Impact of left ventricular ejection fraction on clinical outcomes in bicuspid aortic valve disease

Hecht, S.; Butcher, S.C.; Pio, S.M.; Kong, W.K.F.; Singh, G.K.; Ng, A.C.T.; ... ; Pibarot, P.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 80, NO. 11, 2022

PUBLISHED BY ELSEVIER

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

Sébastien Hecht, MSc,[a,*] Steele C. Butcher, MD,[b,c,*] Stephan M. Pio, MD,[b] William K.F. Kong, MD,[b,d] Gurpreet K. Singh, MD,[b] Arnold C.T. Ng, MD, PhD,[e] Rebecca Perry, MD,[f] Kian Keong Poh, MD,[d] Ana G. Almeida, MD, PhD,[g] Ariana González, MD, MPH,[h] Mylène Shen, PhD,[a] Tiong Cheng Yeo, MD,[d] Miriam Shanks, MD, PhD,[i] Bogdan A. Popescu, MD, PhD,[j] Laura Galian Gay, MD,[k] Marcin Fijałkowski, MD, PhD,[l] Michael Liang, MD,[m] Edgar Tay, MD,[d] Nina Ajmone Marsan, MD, PhD,[b] Joseph Selvanayagam, MD, PhD,[f] Fausto Pinto, MD, PhD,[g] Jose L. Zamorano, MD,[h] Arturo Evangelista, MD,[k] Victoria Delgado, MD, PhD,[b] Jeroen J. Bax, MD, PhD,[b,n] Philippe Pibarot, DVM, PhD[a]

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 purpose 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 = 1,179; 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 when LVEF was <55% in MAVD group. In multivariable analysis, LVEF strata were significantly associated with increased rate of mortality (LVEF 50%-59%: HR: 1.83 [95% CI: 1.09-3.07]; $P = 0.022$; LVEF 30%-49%: HR: 1.97 [95% CI: 1.13-3.41]; $P = 0.016$; LVEF <30%: HR: 4.20 [95% CI: 2.01-8.75]; $P < 0.001$; vs LVEF 60%-70%, reference group).

CONCLUSIONS In BAV patients, the risk of adverse clinical outcomes increases significantly when the LVEF is <60%. These findings suggest that LVEF cutoff values proposed in the guidelines to indicate intervention should be raised from 50% to 60% in AS or AR and 55% in MAVD. (J Am Coll Cardiol 2022;80:1071-1084)

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Quebec Heart and Lung Institute, Laval University, Quebec, Quebec, Canada; [b]Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; [c]Department of Cardiology, Royal Perth Hospital, Perth, Western Australia, Australia; [d]Department of Cardiology, National University Heart Centre, National University Health System, Singapore, Singapore; [e]Department of Cardiology, Princess Alexandra Hospital, The University of Queensland, Brisbane, Queensland, Australia; [f]Department of Cardiovascular Medicine, Flinders Medical Centre, Bedford Park, Adelaide, South Australia, Australia; [g]Cardiology Department, Santa Maria University Hospital (CHLN), CAML, CCUL, Lisbon School of Medicine of the Universidade de Lisboa, Lisbon, Portugal; [h]Department of Cardiology, Hospital Universitario Ramon y Cajal, Madrid, Spain; [i]Division of Cardiology, University of Alberta, Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada; [j]University of Medicine and Pharmacy "Carol Davila"–Euroecolab, Institute of Cardiovascular Diseases "Prof. Dr C. C. Iliescu," Bucharest, Romania; [k]Department of Cardiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [l]First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland; [m]Department of Cardiology, Khoo Teck Puat Hospital, Singapore, Singapore; and the [n]Heart Center, University of Turku and Turku University Hospital, Turku, Finland. *Drs Hecht and Butcher contributed equally to this paper.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2022.06.032

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AS = aortic stenosis

AVR = aortic valve replacement or repair

BAV = bicuspid aortic valve

LV = left ventricular

LVEF = left ventricular ejection fraction

MAVD = mixed aortic valve disease

TAV = tricuspid aortic valve

Bicuspid aortic valve (BAV) is the most frequent congenital heart disease with a prevalence of 1% to 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 or repair (AVR) during their lifetime.[6]

SEE PAGE 1085

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 have suggested that the cutoff 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 recommendation in ESC guidelines) or <55% (Class I recommendation 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 to determine: 1) the prognostic impact (AVR and/or all-cause mortality) of LVEF in patients with BAV disease; and 2) the cutoff 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

