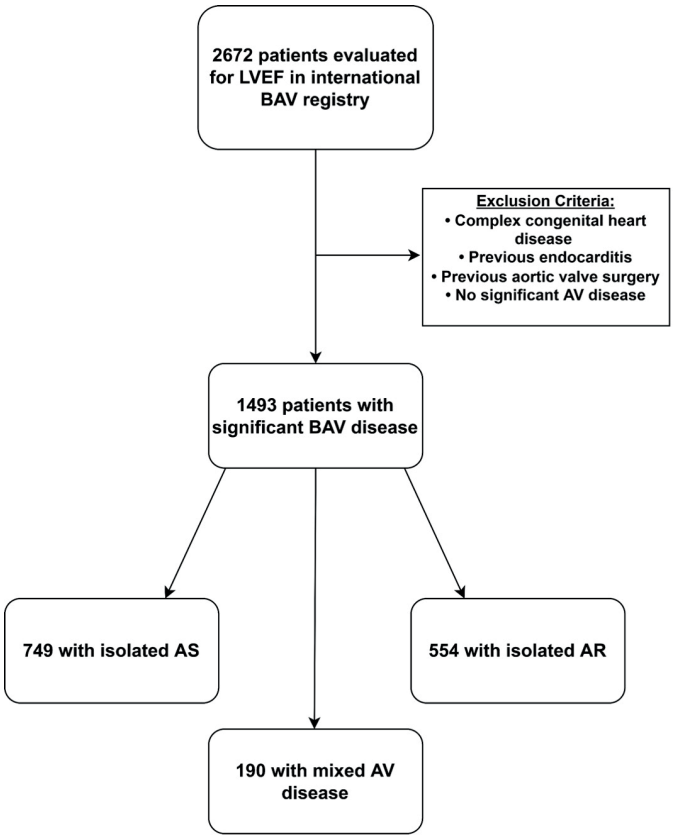

Figure 1:. Study Flow Chart. AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; BAV, bicuspid aortic valve; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease.

[95% CI]: 1.83 [1.09-3.07], p=0.022; LVEF 30-49%: HR [95% CI]: 1.97 [1.13-3.41], p=0.016; LVEF<30%: HR [95% CI]: 4.20 [2.01-8.75], p<0.001) and of the composite endpoint of AVR and mortality (LVEF 60-70% vs. LVEF 50-59%, HR [95% CI]: 1.35 [1.09-1.67], p=0.007; vs. LVEF 30-49%, HR [95% CI]: 1.69 [1.33-2.16], p<0.001; vs. LVEF <30%, HR [95% CI]: 1.82 [1.17-2.81], p=0.007). On the other hand, the >70% LVEF stratum was not associated with all-cause mortality or the composite endpoint in either univariate or multivariate analyses. The adjustment for AVR as a time dependent covariate provided similar results (Table S2).

Moreover, the addition of LVEF to the baseline model improved the predictive value of the model for the primary endpoint of all-cause mortality: C-Index increased from 0.766±0.024 to 0.789±0.023 (p=0.006) and χ^2 from 135.2 to 152.7, change 17.47, p=0.0016. The addition of LVEF to the baseline model improved the predictive value of the model for the composite of AVR and mortality: C-Index from 0.718±0.011 to 0.732±0.01 (p<0.0001) and χ^2 from 350.6 to 380.6, change 29.99, p<0.0001).

There was no significant interaction between LVEF and peak aortic jet velocity with regards to the impact on mortality (p=0.34). However, there was a significant interaction between LVEF and peak aortic velocity with regards to the combined endpoint (p=0.004) (Figure S3). For the LVEF strata > 30% the rate of the composite endpoint was higher in the patients with severe peak aortic velocity (4 m/s) versus mild velocity (2.5 m/s), and this was essentially driven by the higher rate of AVR in the former group, as expected. However, in the LVEF <30% stratum, the rates of the composite endpoint for patients with severe vs. those with mild peak aortic velocity tended to converge due to the mortality excess in this stratum.

