JACC: CARDIOVASCULAR IMAGING
VOL. 14, NO. 9, 2021

ORIGINAL RESEARCH

Prognostic Implications of Associated Cardiac Abnormalities Detected on Echocardiography in Patients With Moderate Aortic Stenosis

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ABSTRACT

OBJECTIVES This study aimed to evaluate the prevalence and prognostic value of the extent of extra-aortic valvular cardiac abnormalities in a large multicenter registry of patients with moderate AS.

BACKGROUND The prognostic significance of a new classification system that incorporates the extent of cardiac injury (beyond the aortic valve) has been proposed in patients with severe aortic stenosis (AS). Whether this can be applied to patients with moderate AS is unclear.

METHODS Based on the echocardiographic findings at the time of diagnosis of moderate AS (aortic valve area between 1.0 and 1.5 cm^2 and dimensionless velocity index ratio of ≥0.25), a total of 1,245 patients were included and analyzed retrospectively. They were recategorized into 5 groups according to the extent of extra-aortic valvular cardiac abnormalities: none (Group 0), involving the left ventricle (Group 1), the left atrial or mitral valve (Group 2), the pulmonary artery vasculature or tricuspid valve (Group 3), or the right ventricle (Group 4). Patients were followed for all-cause mortality and combined endpoint (all-cause mortality, stroke, heart failure, or myocardial infarction).

RESULTS The distribution of patients according to the proposed classification was 13.1%, 26.8%, 42.6%, 10.6%, and 6.9% in Groups 0, 1, 2, 3, and 4, respectively. During a median follow-up of 4.3 (2.4 to 6.9) years, 564 (45.3%) patients died. There was a significant higher mortality rates with increasing extent of extra-aortic valvular cardiac abnormalities (log-rank $p < 0.001$). On multivariable analysis, the presence of extra-aortic valvular cardiac abnormalities remained independently associated with all-cause mortality and combined outcome, adjusted for aortic valve replacement as a time-dependent covariable. In particular, Group 2 and above were independently associated with all-cause mortality.

CONCLUSIONS In patients with moderate AS, the presence of extra-aortic valvular cardiac abnormalities is associated with poor outcome. (J Am Coll Cardiol Img 2021;14:1724–1737) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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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 November 16, 2020; revised manuscript received March 3, 2021, accepted April 1, 2021.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2021.04.009

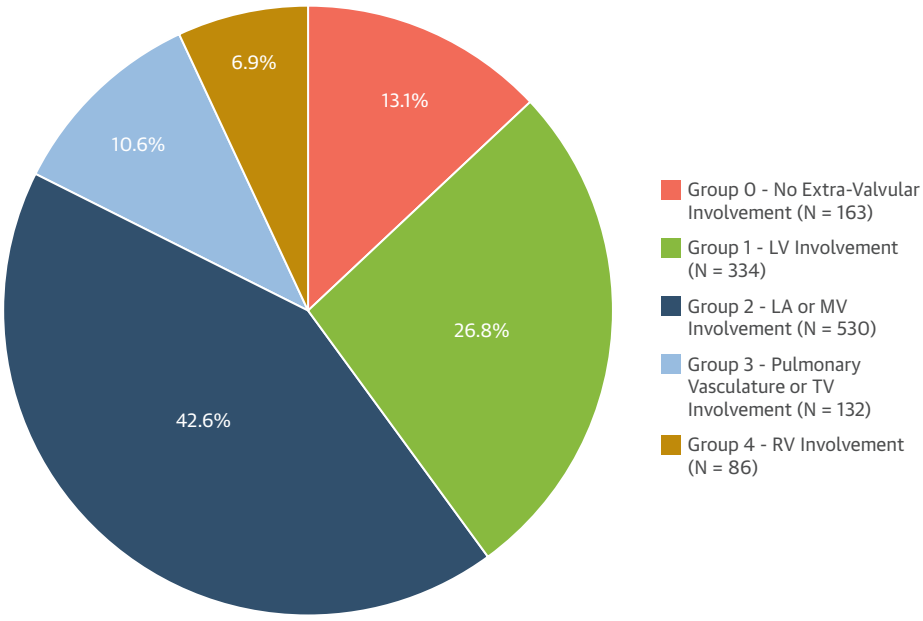
Although it is known that severe symptomatic aortic stenosis (AS) carries a poor prognosis if left untreated (1–3), less is known about the prognosis of moderate AS. Some studies have shown poor clinical outcomes in patients with moderate AS (4,5). In a recent report of a large echocardiographic national database, moderate AS was associated with reduced long-term survival, with a 2-fold increase in 1-year mortality compared with patients without AS and a 5-year mortality rate up to 56% (5). When patients with moderate AS have concomitant left- ventricular (LV) systolic dysfunction (LV ejection fraction [EF] <50%), the reported 4-year all-cause mortality rate was 36%, and the event rate for the combined endpoint of all-cause death and heart failure admissions was 48% over 4 years (6). Hence, identifying patients with moderate AS at risk of adverse clinical events in whom early intervention might be beneficial in an attempt to reverse or halt the disease process, particularly the effect on LV function, is crucial.