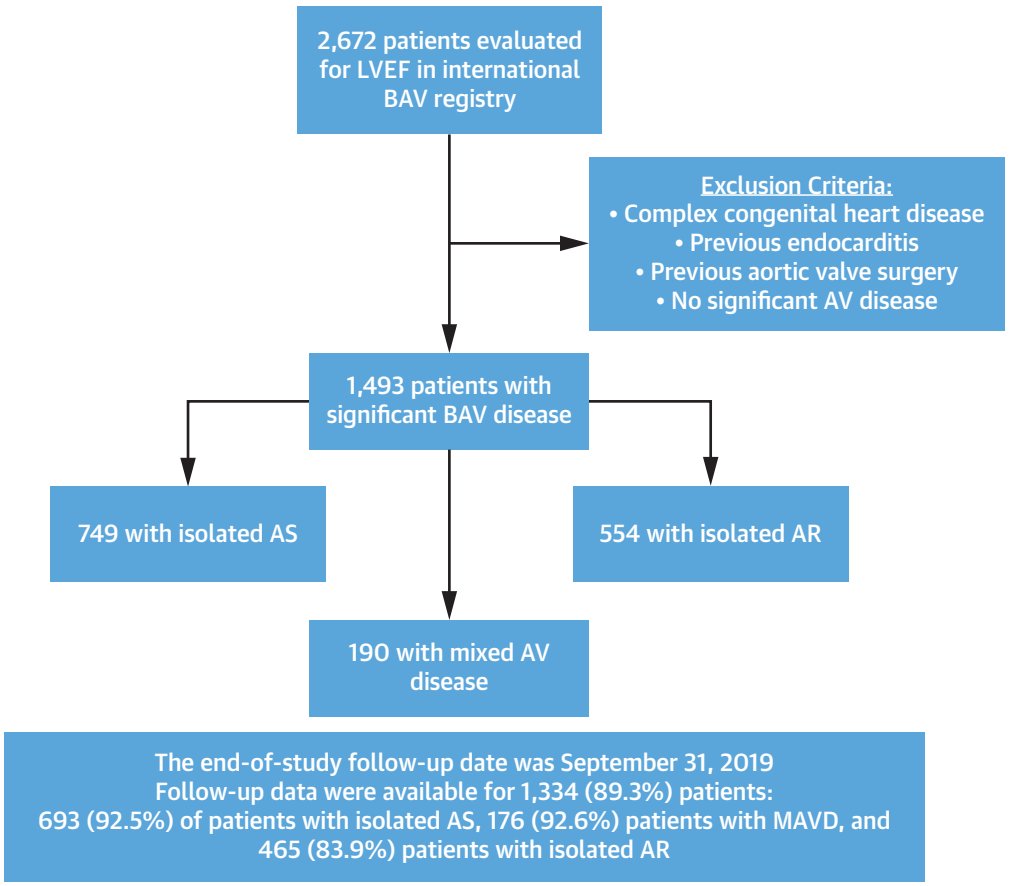
POPULATION. We retrospectively analyzed the data of 2,672 patients from an international BAV registry.[12] Patients with complex congenital heart disease, previous endocarditis, or aortic valve surgery, or without significant (<moderate) aortic valve (AV) disease, were excluded. First, the study population 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) 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 into 4 groups: whole cohort (BAV patients with significant aortic valve dysfunction, n = 1,493), 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 examinations were conducted using commercially available ultrasound systems. Measurements were retrospectively performed by experienced investigators from each center, using the first transthoracic echocardiography that allowed the diagnosis of 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. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured using the 2-dimensional linear method,

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 5, 2022; revised manuscript received June 13, 2022, accepted June 21, 2022.

FIGURE 1 Study Flow Chart



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.

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 before 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 AVR was recorded with data collected by medical record review. The end-of-study follow-up date was September 31, 2019. Follow-up data were available for 1,334 (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 (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 exact test, as appropriate, and are expressed in number of patients with percentages. To account for missing data, analyses were conducted using multiple

TABLE 1 Patient Characteristics According to LVEF Strata

	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, y	51 (37-63)	50 (36-63)	50 (35-62)	51 (37-61)	60 (47-69)[a,b,c]	57 (46-64)	**<0.001**
Male	1,049 (70.0)	178 (66.0)	458 (67.0)	232 (73.0)	145 (80.0)[a,b]	36 (77.0)	**0.005**
Hypertension	531 (38.0)	90 (38.0)	237 (37.0)	109 (36.0)	77 (44.0)	18 (41.0)	0.47
Dyslipidemia	427 (30.0)	58 (24.0)	198 (30.0)	83 (27.0)	75 (42.0)[a,b,c]	13 (28.0)	**0.002**
Current smoker	226 (16.0)	38 (16.0)	95 (16.0)	52 (17.0)	34 (19.0)	7 (15.0)	0.87
Diabetes mellitus	161 (12.0)	27 (11.0)	62 (10.0)	36 (12.0)	26 (15.0)	10 (22.0)	0.13
Coronary artery disease	119 (8.7)	19 (8.1)	49 (7.8)	24 (8.2)	19 (11.0)	8 (18.0)	0.15
BAV morphology							0.07
No raphe	132 (9.6)	17 (7.1)	56 (9.3)	31 (10.0)	21 (12.0)	7 (15.0)	
Type 1 raphe (L-R)	935 (68.0)	159 (67.0)	404 (67.0)	210 (69.0)	128 (72.0)	34 (74.0)	
Type 1 raphe (R-N)	229 (17.0)	46 (19.0)	115 (19.0)	45 (15.0)	19 (11.0)	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 (0.0)	

Values are median (IQR) or n (%). *P* values refer to comparison between LVEF groups. **Bold** values indicate significant difference. [a]$P < 0.05$ vs Group I. [b]$P < 0.05$ vs Group II. [c]$P < 0.05$ vs Group III.

BAV = bicuspid aortic valve; LVEF = left ventricular ejection fraction.

imputations by predictive mean matching using a chained-equation approach and generating 100 imputed data sets.[17] The results of the survival analyses were obtained by averaging the parameter estimates across the multiple data sets 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 prespecified clinical and echocardiographic variables associated with event-free survival specific to each patient group (isolated AS, MAVD, isolated AR). HR and 95% CIs 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 vs the baseline model was assessed by the C-index. Likelihood ratio 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 2-sided, and *P* values <0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 25.0 (IBM Corporation) and R version 4.0.1 (R Foundation for Statistical Computing).

RESULTS

CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS. Baseline characteristics of the study population according to LVEF are shown in Table 1. Among the 1,493 patients with BAV disease, 269 (18.0%) had LVEF >70%, 679 (45.5%) had LVEF between 60% and 70%, 316 (21.2%) had LVEF between 50% and 59%, 182 (12.2%) had LVEF between 30% and 49%, and 47 (3.1%) had LVEF <30%. In the total cohort, the median age was 51 years (IQR: 37-63 years) and 70% were men. Overall, patients with reduced LVEF (<50%) were older, were more frequently men, 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 compared with 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 Supplemental Table 1.