In a sub-group analysis of asymptomatic patients (NYHA Class I), there was a trend toward higher risk of all-cause mortality in the LVEF 50-59% group (HR [95% CI]: 2.36 [0.68 to 8.17], p=0.17

Prognostic value of LVEF in isolated AS

Among the patients with isolated AS, 71 (10%) patients died during a median follow-up of 51 (21-83) months and 381 (55%) met the composite endpoint: 340 (49%) patients underwent AVR and 41 (5.9%) died over a median follow-up of 19 (2-57) months. On Kaplan-Meier analyses, the rate of mortality increased in patients with LVEF <50% (p=0.005, Figure 2B). However, there was only a trend between LVEF strata and the composite endpoint of all-cause mortality and AVR (p=0.075, Figure 3B). On spline curve analyses, the risk of mortality and of the composite of mortality and AVR increased when LVEF becomes <55-60% (Figures S1B and S2B).

Prognostic value of LVEF in isolated AR

For those with AR, during a median follow-up of 57 (20-119) months, 27 (5.8%) patients died and 181 (39%) met the composite endpoint: 162 (35%) patients underwent AVR and 19 (4.1%) died over a median follow-up of 25 (4-79) months. On Kaplan-Meier analyses, there was a significant increased risk of all-cause mortality (p=0.028, Figure 2C) and of the composite of AVR and mortality (p<0.001, Figure 3C) in patients with LVEF <60%. On spline curve analyses, the risk of mortality and of the composite of AVR and mortality increased when LVEF fell below a threshold of ~60% (Figures S1C and S2C).

Prognostic value of LVEF in MAVD

Of the patients with MAVD, 19 (11%) patients died during a median follow-up of 69 (29-120) months and 113 (64%) met the composite endpoint: 100 (57%) AVR and 13 (7.4%) deaths over a median follow-up of 18 (2-76) months. On Kaplan-Meier analyses, there was a significant increase (p<0.001) in the risk of mortality (Figure 2D) and of the composite of AVR and mortality (Figure 3D) with LVEF <50%. On spline curve analyses, the threshold of LVEF below which the risk of mortality and of the composite endpoint appeared to be around 55% (Figures S1D and S2D).

Table 3: Association of LVEF Strata with All-cause Mortality and with the Composite Endpoint (AVR and Mortality)

Variable	LVEF >70% N = 269	LVEF 60-70% N = 679	LVEF 50-59% N = 316	LVEF 30-49% N = 182	LVEF <30% N = 47	LVEF (continuous), %
All-cause mortality						
Events/person-years	21/1631	36/3761	26/1697	22/775	12/169	
Incidence rate, per 1000-person years (95% CI)	12.88 (7.97 to 19.68)	9.57 (6.70 to 13.25)	15.32 (10.01 to 22.44)	28.41 (17.80 to 43.01)	71.18 (36.78 to 124.34)	
Hazard ratio (95% CI)	1.45 (0.84 to 2.48)	*Reference*	1.62 (0.98 to 2.69)	2.80 (1.64 to 4.76)	7.17 (3.71 to 13.85)	0.97 (0.96 to 0.98)
P-value for hazard ratio	0.18		0.06	**<0.001**	**<0.001**	**<0.001**
Adjusted hazard ratio (95% CI)[a]	1.68 (0.97 to 2.92)	*Reference*	1.83 (1.09 to 3.07)	1.97 (1.13 to 3.41)	4.20 (2.01 to 8.75)	0.98 (0.97 to 0.99)
P-value for adjusted hazard ratio	0.064		**0.022**	**0.016**	**<0.001**	**0.003**
Composite of AVR and mortality						
Events/person-years	125/1034	276/2440	141/1002	105/421	28/70	
Incidence rate, per 1000-person years (95% CI)	120.90 (100.64 to 144.05)	113.11 (100.16 to 127.28)	140.74 (118.47 to 165.98)	249.60 (204.15 to 302.16)	401.43 (266.75 to 580.18)	
Hazard ratio (95% CI)	1.13 (0.91 to 1.39)	*Reference*	1.219 (0.99 to 1.49)	1.877 (1.50 to 2.35)	2.491 (1.69 to 3.68)	0.983 (0.98 to 0.99)
P-value for hazard ratio	0.27		0.06	**<0.001**	**<0.001**	**<0.001**
Adjusted hazard ratio (95% CI)[b]	0.95 (0.76 to 1.18)	*Reference*	1.35 (1.09 to 1.67)	1.69 (1.33 to 2.16)	1.82 (1.17 to 2.81)	0.985 (0.98 to 0.99)
P-value for adjusted hazard ratio	0.63		**0.007**	**<0.001**	**0.007**	**<0.001**

Legends: [a] Multivariable model adjusting for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, symptoms and coronary artery disease.
[b] Multivariable model adjusting for age, sex smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation, peak aortic velocity and symptoms.
AVR, aortic valve replacement; CI, confidence interval; LVEF, left ventricular ejection fraction.