Recently, the prognostic significance of a new classification system that includes the extent of cardiac injury (beyond the aortic valve) has been proposed in patients with asymptomatic and symptomatic severe AS, including those who underwent transcatheter aortic valve replacement (AVR) (7–9). Of note, there is a proportional relationship between the extent of cardiac damage in patients with severe AS and all-cause mortality, including major adverse cardiovascular events. Whether the presence of associated cardiac abnormalities detected on

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVA = aortic valve area
AVR = aortic valve replacement
CI = confidence interval
HR = hazard ratio
LA = left atrial
LV = left ventricular
LVEF = left-ventricular ejection fraction
RV = right ventricular
SPAP = systolic arterial pulmonary pressure
TAPSE = tricuspid annular plane systolic excursion

FIGURE 1 Distribution of the Extent of Extra-Aortic Valvular Cardiac Abnormalities in Total Population



Extra-Aortic Valvular Cardiac Abnormalities					
	Group 0	Group 1	Group 2	Group 3	Group 4
Involvement	No Extra-Valvular	Left Ventricular	Left Atrial or Mitral	Pulmonary or Tricuspid	Right Ventricular
Echo-cardiographic criteria		LV mass index ♂ >115 g/m^2 ♀ >95 g/m^2 LV ejection fraction <50% E/e' ratio >14	Left atrial volume index >34 ml/m^2 Atrial fibrillation Moderate or severe mitral regurgitation	Systolic pulmonary arterial pressure >60 mm Hg Moderate or severe tricuspid regurgitation	TAPSE <16 mm

Grouping based on the presence of the extent of echocardiographic signs of extra-aortic valvular cardiac abnormalities and its distribution in patients with moderate aortic stenosis (N = 1,245). LA = left atrial; LV = left ventricular; MV = mitral valve; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TV = tricuspid valve.

TABLE 1 Clinical Characteristics of the Total Patient Population and According to the Presence of the Extent of Extra-Aortic Valvular Cardiac Abnormalities

	Total Population (N = 1,245)	Group 0 (n = 163)	Group 1 (n = 334)	Group 2 (n = 530)	Group 3 (n = 132)	Group 4 (n = 86)	p Value*
Age (yrs)	70.9 ± 12.3	66.0 ± 16.5	71.5 ± 11.8†	71.7 ± 11.3†	70.9 ± 11.3†	72.9 ± 10.6†	<0.001
Male	622 (50.0)	106 (65.0)	168 (50.3)	247 (46.6)	58 (43.9)	43 (50.0)	0.001
Body mass index (kg/m^2)	25.5 ± 5.9	26.7 ± 10.4	25.7 ± 4.7	25.9 ± 5.0	23.6 ± 5.0†‡§	23.5 ± 4.0†‡§	<0.001
Body surface area (m^2)	1.68 ± 0.23	1.75 ± 0.22	1.69 ± 0.22	1.69 ± 0.24	1.58 ± 0.21†‡§	1.57 ± 0.19†‡§	<0.001
Hypertension	986 (79.2)	114 (69.9)	267 (79.9)	430 (81.1)	100 (75.8)	75 (87.2)	0.008
Hypercholesterolemia	998 (80.2)	126 (77.8)	276 (82.6)	413 (77.9)	104 (78.8)	79 (91.9)	0.016
Diabetes mellitus	435 (34.9)	39 (23.9)	121 (36.2)	188 (35.5)	48 (36.4)	39 (45.3)	0.009
Coronary artery disease	598 (48.0)	59 (36.2)	169 (50.6)	265 (50.0)	54 (40.9)	51 (59.3)	0.001
Previous myocardial infarction	215 (17.3)	7 (4.3)	63 (18.9)	101 (19.1)	21 (15.9)	23 (26.7)	<0.001
History of smoking	254 (20.4)	26 (16.0)	75 (22.5)	119 (22.5)	23 (17.4)	11 (12.8)	0.092
Chronic obstructive pulmonary disease	70 (5.6)	6 (3.7)	27 (8.1)	30 (5.7)	5 (3.8)	2 (2.3)	0.143
History of atrial fibrillation	298 (23.9)	3 (1.8)	17 (5.1)	163 (30.8)	73 (55.3)	42 (48.8)	<0.001
Symptoms	418 (33.6)	28 (17.2)	94 (28.1)	183 (34.5)	67 (50.8)	46 (53.5)	<0.001
NYHA functional class ≥III	145 (11.6)	5 (3.1)	25 (7.5)	70 (13.2)	26 (19.7)	19 (22.1)	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	60.1 ± 32.2	77.5 ± 29.0	61.5 ± 29.9†	58.1 ± 32.4†	52.8 ± 32.9†	45.8 ± 30.8†‡§	<0.001
Systolic blood pressure (mm Hg)	136.4 ± 22.8	136.8 ± 21.4	139.8 ± 22.6	137.7 ± 23.0	129.5 ± 21.2‡§	125.7 ± 22.9†‡§	<0.001
Diastolic blood pressure (mm Hg)	64.9 ± 12.1	71.2 ± 11.5	71.3 ± 12.2	69.8 ± 11.8	66.1 ± 11.5†‡§	64.9 ± 12.1†‡§	<0.001
Medication:							
Beta blocker	646 (51.9)	61 (37.4)	153 (45.8)	305 (57.5)	72 (54.5)	55 (64.0)	<0.001
ACE inhibitor/ARB	631 (50.7)	62 (38.0)	170 (50.9)	293 (55.3)	59 (44.7)	47 (54.7)	0.001
Aspirin/thienopyridines	628 (50.4)	65 (39.9)	181 (54.2)	262 (49.4)	68 (51.5)	52 (60.5)	0.011
Oral anticoagulant	215 (17.3)	2 (1.2)	16 (4.8)	114 (21.5)	57 (43.2)	26 (30.2)	<0.001
Statin	930 (74.7)	115 (70.6)	261 (78.1)	391 (73.8)	93 (70.5)	70 (81.4)	0.113
Calcium channel blocker	524 (42.1)	61 (37.4)	156 (46.7)	229 (43.2)	50 (37.9)	28 (32.6)	0.062
Diuretics	416 (33.4)	23 (14.1)	92 (27.5)	191 (36.0)	64 (48.5)	46 (53.5)	<0.001