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 months (IQR: 22-

TABLE 2 Echocardiographic Characteristics According to LVEF Strata

	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)[a]	5.20 (4.80-5.80)[a,b]	5.80 (5.20-6.40)[a,b,c]	6.80 (5.60-7.60)[a,b,c]	**<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)[a]	3.70 (3.30-4.10)[a,b]	4.60 (4.00-5.20)[a,b,c]	6.20 (5.20-6.70)[a,b,c]	**<0.001**
LV end-diastolic volume, mL	127 (97-166)	108 (86-137)	122 (95-154)[a]	129 (103-167)[a]	163 (129-211)[a,b,c]	227 (172-294)[a,b,c,d]	**<0.001**
LV end-systolic volume, mL	47 (32-69)	27 (20-35)	42 (32-56)[a]	58 (47-74)[a,b]	97 (71-130)[a,b,c]	174 (130-228)[a,b,c,d]	**<0.001**
LVEF, %	63 (55-69)	75 (73-79)	65 (62-67)[a]	55 (53-58)[a,b]	42 (36-46)[a,b,c]	23 (20-26)[a,b,c]	–
LV mass index, g/m^2	117 (93-150)	111 (90-143)	111 (88-138)	119 (93-150)	145 (116-188)[a,b,c]	167 (144-221)[a,b,c]	**<0.001**
Left atrial volume index, mL/m^2	28 (21-37)	24 (20-34)	27 (21-36)	27 (20-36)	32 (23-48)[a,b,c]	37 (26-56)[a,b,c]	**<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)[a,b,c,d]	**0.014**
MR							
Moderate	82 (5.5)	5 (1.9)	22 (3.2)	12 (3.8)	27 (15.0)[a,b,c]	15 (32.0)[a,b,c,d]	**<0.001**
Severe	25 (1.7)	5 (1.9)	3 (0.4)	5 (1.6)	5 (2.7)[a,b,c]	7 (15.0)[a,b,c,d]	**<0.001**
AS							
Moderate	458 (31.0)	87 (32.0)	221 (32.0)[a]	95 (30.0)[a]	48 (26.0)	7 (15.0)[c]	**<0.001**
Severe	481 (32.0)	113 (42.0)	208 (31.0)[a]	81 (26.0)[a]	57 (31.0)	22 (47.0)[c]	**<0.001**
AR							
Moderate	487 (33.0)	87 (32.0)	209 (31.0)	122 (39.0)	56 (31.0)[a,b]	13 (28.0)[a,c]	**<0.001**
Severe	257 (17.0)	31 (12.0)	105 (15.0)	59 (19.0)	48 (26.0)[a,b]	14 (30.0)[a,b]	**<0.001**
Severe MAVD	190 (13.0)	49 (18.0)	64 (9.0)[a]	41 (13.0)	27 (15.0)	9 (19.0)	**0.002**
Mean pressure gradient, mm Hg	20 (10-35)	27 (15-41)	20 (10-34)[a]	17 (8-30)[a,b]	16 (9-29)[a]	19 (8-34)[a]	**<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)[a]	2.68 (2.00-3.55)[a,b]	2.66 (2.05-3.52)[a]	2.80 (1.84-3.62)[a]	**<0.001**
Aortic valve area, cm	1.30 (1.00-2.10)	1.10 (0.90-1.50)	1.30 (1.00-2.10)[a]	1.36 (1.00-2.50)[a]	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)[a]	18.7 (16.6-20.7)[a]	19.4 (17.1-21.8)[a,b]	18.8 (16.8-20.9)[a]	**<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)[a]	16.7 (14.6-19.0)[a,b]	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)[a]	19.3 (16.9-22.3)[a,b]	20.1 (17.5-23.5)[a,b,c]	19.8 (17.8-22.4)[a,b,c,d]	0.41

Values are median (IQR) or n (%). **Bold** values indicate significant difference. [a]$P < 0.05$ vs Group I. [b]$P < 0.05$ vs Group II. [c]$P < 0.05$ vs Group III. [d]$P < 0.05$ vs Group IV.

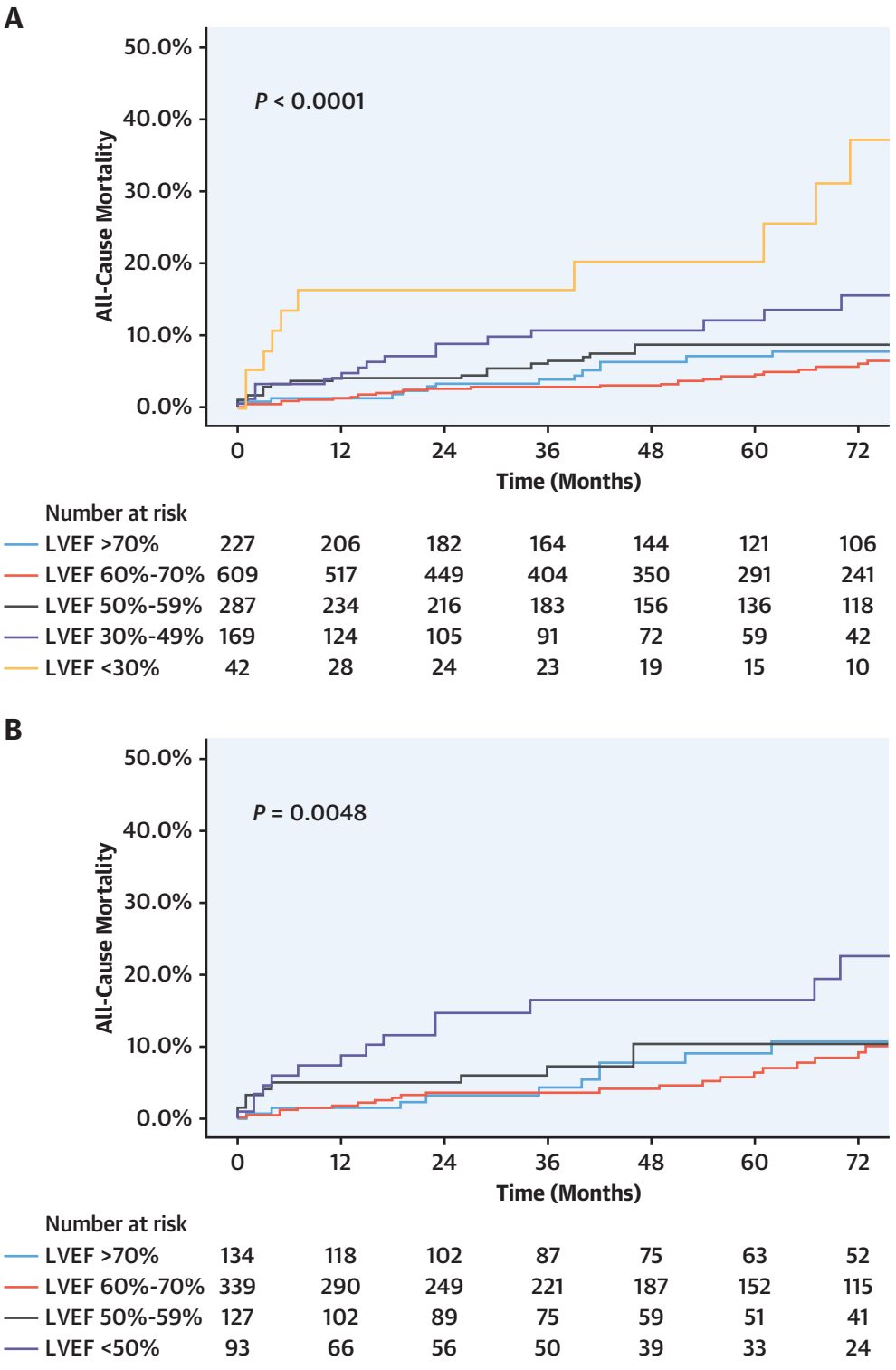
AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; BAV = bicuspid aortic valve; LV = left ventricle; LVEF = left ventricular ejection fraction; MAVD = mixed aortic valve disease; MR = mitral regurgitation; SOV = sinus of Valsalva; STJ = sinotubular junction.