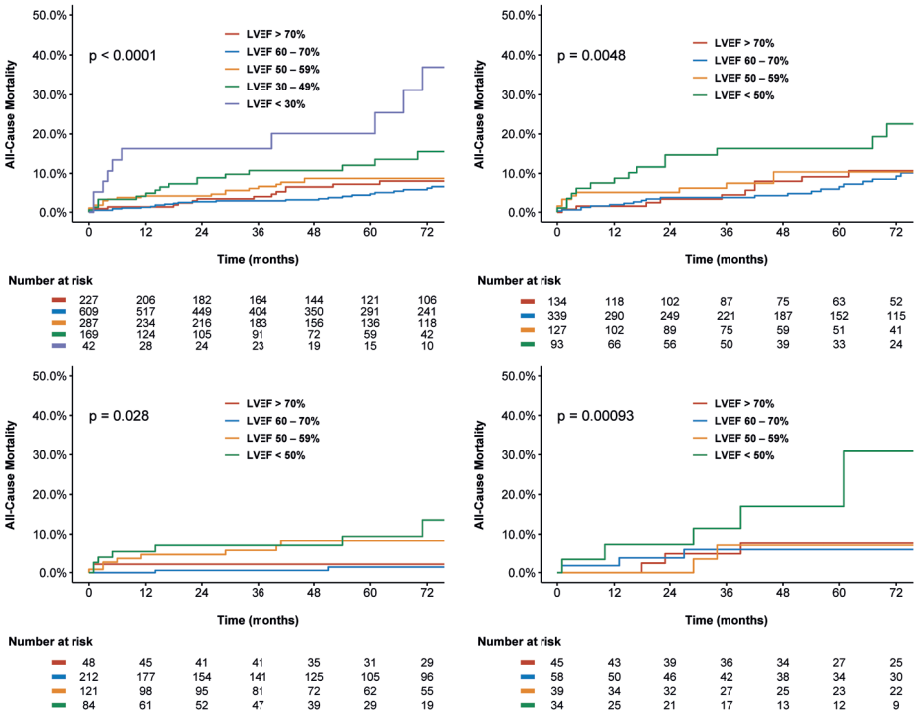

Figure 2: Event (AVR or death)-Free Survival According to the Type of aortic valve dysfunction and LVEF strata
Legends: Panel A shows the Kaplan-Meier survival estimates according to LVEF strata in the whole BAV population. Panel B, C, D demonstrate Kaplan-Meier survival estimates according to LVEF strata and isolated AS, isolated AR and MAVD, respectively. In the whole cohort, 5 strata of LVEF were analyzed, whereas the AS, AR, and MAVD subgroups, 4 strata were analyzed: i.e. the <30% and 30-49% strata were indeed merged together because of too small number of patients in the <30% stratum. AV, aortic valve; LVEF, left ventricular ejection fraction; AVR, aortic valve replacement; BAV, bicuspid aortic valve; AS, aortic stenosis; AR, aortic regurgitation; MAVD, mixed aortic valve disease.

DISCUSSION

The main findings of this study are: i) There is a stepwise increase in the risk of all-cause mortality with decreasing strata of LVEF in patients with BAV disease; ii) This increase in the risk of adverse outcomes appears to become significant with LVEF ≤60% rather than ≤50%, which is the traditional cut-off value of LVEF generally recommended in the guidelines and used in practice to identify LV systolic dysfunction and consider intervention in patients with AS and/or AR.