Values are mean ± SD or n (%). *The p values depict differences between grades of extra-aortic valvular cardiac abnormalities and are calculated by analysis of variance (ANOVA) and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by chi-square test for categorical data. †$p < 0.05$ vs. Group 0 with Bonferroni's post hoc analysis. ‡$p < 0.05$ vs. Group 1 with Bonferroni's post hoc analysis. §$p < 0.05$ vs. Group 2 with Bonferroni's post hoc analysis.

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blocker; NYHA = New York Heart Association.

echocardiography (in addition to aortic valve disease) confers an adverse prognosis in an unselected population with moderate AS has not been evaluated. Accordingly, the aim of the current study was 2-fold: 1) to evaluate the prevalence of associated extra-aortic valvular cardiac abnormalities in a large multicenter cohort of patients with moderate AS; and to 2) examine the impact of the extent of cardiac abnormalities on clinical outcomes in patients with moderate AS.

METHODS

PATIENT POPULATION AND DATA COLLECTION. A total of 1,245 patients with echocardiographic diagnosis of moderate AS at baseline were identified (defined as the first available echocardiogram with moderate AS), from the ongoing registries of patients who were followed up for aortic valve disease in 2 academic institutions (National Heart Centre, Singapore, and Leiden University Medical Center, Leiden, the Netherlands), between the years 2001 and 2018. Moderate AS was defined based on the echocardiographic aortic valve area (AVA) between 1.0 and 1.5 cm^2 (10). In addition, patients with dimensionless velocity index ratio of <0.25 suggestive of severe AS (11) or with previous AVR were excluded. Baseline demographic and clinical data, including cardiovascular risk factors and medication use and clinical follow-up data, were collected using the hospital records and departmental patient information systems, and analyzed retrospectively. This retrospective analysis of clinically acquired data was approved by the respective institutional review boards of each participating center. The need for patient written informed consent was waived because of the retrospective nature of the study.

TRANSTHORACIC ECHOCARDIOGRAPHY. Using commercially available ultrasound systems, 2-dimensional, color, pulsed, and continuous-wave Doppler images were obtained from the apical and parasternal views according to current recommendations (12). Continuous-wave Doppler recordings were obtained from the apical 3- or 5-chamber views to estimate peak aortic jet velocity (11). Mean and

TABLE 2 Echocardiographic Characteristics of the Total Patient Population and According to the Presence of the Extent of Extra-Aortic Valvular Cardiac Abnormalities