102 months). The secondary endpoint occurred in 675 (51%) patients: ie, 602 (45%) patients underwent AVR and 73 (5.5%) died over a median follow-up of 21 months (IQR: 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 transcatheter aortic valve replacement, and 18 (3.0%) underwent aortic valve repair; 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 LVEF 50% to 59%. Using spline curve analysis, LVEF <60% was found to be associated with increased risk of mortality (Supplemental Figure 1A) and of the composite endpoint of mortality and AVR (Supplemental Figure 2A, **Central Illustration**).

In univariate Cox regression analysis, using LVEF 60% to 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% to 59% stratum where a strong trend was noted (**Table 3**). In multivariable analysis, when compared with the LVEF 60% to 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: 1.83 [95% CI: 1.09-3.07]; $P = 0.022$; LVEF 30%-49%: HR: 1.97 [95% CI: 1.13-3.41]; $P = 0.016$; LVEF <30%: HR: 4.20 [95% CI: 2.01-8.75]; $P < 0.001$) and of the composite endpoint of AVR and mortality (LVEF 60%-70% vs LVEF 50%-59%, HR: 1.35 [95% CI: 1.09-1.67]; $P = 0.007$; vs LVEF 30%-49%, HR: 1.69 [95% CI: 1.33-2.16]; $P < 0.001$; vs LVEF <30%, HR: 1.82 [95% CI: 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 (Supplemental Table 2).

FIGURE 2 All-Cause mortality According to Aortic Valve Dysfunction and LVEF Strata

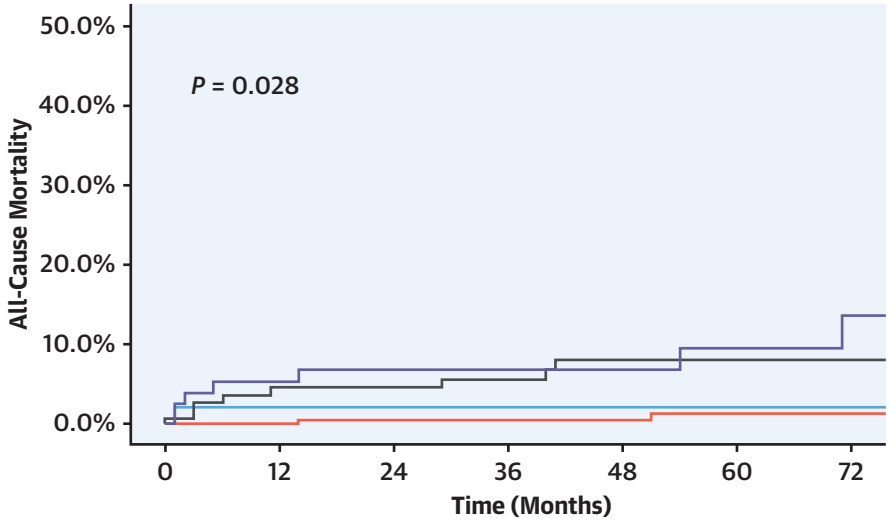


Kaplan-Meier estimates of all-cause mortality according to aortic valve dysfunction and LVEF strata. **(A)** All-cause mortality estimates according to LVEF strata in the whole BAV population. **(B to D)** All-cause mortality estimates according to LVEF strata and isolated AS, isolated AR, and MAVD, respectively. Abbreviations as in Figure 1.