In aortic valve disease, the LVEF measured by 2D TTE is commonly used to assess LV systolic dysfunction and indicate intervention since its deterioration is associated with poor short- and long-term outcomes[19,20]. LV systolic dysfunction has been traditionally defined in the guidelines as LVEF <50% when AVR is then recommended (Class I) in patients with severe aortic valve disease who present with symptoms and/or LVEF <50%. However, the deterioration of LVEF generally occurs late in the course of the disease and

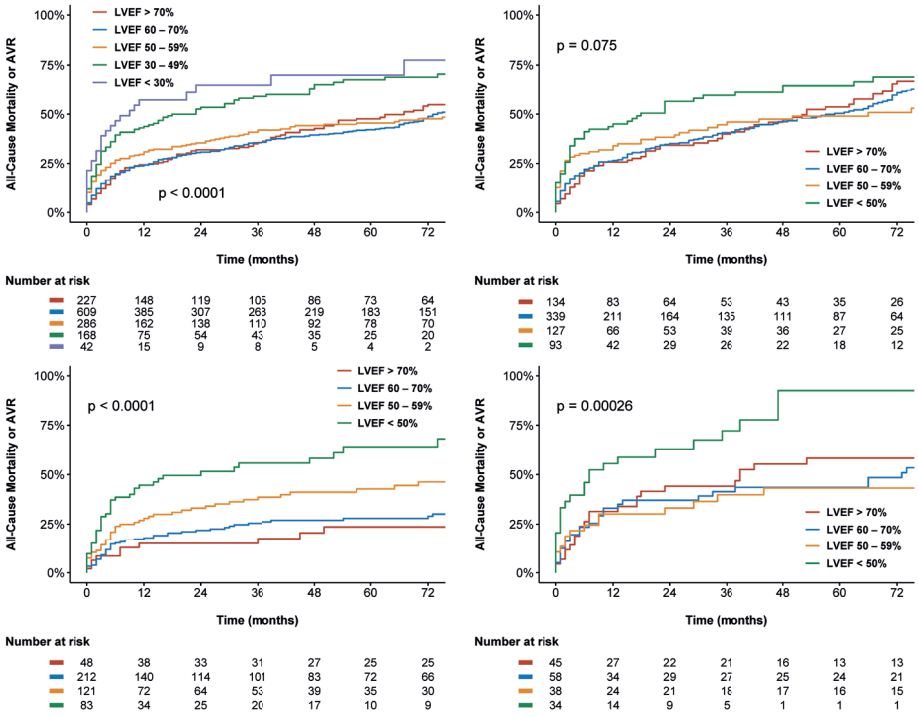

Figure 3: Survival Analysis According to the Type of aortic valve dysfunction and LVEF strata

Legends: Panel A shows the Kaplan-Meier survival estimates according to LVEF strata in the whole BAV population. Panels B, C, D demonstrate Kaplan-Meier survival estimates according to LVEF strata and isolated AS, isolated AR and MAVD, respectively. AV, aortic valve; LVEF, left ventricular ejection fraction; BAV, bicuspid aortic valve; AS, aortic stenosis; AR, aortic regurgitation; MAVD, mixed aortic valve disease.

an LVEF <50% may represent an advanced stage of LV systolic dysfunction in patients with aortic valve disease. Recent studies in AS suggested that a large proportion of patients with LVEF >50% have subclinical LV systolic dysfunction and are at higher risk for adverse events[11,21-24]. Indeed, LVEF markedly underestimates the extent of myocardial systolic dysfunction in the presence of LV concentric remodeling or hypertrophy, which is generally present in most patients with AS or MAVD. Several studies also reported that the cut-off value of LVEF associated with increased risk of adverse outcomes in AR is closer to <55% rather than <50%[25-32]. These findings underline the lack of sensitivity of an LVEF <50% to identify patients with subclinical LV systolic dysfunction who may be at higher risk of adverse events in the short-term and who may thus benefit from earlier intervention. These findings have led to some changes or addition of recommendations in the recent editions of guidelines for the management of aortic valve disease. The 2020 American guidelines state that AVR may be considered (Class IIb) in patients with severe AS if LVEF is <60% on at least 3 serial imaging studies[9], whereas in the 2021 European guidelines, AVR should be considered (Class IIa) when LVEF is <55%[10]. In patients with

severe AR, AVR is recommended (Class I) when LVEF is ≤55%, and may be considered (Class IIb) when there is a progressive decline in LVEF on at least 3 serial studies to the low–normal range (LVEF 55-60%)[9]. In contrast, the European guidelines recommend AVR (Class I) when LVEF is ≤50% and suggest that AVR may be considered (Class IIb) if LVEF is ≤55% and surgery is at low risk[10]. In asymptomatic patients with severe MAVD, AVR is indicated if LVEF is <50%[9].