	Total Population (N = 1,245)	Group 0 (n = 163)	Group 1 (n = 334)	Group 2 (n = 530)	Group 3 (n = 132)	Group 4 (n = 86)	p Value*
Heart rate at the time of TTE (beats/min)	73.7 ± 14.7	76.5 ± 13.9	74.0 ± 14.5	72.2 ± 14.1†	74.5 ± 17.6	75.6 ± 15.1	0.010
Valve morphology							<0.001
Tricuspid	1,120 (90.0)	118 (72.4)	296 (88.6)	497 (93.8)	129 (97.7)	80 (93.0)	
Bicuspid	125 (10.0)	45 (27.6)	38 (11.4)	33 (6.2)	3 (2.3)	6 (7.0)	
Heart rhythm at the time of TTE							<0.001
Sinus rhythm	1,064 (85.5)	163 (100)	334 (100)	449 (84.7)	70 (53.0)	49 (57.0)	
Atrial fibrillation	181 (14.5)	0 (0.0)	0 (0.0)	81 (15.3)	62 (47.0)	37 (43.0)	
LV end-diastolic diameter (mm)	48.0 ± 7.0	44.2 ± 4.6	46.8 ± 6.0†	49.4 ± 7.1†‡	49.2 ± 8.2†‡	49.1 ± 8.0†	<0.001
LV end-systolic diameter (mm)	30.3 ± 8.1	25.7 ± 3.7	28.7 ± 6.2†	30.9 ± 8.2†‡	33.1 ± 9.9†‡	35.0 ± 9.7†‡§	<0.001
Septal wall thickness (mm)	11.2 ± 1.9	10.5 ± 1.6	11.5 ± 2.0†	11.5 ± 1.9†	10.9 ± 2.1‡§	10.7 ± 1.7‡§	< 0.001
Posterior wall thickness (mm)	10.7 ± 1.8	9.9 ± 1.5	10.9 ± 1.6†	11.0 ± 1.8†	10.6 ± 2.1†	10.5 ± 1.7	<0.001
LV mass index (g/m^2)	118.4 ± 34.6	88.4 ± 15.1	115.1 ± 26.8†	125.9 ± 35.2†‡	127.7 ± 43.2†‡	125.1 ± 36.7†	<0.001
LV end-diastolic volume (ml)	105.8 ± 37.2	91.7 ± 23.8	98.9 ± 29.4	111.1 ± 38.6†‡	115.6 ± 50.7†‡	111.1 ± 41.1†	<0.001
LV end-systolic volume (ml)	45.9 ± 28.9	32.0 ± 10.3	40.3 ± 19.8†	48.5 ± 29.8†‡	56.4 ± 41.2†‡§	62.5 ± 36.9†‡§	<0.001
Impaired LVEF (<50%)	222 (17.8)	0 (0.0)	47 (14.1)	95 (17.9)	36 (27.3)	44 (51.2)	<0.001
LVEF (%)	58.3 ± 12.7	64.9 ± 6.4	60.1 ± 11.5†	58.1 ± 12.2†	54.2 ± 14.2†‡§	46.1 ± 16.1†‡§‖	<0.001
Average E/e' ratio	16.5 ± 7.3	10.3 ± 2.2	15.1 ± 5.6†	18.2 ± 7.7†‡	19.5 ± 8.5†‡	21.1 ± 7.5†‡§	<0.001
Left atrial volume index (ml/m^2)	41.8 ± 22.5	25.9 ± 5.3	27.7 ± 4.7	45.9 ± 15.4†‡	66.6 ± 42.3†‡§	54.0 ± 22.6†‡§‖	<0.001
Mitral regurgitation ≥ moderate	123 (9.9)	0 (0.0)	0 (0.0)	62 (11.7)	42 (31.8)	19 (22.1)	<0.001
Systolic pulmonary arterial pressure (mm Hg)	36.9 ± 13.0	29.2 ± 6.8	32.1 ± 8.5	35.0 ± 9.3†‡	52.6 ± 15.3†‡§	45.1 ± 17.6†‡§‖	<0.001
Tricuspid regurgitation ≥ moderate	141 (11.3)	0 (0.0)	0 (0.0)	0 (0.0)	110 (83.3)	31 (36.0)	<0.001
Mean aortic valve gradient (mm Hg)	24.4 ± 7.6	26.0 ± 7.0	25.6 ± 7.8	24.5 ± 7.0	23.0 ± 7.3†‡	17.9 ± 7.6†‡§‖	<0.001
Peak aortic jet velocity (m/s)	3.2±0.5	3.3 ± 0.4	3.3 ± 0.5	3.2 ± 0.5	3.1 ± 0.5†	2.8 ± 0.6†‡§‖	<0.001
Aortic valve area (cm^2)	1.20 ± 0.15	1.23 ± 0.16	1.20 ± 0.16	1.22 ± 0.15	1.17 ± 0.14†	1.19 ± 0.14	0.010
Dimensionless velocity index	0.33 ± 0.06	0.33 ± 0.05	0.33 ± 0.06	0.33 ± 0.05	0.34 ± 0.06	0.34 ± 0.06	0.161

Values are mean ± SD or (%). *The p values depict differences between grades of extra-aortic valvular cardiac abnormalities and are calculated by analysis of variance (ANOVA) and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by chi-square test for categorical data. †p < 0.05 vs. Group 0 with Bonferroni's post hoc analysis. ‡p < 0.05 vs. Group 1 with Bonferroni's post hoc analysis. §p < 0.05 vs. Group 2 with Bonferroni's post hoc analysis. ‖p < 0.05 vs. Group 3 with Bonferroni's post hoc analysis.

LV = left ventricular; LVEF = left ventricular ejection fraction; TTE = transthoracic echocardiogram.

peak transvalvular pressure gradients were calculated using the Bernoulli equation (11). AVA was calculated according to the continuity equation using velocity time integrals of the LV outflow tract and aortic valve flow recordings (11). In patients with atrial fibrillation at the time of echocardiography, all the relevant Doppler parameters were calculated as the average of 5 cycles with the least variation of R-R intervals and as close as possible to normal resting heart rate, as recommended (13,11). In the parasternal long-axis view, LV dimensions were assessed, and LV mass was calculated by Devereux's formula and indexed for body mass index (LV mass index) (12). LV end-diastolic and end-systolic volumes were evaluated in the apical 2- and 4-chamber views and the LV ejection fraction (LVEF) was calculated according to the Simpson's biplane method (12). Using the biplane method of disks, left-atrial (LA) volumes were measured at end-systole in the apical 2- and 4-chamber views and indexed for body surface area (LA volume index) (12). Pulsed-wave Doppler recordings of the transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities to assess LV diastolic function (14). Using tissue Doppler imaging of the mitral annulus on the apical 4-chamber view, the e' was measured at both the lateral and septal side and averaged to calculate the E/e' ratio for estimation of LV filling pressures (14). Severity of mitral and tricuspid regurgitation was graded according to a multiparametric approach from continuous and color wave Doppler data, as recommended (15). The right-ventricular (RV) pressure was calculated from the peak velocity of the tricuspid regurgitant jet, according to the Bernoulli equation, adding the right-atrial pressure, determined by the inspiratory collapse and diameter of the inferior vena cava to estimate the systolic arterial pulmonary pressure (SPAP) (16). For the evaluation of RV systolic function, anatomic M-mode was applied on the focused apical 4-chamber view of the RV to measure tricuspid annular plane systolic excursion (TAPSE) (16).