Continued on the next page

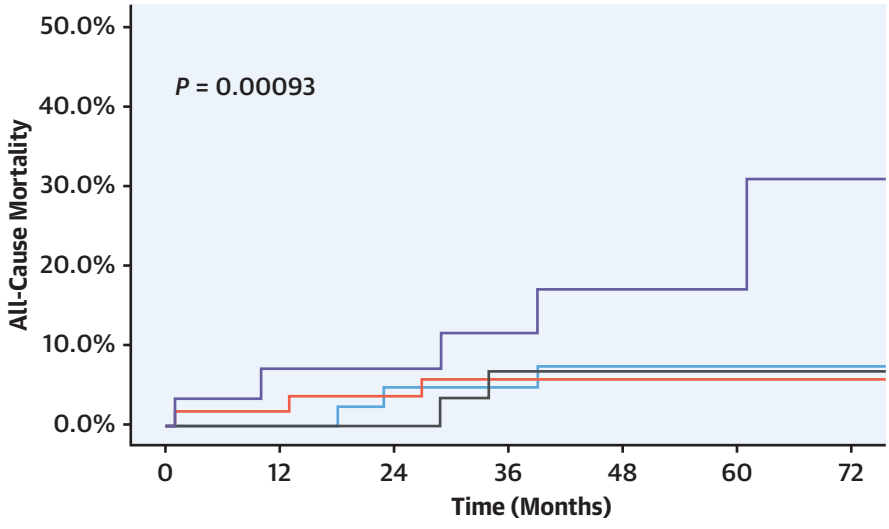
FIGURE 2 Continued

C



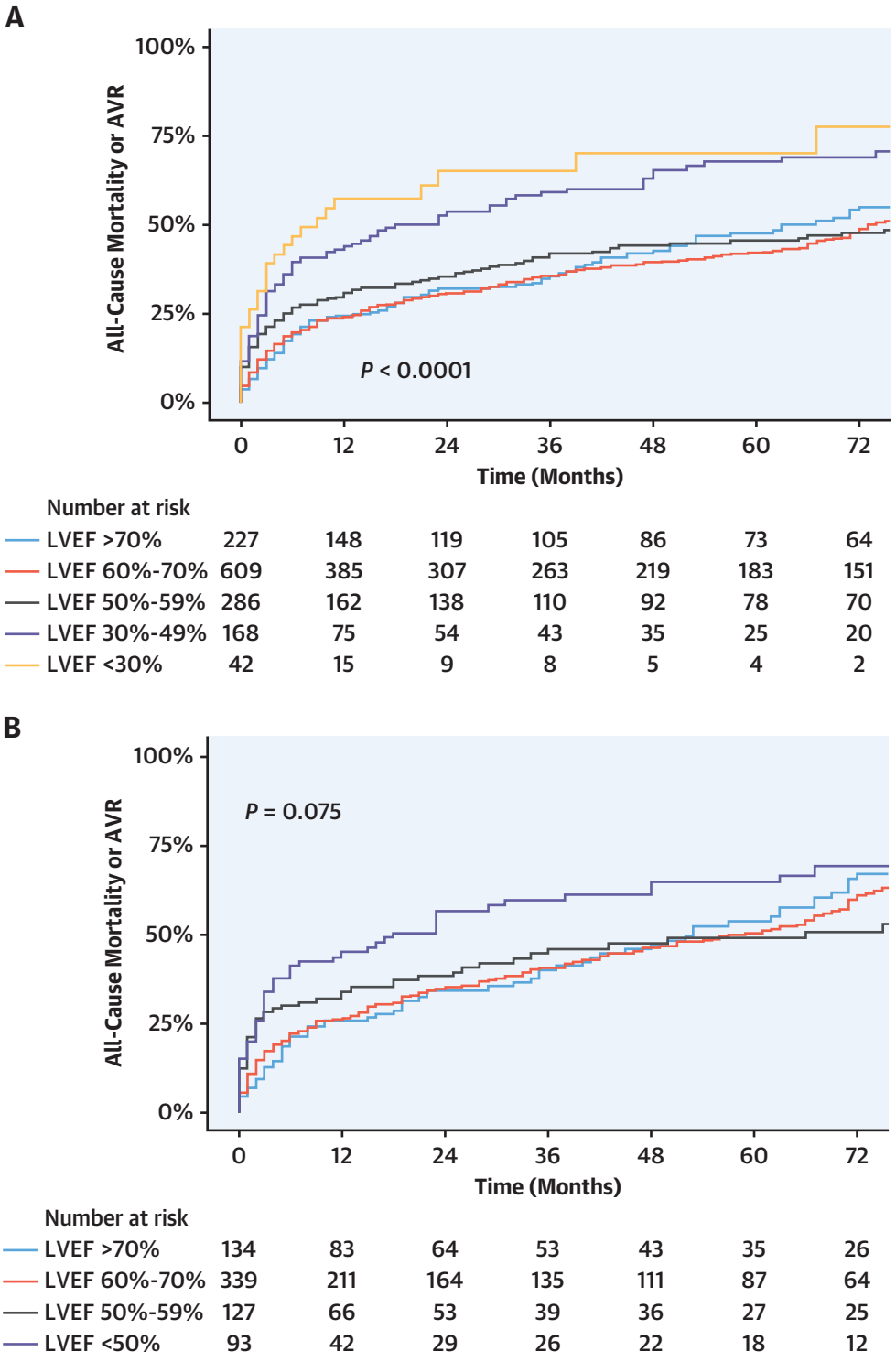
Number at risk							
LVEF >70%	48	45	41	41	35	31	29
LVEF 60%-70%	212	177	154	141	125	105	96
LVEF 50%-59%	121	98	95	81	72	62	55
LVEF <50%	84	61	52	47	39	29	19

D



Number at risk							
LVEF >70%	45	43	39	36	34	27	25
LVEF 60%-70%	58	50	46	42	38	34	30
LVEF 50%-59%	39	34	32	27	25	23	22
LVEF <50%	34	25	21	17	13	12	9

FIGURE 3 Composite Endpoint According to Aortic Valve Dysfunction and LVEF Strata

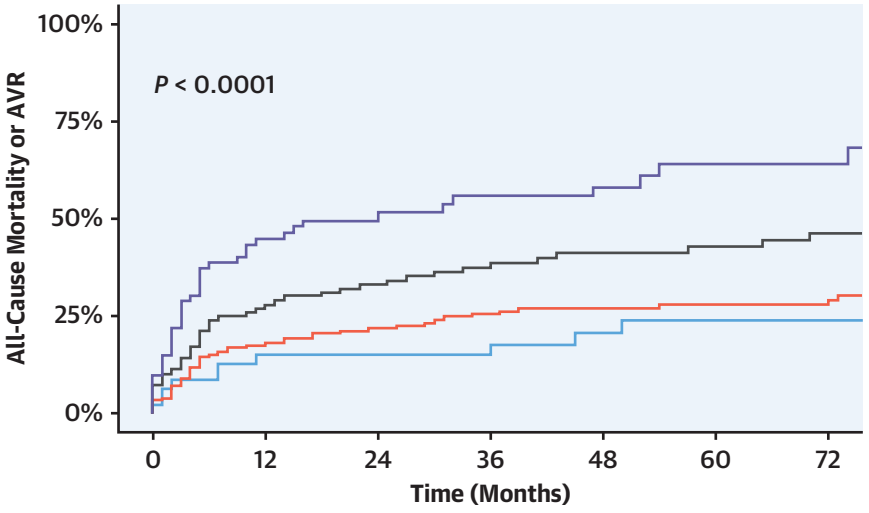


Kaplan-Meier estimates of all-cause mortality or AVR according to aortic valve dysfunction and LVEF strata. **(A)** All-cause mortality or AVR estimates according to LVEF strata in the whole BAV population. **(B, C, and D)** All-cause mortality or AVR estimates according to LVEF strata and isolated AS, 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: ie, the <30% and 30% to 49% strata were merged together because of the too small number of patients in the <30% stratum. AVR = aortic valve replacement or repair; other abbreviations as in Figure 1.