The findings of the present study provide support and reinforce these changes of these recommendations with regard to the LVEF threshold to consider intervention in aortic valve disease. Our findings strongly suggest that an LVEF <60% should be applied to trigger intervention in patients with bicuspid aortic valve disease, regardless of the type of valve dysfunction: AS, AR or MAVD. Furthermore, our study extends the previously reported results from series predominantly composed of patients with tricuspid aortic valve to patients with BAV disease.

Our findings further support and expand the concept that LVEF lacks sensitivity to detect subclinical LV dysfunction in patients with aortic valve disease. One option to overcome this limitation is to raise the cut-off value of LVEF to identify LV systolic dysfunction from 50% to 60%. Another but more complex option is to use other echocardiographic parameters that are more sensitive to assess myocardial systolic dysfunction, such as global longitudinal strain. A previous meta-analysis reported that a global longitudinal strain <14.7% is associated with higher risk of rapid progression to symptoms and worse outcomes in asymptomatic patients with severe AS[33]. Inter-vendor differences in the measurements as well as the afterload dependence of global longitudinal strain remain limitations to widespread use of this parameter in clinical practice. Nonetheless, a report from the EACVI-ASE strain standardization task force nevertheless reported a good reproducibility of LV global longitudinal strain[34].

Egbe et al. reported that patients with MAVD had similar clinical outcomes compared to those with severe AS[35]. Furthermore, MAVD is associated with larger LV mass index compared to isolated AS or AR, and smaller LV end diastolic/systolic diameters compared to isolated AR but larger diameters compared to AS[35,36]. This hybrid concentric / eccentric LV remodeling pattern associated with MAVD may increase the tolerance of the LV to the hemodynamic burden related to the valve dysfunction. In particular, the LV hypertrophy induced by the AS component of MAVD may protect the LV against excessive LV dilatation and ensuing dysfunction caused by the AR component. These findings may explain, at least in part, that the impact of LVEF on clinical outcomes occurs at a slightly lower threshold (<55% vs. 60%) in MAVD vs. isolated AS or AR. This difference could also be related to the limited statistical power in the MAVD subset.

Finally, our results suggest a “U-shape” relationship between LVEF and mortality hazard, where both lower LVEF (<60%) and elevated LVEF (>70%) are associated with

worse outcomes. High LVEF may be a marker for "hyperdynamic" LV, which may be at higher risk for earlier decompensation.

Study Limitations

This is a retrospective, observational and non-randomized study and it is thus subject to inherent limitations associated with this type of study. The echocardiography data were reported by the participating sites and were not centrally adjudicated by an echocardiographic core laboratory. In addition, the diagnosis of BAV was ascertained primarily using echocardiography, and was not systematically confirmed by CT or surgical inspection in all patients. Although the LVEF data was available for the whole cohort at baseline, it was not systematically collected at the time of AVR. It was thus not possible to determine whether the LVEF had declined prior to AVR compared to baseline. Given that this was a retrospective study, the indications and criteria for valvular intervention, whilst broadly following contemporary guidelines, may have varied across each center, and the specific reason for AVR was not available. Another limitation was the small number of events in some subsets of patients, especially in patients with MAVD, therefore limiting the statistical power and accuracy for some analyses in these subsets.

CONCLUSION

This study shows that there is a progressive increase in the risk of mortality with decreasing LVEF in patients with BAV disease. A significant increase in the risk of mortality was observed at a LVEF threshold of <60% in AS and AR and <55% in MAVD. These results suggest that the current guidelines thresholds to define LV dysfunction may need to be re-evaluated in patients with BAV disease and should be raised from 50 to 60% in isolated AS or AR and 55% in MAVD. Ideally, randomized strategy trials would be necessary to determine if asymptomatic patients with severe BAV disease and LVEF <60% benefit of early AVR.