TABLE 3 Incidence of the Individual Components of Cardiac Involvement in the Total Population

Group 0: No extra-aortic valvular involvement	**163/1,245**
Group 1: Left-ventricular involvement	**334/1,245**
Increased LV mass index (>95 for women or >115 g/m^2 for men)	754 (60.6)
LV ejection fraction <50%	222 (17.8)
E/e' ratio >14	592 (47.6)
Group 2: Left atrial or mitral-valve involvement	**530/1,245**
Indexed left-atrial volume >34 ml/m^2	634 (50.9)
Moderate or severe mitral regurgitation (≥grade 3)	123 (9.9)
Presence of atrial fibrillation at time echocardiography	181 (14.5)
Group 3: Pulmonary vasculature or tricuspid-valve involvement	**132/1,245**
Systolic pulmonary artery pressure ≥60 mm Hg	58 (4.7)
Moderate or severe tricuspid regurgitation (≥grade 3)	141 (11.3)
Group 4: Right-ventricular involvement	**86/1,245**
Tricuspid annular plane systolic excursion <16 mm	86 (6.9)

Values are n/N or n (%).
LV = left ventricular.

DEFINITION AND CLASSIFICATION OF THE EXTENT OF ASSOCIATED CARDIAC ABNORMALITIES. Adapted from the staging algorithm previously applied in patients with severe AS (7), the presence and extent of extra-aortic valvular cardiac abnormalities was evaluated using baseline transthoracic echocardiography (i.e., the first available echocardiogram with moderate AS). Next, depending on the extent of concomitant cardiac abnormalities, patients were categorized into 5 groups (**Figure 1**): Group 0, no extra-aortic valve cardiac involvement; Group 1, LV involvement as defined by the presence of LV hypertrophy (LV mass index >95 g/m^2 in women or >115 g/m^2 in men), and/or LV systolic dysfunction (LVEF <50%), and/or elevated LV filling pressure (E/e' ratio >14) (12,14); Group 2, LA and/or mitral valve involvement as defined by the presence of LA dilatation (LA volume index >34 ml/m^2) (12), and/or ≥ moderate mitral regurgitation (15), and/or the presence of atrial fibrillation at the time of echocardiography; Group 3, pulmonary artery vasculature and/or tricuspid valve involvement as defined by the presence of systolic pulmonary hypertension (SPAP ≥60 mm Hg), and/or ≥ moderate tricuspid regurgitation (15,16); Group 4, RV involvement as defined by the presence of moderate or greater RV systolic dysfunction (TAPSE <16 mm) (16). If more than 1 of the proposed criteria were present, patients were hierarchically classified in the highest (i.e., worst) group if ≥1 of the proposed criteria was met within that group.

CLINICAL ENDPOINTS AND FOLLOW-UP. All patients were followed up for the occurrence of all-cause mortality, surgical or transcatheter AVR, and cardiac-related hospitalization. The primary outcome was all-cause mortality, as ascertained by review of hospital records and/or governmental death registry database. The secondary outcome was a composite of all-cause mortality and hospitalization for stroke (major or minor), heart failure, and myocardial infarction or unstable angina occurring between baseline echocardiography and last follow-up. In addition, to examine the impact of the extent of associated extra-aortic valvular cardiac abnormalities in patients with moderate AS on medical therapy, the Kaplan-Meier analysis was censored at the time of AVR.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or median (interquartile range [IQR]), as appropriate and tested for the normality of distribution and homogeneity of variances with Shapiro-Wilk and Levene's tests, respectively. Categorical data are presented as frequencies and percentages. Patients were categorized according to the extent of extra-aortic valvular cardiac abnormalities. For comparison of continuous variables among groups, the analysis of variance (ANOVA) test with Bonferroni's post hoc analysis, or the Kruskal-Wallis test was used for normally and non-normally distributed variables, respectively. Categorical variables were compared using the chi-square test. The Kaplan-Meier curves and log-rank tests were used to calculate and compare the survival and event rates for the different groups of associated cardiac abnormalities. For the secondary outcome, patients were censored at the occurrence of the first event.

To evaluate the association of the extent of concomitant cardiac abnormalities and other clinical and echocardiographic parameters with the primary and secondary endpoints, univariable Cox proportional hazards analyses were performed. Subsequently, statistically significant ($p \leq 0.05$) or clinically relevant variables were selected and introduced as covariates in multivariable Cox proportional hazards models. The occurrence of surgical or transcatheter AVR was entered as time-dependent covariate. The presence and extent (in terms of grouping) of cardiac abnormalities was introduced into the model as a categorical variable, with Group 0 (no extra-aortic valve cardiac involvement) as the reference. For both the univariable and multivariable analyses, hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. Next, to examine the outcomes of patients with moderate AS on medical therapy, the survival analysis was censored at the time of AVR. Statistically significant ($p \leq 0.05$) or clinically relevant variables were selected and introduced as covariates in

TABLE 4 Clinical Outcomes During Follow-Up per Presence of the Extent of Extra-Aortic Valvular Cardiac Abnormalities