Continued on the next page

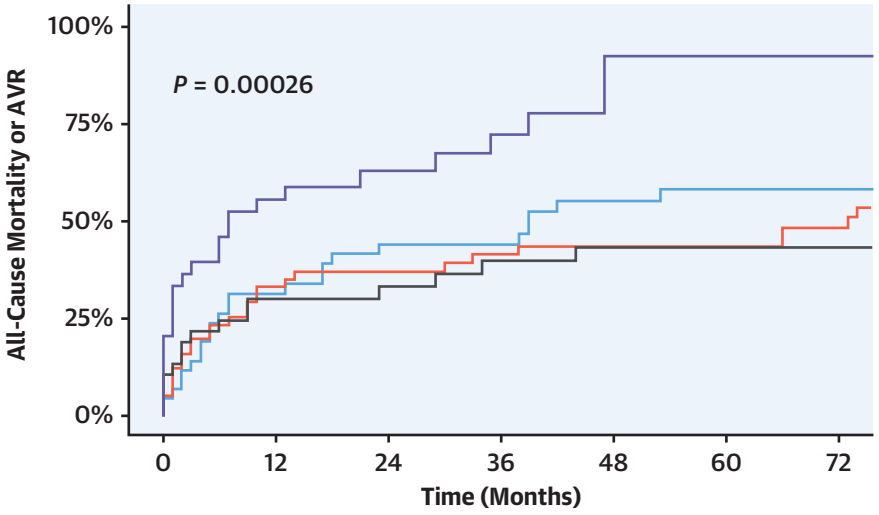
FIGURE 3 Continued

C



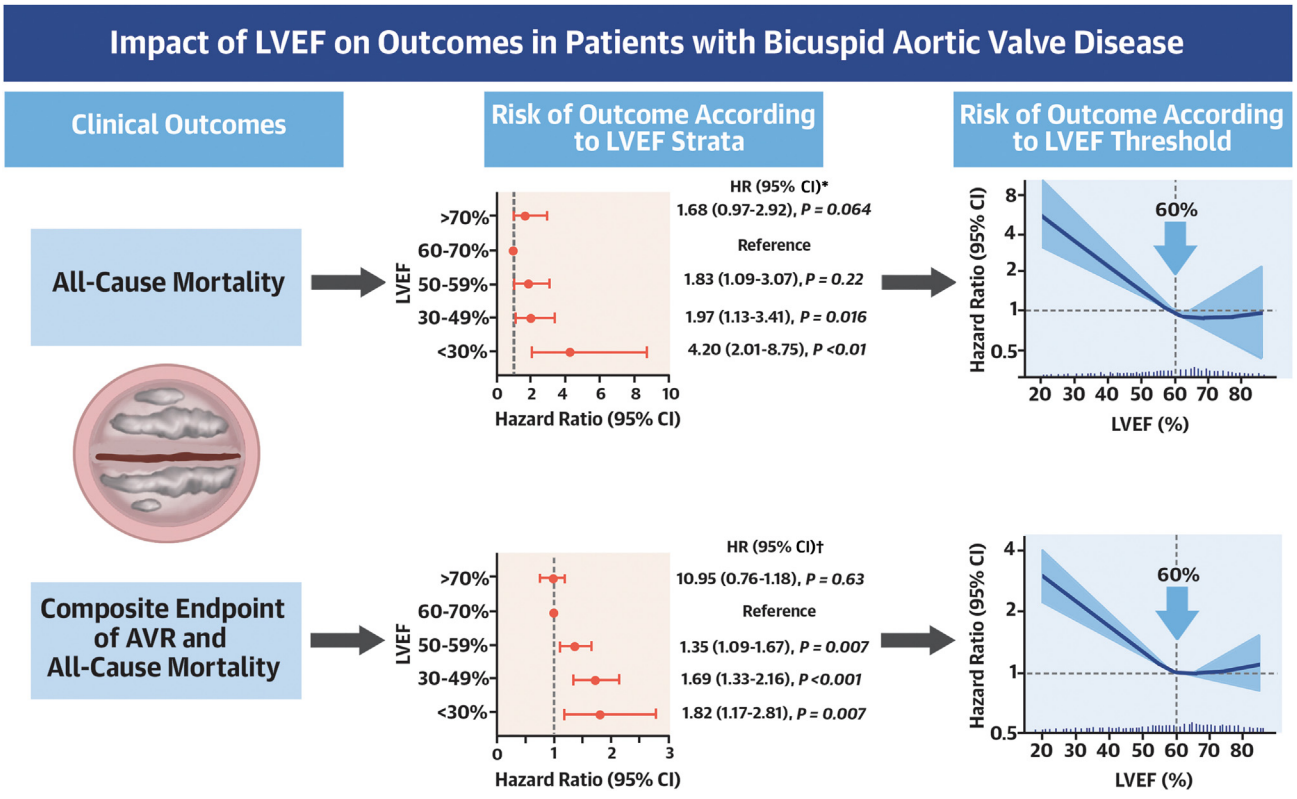
Number at risk							
LVEF >70%	48	38	33	31	27	25	25
LVEF 60%-70%	212	140	114	101	83	72	66
LVEF 50%-59%	121	72	64	53	39	35	30
LVEF <50%	83	34	25	20	17	10	9

D



Number at risk							
LVEF >70%	45	27	22	21	16	13	13
LVEF 60%-70%	58	34	29	27	25	24	21
LVEF 50%-59%	38	24	21	18	17	16	15
LVEF <50%	34	14	9	5	1	1	1

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



Hecht S, et al. J Am Coll Cardiol. 2022;80(11):1071–1084.