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SUPPLEMENTARY MATERIAL

Table S1: Echocardiographic Characteristics According to Aortic Valve Dysfunction

Variable	Overall N = 1,493	Isolated Significant AS N = 749	Significant MAVD N = 190	Isolated Significant AR N = 554	P-value
LV end-diastolic diameter, cm	5.20 (4.60 – 5.80)	4.80 (4.30 – 5.20)	5.38 (4.97 – 5.82)*	5.70 (5.20 – 6.30)*†	**<0.001**
LV end-systolic diameter, cm	3.40 (2.90 – 4.00)	3.00 (2.60 – 3.50)	3.50 (3.00 – 4.00)*	3.80 (3.30 – 4.40)*†	**<0.001**
LV end diastolic volume, ml	127 (97 – 166)	104 (83 – 129)	136 (113 – 173)*	157 (128 – 207)*†	**<0.001**
LV end systolic volume, ml	47 (32 – 69)	36 (26 – 51)	52 (36 – 71)*	60 (45 – 88)*†	**<0.001**
LVEF, %	63 (55 – 69)	64 (57 – 70)	61 (53 – 71)	61 (54 – 66)*	**<0.001**
LV mass index, g/m^2	117 (93 – 150)	107 (85 – 134)	132 (102 – 168)*	127 (102 – 169)*	**<0.001**
Left atrial volume index, ml/m^2	28 (21 – 37)	28 (21 – 37)	31 (22 – 42)	26 (20 – 36)*†	**0.003**
Mitral inflow E wave velocity, m/s	0.80 (0.60 – 0.91)	0.80 (0.60 – 0.95)	0.80 (0.67 – 1.00)	0.78 (0.60 – 0.90)*†	**0.005**
Mitral inflow E/A ratio	1.14 (0.82 – 1.55)	1.00 (0.78 – 1.46)	1.15 (0.82 – 1.71)*	1.22 (0.87 – 1.60)*	**<0.001**
MR ≥ moderate	107 (7.2%)	48 (6.4%)	18 (9.5%)	41 (7.4%)	0.33
Severe AR	257 (17%)	0 (0%)	55 (29%)*	202 (36%)*	**<0.001**
Severe AS	481 (32%)	401 (54%)	80 (42%)*	0 (0%)*†	**<0.001**
Mean pressure gradient, mmHg	20 (10 – 35)	29 (18 – 44)	30 (21 – 41)	9 (6 – 13)*†	**<0.001**
Peak aortic velocity, m/s	2.97 (2.12 – 3.80)	3.50 (2.80 – 4.20)	3.60 (3.00 – 4.23)	2.00 (1.70 – 2.53)*†	**<0.001**
Aortic valve area, cm	1.30 (1.00 – 2.10)	1.00 (0.80 – 1.23)	1.10 (0.85 – 1.30)	2.50 (2.00 – 3.15)*†	**<0.001**
SOV diameter indexed, mm/m^2	18.3 (16.3 – 20.5)	17.7 (15.9 – 19.8)	18.4 (16.5 – 20.2)	19.2 (17.0 – 21.3)*†	**<0.001**
STJ diameter indexed, mm/m^2	15.8 (13.8 – 17.9)	15.6 (13.7 – 17.7)	15.6 (13.9 – 17.3)	16.3 (14.1 – 18.5)*†	**0.001**
Ascending aorta diameter indexed, mm/m^2	19.7 (17.2 – 22.5)	20.0 (17.3 – 22.7)	19.8 (17.6 – 22.4)	19.2 (16.9 – 22.3)*	**0.041**

Legends: AR, aortic regurgitation; AS, aortic stenosis; LV, left ventricle; LVEF, left ventricular ejection fraction; MAVD, mixed aortic valve disease; MR, mitral regurgitation; SOV, sinus of Valsalva; STJ, sinotubular junction.