	Group 0 (n = 163)	Group 1 (n = 334)	Group 2 (n = 530)	Group 3 (n = 132)	Group 4 (n = 86)	p Value*
Surgical or transcatheter AVR	30.7 (50)	36.8 (123)	30.2 (160)	22.0 (29)	12.8 (11)	<0.001
Time to surgical or transcatheter AVR (in yrs)	2.4 (1.3–3.7)	2.6 (1.1–4.6)	2.3 (0.8–4.3)	2.3 (0.4–3.3)	2.0 (1.4–5.1)	
All-cause death	24.5 (40)	42.2 (141)	47.0 (249)	58.3 (77)	66.3 (57)	<0.001
Time to all cause death (in yrs)	4.8 (3.4–8.2)	4.5 (2.8–8.1)	4.4 (2.4–6.8)	3.1 (1.6–5.6)	2.9 (0.7–4.8)	
Stroke	1.8 (3)	1.2 (4)	1.3 (7)	2.3 (3)	0.0 (0)	0.684
Heart failure	1.8 (3)	2.1 (7)	5.1 (27)	9.1 (12)	0.0 (0)	0.001
Myocardial infarction or unstable angina	4.9 (8)	6.6 (22)	5.3 (28)	0.8 (1)	2.3 (2)	0.054
Combined endpoint (all-cause death and hospitalization for stroke, heart failure, and MI)†	31.3 (51)	46.4 (155)	52.1 (276)	60.6 (80)	67.4 (58)	<0.001
Time to combined endpoint (in yrs)	4.6 (3.1–7.9)	4.2 (2.5–7.6)	4.1 (2.1–6.3)	2.9 (1.6–4.8)	2.8 (0.6–4.6)	

Values are n (%) or median (interquartile range). *The p values are calculated by chi-square test. †For the secondary outcome, patients were censored at the occurrence of the first event.
AVR = aortic valve replacement; MI = myocardial infarction or unstable angina.

multivariable Cox proportional hazards models, without the need for time-dependent AVR. All statistical analyses were performed using SPSS software version 23.0 (IBM, Armonk, New York) and STATA version 10 (StataCorp, College Station, Texas). A 2-sided p value <0.05 was considered statistically significant.

RESULTS

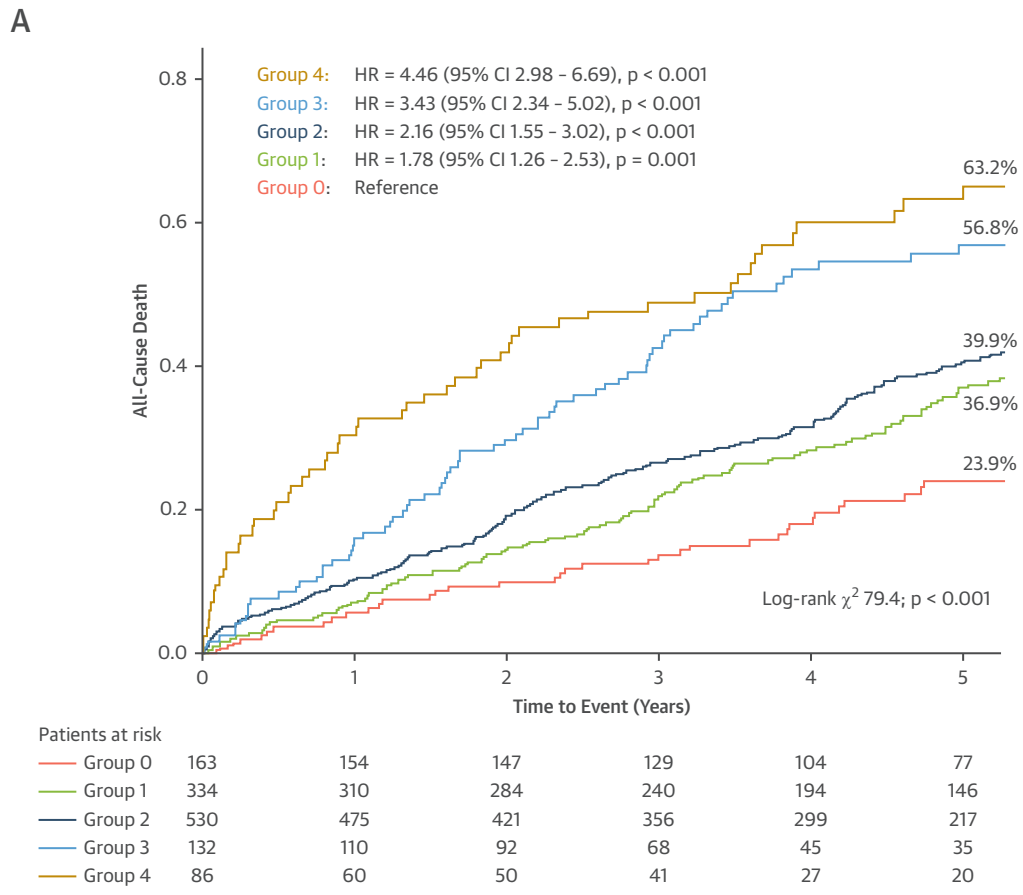
PATIENT CHARACTERISTICS. Baseline clinical characteristics of the total study population (mean age 71 ± 12 years, 50.0% male) with moderate AS are listed in Table 1. The majority of patients had cardiovascular risk factors, including hypertension (79.2%) and hypercholesterolemia (80.2%), whereas diabetes was not as common (34.9%). Of note, coronary artery disease was prevalent in 48.0% of the population, and 17.3% of patients had previous myocardial infarction. At the time of echocardiographic diagnosis of moderate AS, 33.6% (n = 418) of the patients were symptomatic at baseline. The most common symptom was dyspnea (n = 253, 60.5%), followed by angina (n = 109, 26.1%). Of these symptomatic patients, 34.7% (n = 145) were in New York Heart Association (NYHA) functional class III or IV at the time of presentation.