Impact of left ventricular ejection fraction on all-cause mortality **(top)** and on the composite endpoint of aortic valve replacement or repair (AVR) and all-cause mortality **(bottom)** in bicuspid aortic valve disease. *Adjusted HR for age, sex, smoking, hypertension, diabetes mellitus, dyslipidemia, symptoms, and coronary artery disease. †Adjusted HR for age, sex smoking, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, aortic root or ascending aorta dilation, peak aortic velocity, and symptoms. LVEF = left ventricular ejection fraction.

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 chi-square 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 chi-square 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 regard to the impact on mortality ($P = 0.34$). However, there was a significant interaction between LVEF and peak aortic velocity with regard to the combined endpoint ($P = 0.004$) (Supplemental Figure 3). For the LVEF strata >30%, the rate of the composite endpoint was higher in the patients with severe peak aortic velocity (4 m/s) vs 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 because of the mortality excess in this stratum.

In a subgroup analysis of asymptomatic patients (New York Heart Association functional class I), there was a trend toward higher risk of all-cause mortality in the LVEF 50% to 59% group (HR: 2.36; 95% CI: 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 months (IQR: 21-83 months) and 381 (55%) met the composite

TABLE 3 Association of LVEF Strata With All-Cause Mortality and With the Composite Endpoint (AVR and Mortality)

	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-y	21/1,631	36/3,761	26/1,697	22/775	12/169	
Incidence rate, per 1,000 person-y (95% CI)	12.88 (7.97-19.68)	9.57 (6.70-13.25)	15.32 (10.01-22.44)	28.41 (17.80-43.01)	71.18 (36.78-124.34)	
HR (95% CI)	1.45 (0.84-2.48)	*Reference*	1.62 (0.98-2.69)	2.80 (1.64-4.76)	7.17 (3.71-13.85)	0.97 (0.96-0.98)
P value for HR	0.18		0.06	**<0.001**	**<0.001**	**<0.001**
Adjusted HR (95% CI)[a]	1.68 (0.97-2.92)	*Reference*	1.83 (1.09-3.07)	1.97 (1.13-3.41)	4.20 (2.01-8.75)	0.98 (0.97-0.99)
P value for adjusted HR	0.064		**0.022**	**0.016**	**<0.001**	**0.003**
Composite of AVR and mortality						
Events/person-y	125/1,034	276/2,440	141/1,002	105/421	28/70	
Incidence rate, per 1,000 person-y (95% CI)	120.90 (100.64-144.05)	113.11 (100.16-127.28)	140.74 (118.47-165.98)	249.60 (204.15-302.16)	401.43 (266.75-580.18)	
HR (95% CI)	1.13 (0.91-1.39)	*Reference*	1.219 (0.99-1.49)	1.877 (1.50-2.35)	2.491 (1.69-3.68)	0.983 (0.98-0.99)
P value for HR	0.27		0.06	**<0.001**	**<0.001**	**<0.001**
Adjusted HR (95% CI)[b]	0.95 (0.76-1.18)	*Reference*	1.35 (1.09-1.67)	1.69 (1.33-2.16)	1.82 (1.17-2.81)	0.985 (0.98-0.99)
P value for adjusted HR	0.63		**0.007**	**<0.001**	**0.007**	**<0.001**

Bold values indicate significant associations. [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 or repair; LVEF = left ventricular ejection fraction.

endpoint: 340 (49%) patients underwent AVR and 41 (5.9%) died over a median follow-up of 19 months (IQR: 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 became <55% to 60% (Supplemental Figures 1B and 2B).

PROGNOSTIC VALUE OF LVEF IN ISOLATED AR. For those with AR, during a median follow-up of 57 months (IQR: 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 months (IQR: 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% (Supplemental Figures 1C and 2C).

PROGNOSTIC VALUE OF LVEF IN MAVD. Of the patients with MAVD, 19 (11%) patients died during a median follow-up of 69 months (IQR: 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 months (IQR: 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% (Supplemental Figures 1D and 2D).

DISCUSSION

The main findings of this study are: 1) there is a stepwise increase in the risk of all-cause mortality with decreasing strata of LVEF in patients with BAV disease; and 2) this increase in the risk of adverse outcomes appears to become significant with LVEF ≤60% rather than ≤50%, which is the traditional cutoff 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 2-dimensional TEE is commonly used to assess LV systolic dysfunction and indicate intervention because 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 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 cutoff 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 the 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 AV disease. One option to overcome this limitation is to raise the cutoff 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] Intervendor 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 European Association of Cardiovascular Imaging-American Society of Echocardiography Strain Standardization Task Force nevertheless reported a good reproducibility of LV global longitudinal strain.[34]

Egbe et al[35] reported that patients with MAVD had similar clinical outcomes compared with those with severe AS. Furthermore, MAVD is associated with larger LV mass index compared with isolated AS or AR and smaller LV end-diastolic/systolic diameters compared with isolated AR, but larger diameters compared with 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 because of the AR component. These findings may explain, at least in part, why 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, nonrandomized 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 before AVR compared with baseline. Given that this was a retrospective study, the indications

and criteria for valvular intervention, although 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.

CONCLUSIONS

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 an 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.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Department of Cardiology of the Leiden University Medical Center has received research grants from Abbott Vascular, Bioventrix, Medtronic, Biotronik, Boston Scientific, GE Healthcare, and Edwards Lifesciences. Dr Butcher has received funding from the European Society of Cardiology (ESC Research Grant App000080404). Drs Marsan and Bax have received speaker fees from Abbott Vascular. Dr Delgado has received speaker fees from Abbott Vascular, Medtronic, Edwards Lifesciences, Merck Sharp & Dohme, Novartis, and GE Healthcare. Dr Pibarot holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research; and has received funding from Edwards Lifesciences and Medtronic for echocardiography CoreLab analyses with no personal compensation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Jeroen J. Bax, Department of Cardiology, Heart Lung Center, Albinusdreef 2 2300 RC, Leiden, the Netherlands. E-mail: j.j.bax@lumc.nl. OR Dr Philippe Pibarot, Department of Cardiology, Québec Heart and Lung Institute, 2725 Chemin Sainte-Foy, Québec City, Québec G1V 4G5, Canada. E-mail: philippe.pibarot@med.ulaval.ca. Twitter: @ppibarot.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with a BAV and at least moderate stenosis and/or regurgitation, a progressive reduction of LVEF is associated with an increased risk of all-cause mortality warranting earlier intervention with AVR.