*p<0.05 vs Group I; †p<0.05 vs Group II

Table S2: Sensitivity Analysis with AVR As Time-dependent Covariate

Total Population (n=1493)	All-cause mortality[a]		Composite endpoint of AVR and all-cause mortality[b]	
	HR (95% CI)	P value	HR (95% CI)	P value
Univariable analysis				
LVEF > 70%	1.45 (0.84 to 2.48)	0.180	1.13 (0.91 to 1.39)	0.268
LVEF 60-70%	*Reference*		*Reference*	
LVEF 50-59%	1.62 (0.98 to 2.68)	0.062	1.22 (0.99 to 1.49)	0.057
LVEF 30-49%	2.80 (1.64 to 4.76)	**<0.001**	1.88 (1.50 to 2.35)	**<0.001**
LVEF <30%	7.17 (3.71 to 13.85)	**<0.001**	2.49 (1.69 to 3.68)	**<0.001**
LVEF (continuous), %	0.97 (0.96 to 0.98)	**<0.001**	0.98 (0.98 to 0.99)	**<0.001**
Multivariable analysis				
LVEF > 70%	1.66 (0.96 to 2.86)	0.068	0.95 (0.76 to 1.18)	0.63
LVEF 60-70%	*Reference*		*Reference*	
LVEF 50-59%	1.80 (1.08 to 3.01)	**0.025**	1.35 (1.09 to 1.67)	**0.007**
LVEF 30-49%	1.97 (1.14 to 3.38)	**0.014**	1.69 (1.33 to 2.16)	**<0.001**
LVEF <30%	4.73 (2.34 to 9.54)	**<0.001**	1.82 (1.17 to 2.81)	**0.007**
LVEF (continuous), %	0.98 (0.97 to 0.99)	**<0.001**	0.98 (0.98 to 0.99)	**<0.001**

Legends: [a] Multivariable model adjusting for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, symptoms and coronary artery disease and AVR as a time-dependent covariate.
[b] Multivariable model adjusting for age, sex smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation, peak aortic velocity and symptoms. AVR, aortic valve replacement; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.

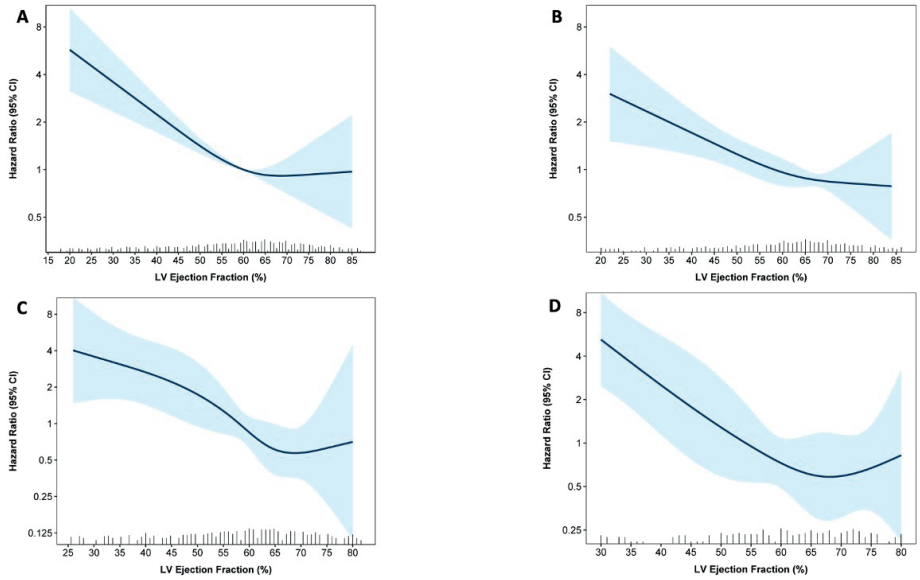

Figure S1: Spline Curves Analysis of All-cause Mortality According to AV Disease and LVEF

Legends: Spline curves analysis of all-cause mortality according to the type of aortic valve disease and LVEF. Panel A: whole BAV cohort. Panel B, C, D demonstrate spline curve survival estimates according to aortic valve disease: isolated AS, isolated AR and MAVD, respectively. AV, aortic valve; CI, confidence interval; LV, left ventricle; LVEF, left ventricular ejection fraction.