According to the presence and extent of extra-aortic valvular cardiac abnormalities documented on echocardiography at the time of inclusion (Figure 1), 13.1% (n = 163) of the patients were classified as Group 0 (no extra-aortic valvular involvement), 26.8% (n = 334) as Group 1 (LV involvement), 42.6% (n = 530) as Group 2 (LA or mitral-valve involvement), 10.6% (n = 132) as Group 3 (pulmonary artery vasculature or tricuspid-valve involvement), 6.9% (n = 86) as Group 4 (RV involvement). Patients with greater extent of cardiac involvement were older, had more cardiovascular risk factors, with a higher prevalence of coronary artery disease and previous myocardial infarction (Table 1). In addition, they were more frequently symptomatic at baseline, with more patients in the advanced groups of cardiac involvement experiencing more severe symptoms (NYHA functional class ≥III). In parallel, these patients also had worse kidney function and required more cardiac medications, including anticoagulation (for history of atrial fibrillation) and diuretic agents (for relief of symptoms).

Baseline echocardiographic parameters for the overall population and their respective distribution of these parameters in individual groups of extra-aortic valvular involvement are presented in Table 2. As expected, patients in the groups with more advanced extra-aortic cardiac involvement had lower LVEF, higher E/e' ratio and LA volume indices, together with a higher prevalence of significant mitral and tricuspid regurgitation, compared with patients with less advanced cardiac involvement. Interestingly, bicuspid aortic valve anatomy was more commonly observed in patients with moderate AS with no extravalvular involvement at baseline (n = 45, 27.6% of Group 0), compared with patients with extravalvular abnormalities (n = 80, 7.4% of all patients from Groups 1 to 4). The incidences of the individual components of the extent of cardiac involvement in the total population are presented in Table 3.

LONG-TERM OUTCOMES. During follow-up, 373 (30.0%) patients underwent surgical or transcatheter AVR within a median time of 2.4 years (IQR: 1.0 to 4.3 years). During a median follow-up of 4.3 years (IQR: 2.4 to 6.9 years), 564 (45.3%) patients died, and over a median time of 4.0 years (IQR: 2.2 to 6.6 years), 620

FIGURE 2 Survival Analyses According to the Extent of Extra-Aortic Valvular Cardiac Abnormalities in Patients With Moderate Aortic Stenosis



Kaplan-Meier estimates for the cumulative event rates of all-cause mortality **(A)** and the combined endpoint **(B)** according to the presence of the extent of extra-aortic valvular cardiac abnormalities in patients with moderate aortic stenosis.