TRANSLATIONAL OUTLOOK:

Further investigations are needed to determine the optimum LVEF threshold warranting intervention in patients with BAV, particularly those with mixed forms of valve dysfunction.

REFERENCES

1. Coffey S, Cairns BJ, Iung B. The modern epidemiology of heart valve disease. *Heart*. 2016;102:75–85.

2. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation*. 2002;106:900–904.

3. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*. 2005;111:920–925.

4. Roberts WC, Ko JM, Moore TR, Jones WH 3rd. Causes of pure aortic regurgitation in patients having isolated aortic valve replacement at a single US tertiary hospital (1993 to 2005). *Circulation*. 2006;114:422–429.

5. Egbe AC, Connolly HM, Poterucha JT, Warnes CA. Bicuspid and unicuspid aortic valve: fate of moderate/severe mixed aortic valve disease. *Congenit Heart Dis*. 2017;12:24–31.

6. Beppu S, Suzuki S, Matsuda H, Ohmori F, Nagata S, Miyatake K. Rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves. *Am J Cardiol*. 1993;71:322–327.

7. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease: The Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2017;38:2739–2791.

8. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(22):e57–e185.

9. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2021;77:450–500.

10. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43:561–632.

11. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. *J Am Coll Cardiol*. 2018;71:1313–1321.

12. Kong WK, Delgado V, Poh KK, et al. Prognostic implications of raphe in bicuspid aortic valve anatomy. *JAMA Cardiol*. 2017;2:285–292.

13. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. *J Thorac Cardiovasc Surg*. 2007;133:1226–1233.

14. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30:372–392.

15. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association

of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611–644.

16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.

17. Harrell JFE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Springer Series in Statistics*. 2nd ed. Springer International Publishing; 2015.

18. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ: Wiley-Interscience; 2004.

19. Morris JJ, Schaff HV, Mullany CJ, et al. Determinants of survival and recovery of left ventricular function after aortic valve replacement. *Ann Thorac Surg*. 1993;56:22–29.

20. Mihaljevic T, Nowicki ER, Rajeswaran J, et al. Survival after valve replacement for aortic stenosis: implications for decision making. *J Thorac Cardiovasc Surg*. 2008;135:1270–1278.

21. Dahl JS, Eleid MF, Michelena HI, et al. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. *Circ Cardiovasc Imaging*. 2015;8(4):e002917. https://doi.org/10.1161/CIRCIMAGING.114.002917

22. Capoulade R, Le Ven F, Clavel MA, et al. Echocardiographic predictors of outcomes in adults with aortic stenosis. *Heart*. 2016;102:934–942.

23. Taniguchi T, Morimoto T, Shiomi H, et al. Prognostic impact of left ventricular ejection fraction in patients with severe aortic stenosis. *J Am Coll Cardiol Intv*. 2018;11:145–157.

24. Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol*. 2018;3:1060–1068.

25. de Meester C, Gerber BL, Vancraeynest D, et al. Do guideline-based indications result in an outcome penalty for patients with severe aortic regurgitation? *J Am Coll Cardiol Img*. 2019;12:2126–2138.

26. Murashita T, Schaff HV, Suri RM, et al. Impact of left ventricular systolic function on outcome of correction of chronic severe aortic valve regurgitation: implications for timing of surgical intervention. *Ann Thorac Surg*. 2017;103:1222–1228.

27. Zhang Z, Yang J, Yu Y, et al. Preoperative ejection fraction determines early recovery of left ventricular end-diastolic dimension after aortic valve replacement for chronic severe aortic regurgitation. *J Surg Res*. 2015;196:49–55.

28. Sambola A, Tornos P, Ferreira-Gonzalez I, Evangelista A. Prognostic value of preoperative indexed end-systolic left ventricle diameter in the outcome after surgery in patients with chronic aortic regurgitation. *Am Heart J*. 2008;155:1114–1120.

29. Bhudia SK, McCarthy PM, Kumpati GS, et al. Improved outcomes after aortic valve surgery for chronic aortic regurgitation with severe left ventricular dysfunction. *J Am Coll Cardiol*. 2007;49:1465–1471.

30. Forman R, Firth BG, Barnard MS. Prognostic significance of preoperative left ventricular ejection fraction and valve lesion in patients with aortic valve replacement. *Am J Cardiol*. 1980;45:1120–1125.

31. Tornos P, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation influence of guideline adherence toward early surgery. *J Am Coll Cardiol*. 2006;47:1012–1017.

32. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of severe Aortic regurgitation: a long-term follow up study. *Circulation*. 1999;99:1851–1857.

33. Magne J, Cosyns B, Popescu BA, et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis: An individual participant data meta-analysis. *J Am Coll Cardiol Img*. 2019;12:84–92.

34. Mirea O, Pagourelias ED, Duchenne J, et al. Variability and reproducibility of segmental longitudinal strain measurement: a report from the EACVI-ASE Strain Standardization Task Force. *J Am Coll Cardiol Img*. 2018;11:15–24.

35. Egbe AC, Luis SA, Padang R, Warnes C. Outcomes in moderate mixed aortic valve disease: Is it time for a paradigm shift? *J Am Coll Cardiol*. 2016;67:2321–2329.

36. Parker MW, Aurigemma GP. The simple arithmetic of mixed aortic valve disease: LVH + volume load = trouble. *J Am Coll Cardiol*. 2016;67:2330–2333.

KEY WORDS aortic regurgitation, aortic stenosis, bicuspid aortic valve, left ventricular ejection fraction, mixed aortic valve disease

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