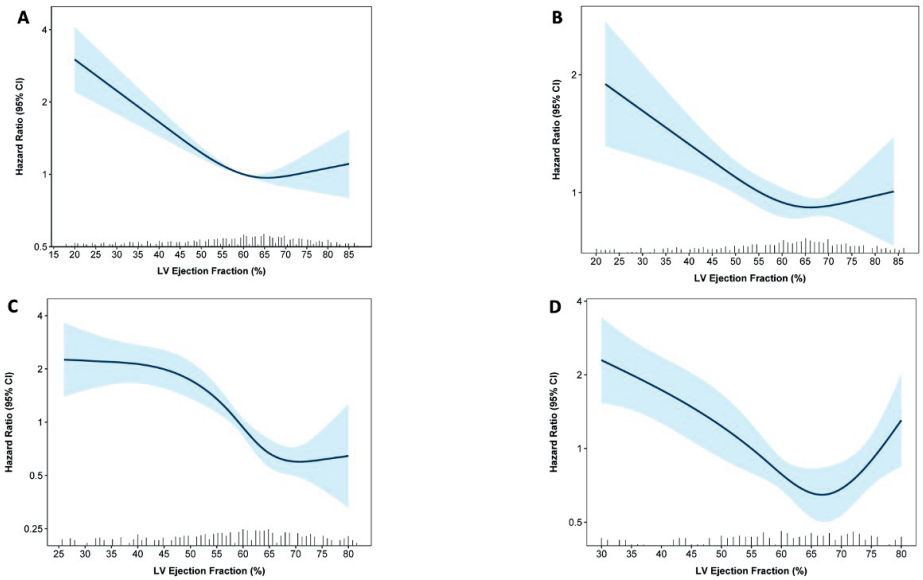

Figure S2: Spline Curves Analysis of the Composite Endpoint According to AV Disease and LVEF

Legends: Spline curves analysis of the composite endpoint of AVR and all-cause mortality according to the type of AV disease and LVEF. Panel A: whole BAV cohort. Panel B, C, D demonstrate spline curve event-free survival estimates according to aortic valve disease: isolated AS, isolated AR and MAVD, respectively. Legends as Online Figure 1. AVR, aortic valve replacement or repair.

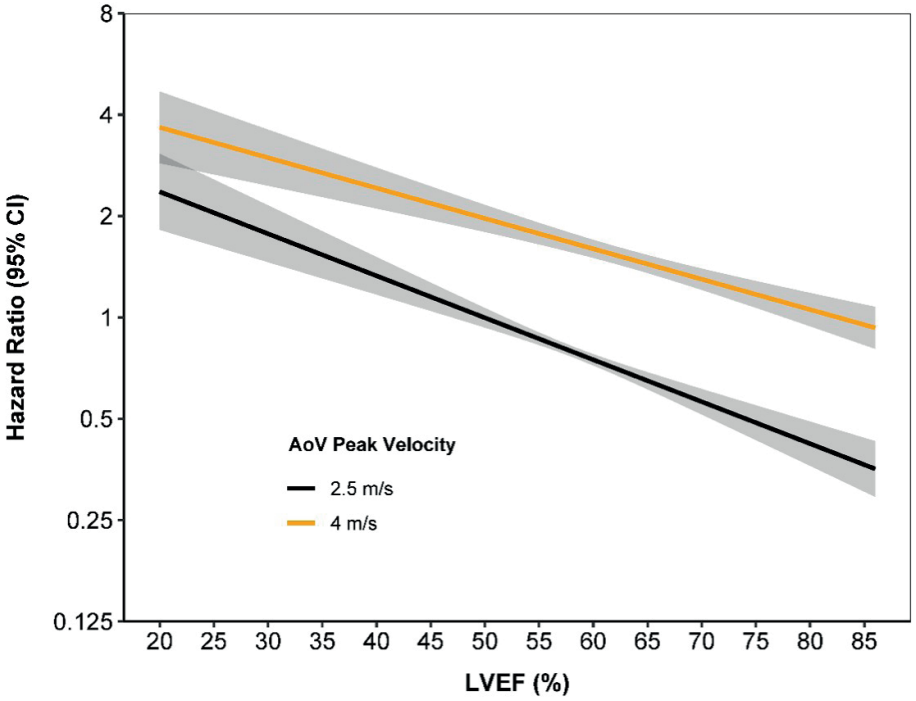

Figure S3: Interaction Analysis Between LVEF, Vmax and the Composite Endpoint of AVR and mortality.
Legends: Interaction analysis between LVEF, peak aortic jet velocity, and the composite endpoint of AVR and mortality. AVR, aortic valve replacement or repair; CI, confidence interval; LVEF, left ventricular ejection fraction; Vmax, peak aortic jet velocity.