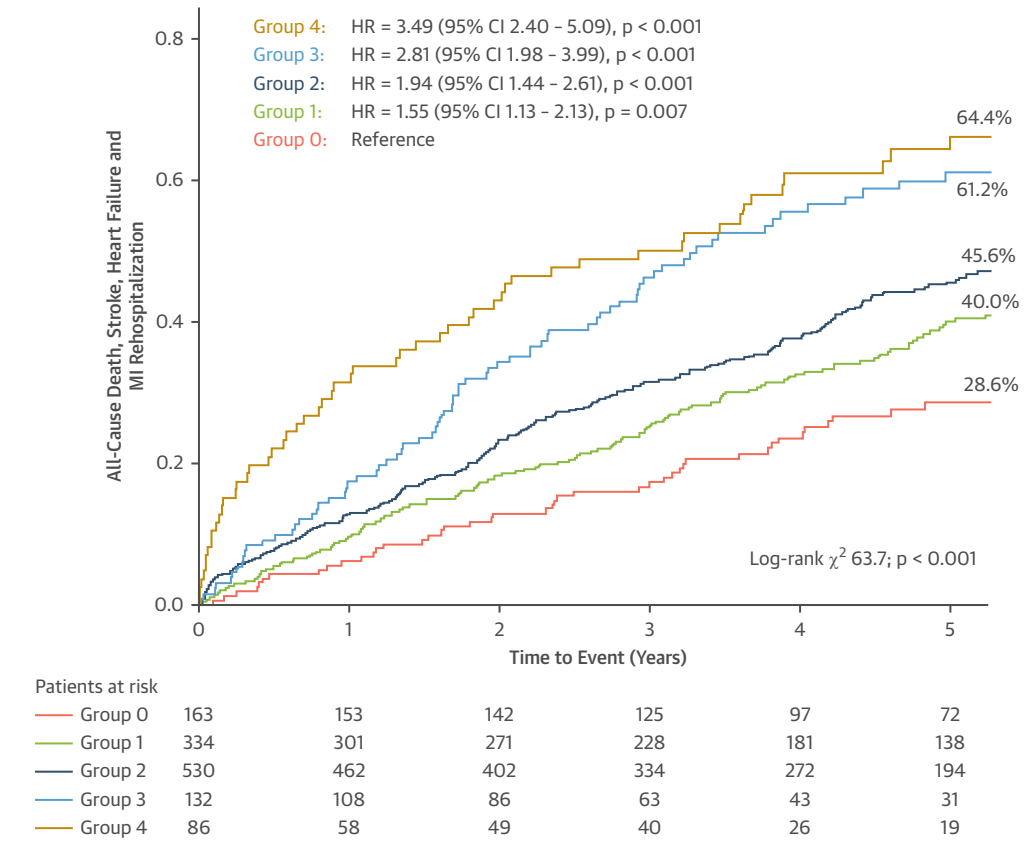
Continued on the next page

(49.8%) patients reached the combined endpoint (all-cause mortality, and rehospitalization for stroke, heart failure, and myocardial infarction or unstable angina). The clinical outcomes during follow-up, according to the extent of extra-aortic cardiac involvement, are presented in **Table 4**. Interestingly, despite being more symptomatic at baseline, fewer patients with moderate AS and more advanced extra-aortic cardiac involvement underwent surgical or transcatheter AVR compared with those with less extent of cardiac abnormalities.

SURVIVAL ANALYSIS. Kaplan-Meier curve analysis showed that patients with more advanced extra-aortic cardiac involvement had significantly higher 5-year cumulative mortality rates (**Figure 2A**) (log-rank chi-square test 79.4; $p < 0.001$; Harrell's $c = 0.60$). Similarly, for the combined outcome, patients with more extensive cardiac abnormalities showed significantly higher cumulative 5-year event rates (**Figure 2B**) (log-rank chi-square test 63.7; $p < 0.001$; Harrell's $c = 0.59$). With increasing extent of cardiac involvement (beyond the aortic valve), from LV, to LA or mitral valve, to pulmonary vasculature or tricuspid valve to RV, there was a significant increase in the risk of either all-cause mortality or combined endpoint (all-cause mortality, rehospitalization for stroke, heart failure and myocardial infarction, or unstable angina) compared with patients with no extra-aortic cardiac involvement ($p < 0.01$ for all vs. Group 0, respectively).

To examine the outcomes of moderate AS patients on medical therapy, the Kaplan-Meier analysis was

FIGURE 2 Continued

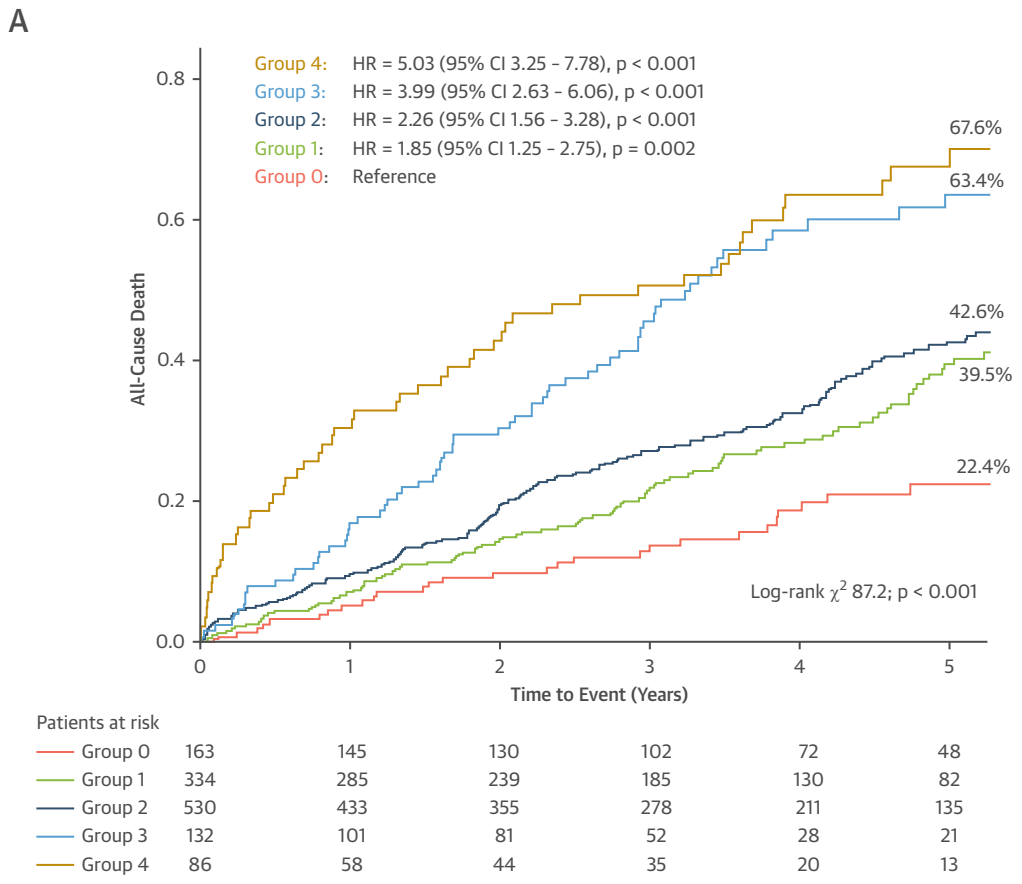


performed and censored at the time of AVR. Similar to previous observation, patients had significantly higher 5-year cumulative event rates for both all-cause mortality (Figure 3A) (log-rank chi-square test 87.2; $p < 0.001$; Harrell's $c = 0.62$) and combined endpoint (Figure 3B) (log-rank chi-square test 77.3; $p < 0.001$; Harrell's $c = 0.61$) with increasing extent of extra-aortic cardiac involvement, in terms of categorizing into groups of cardiac abnormalities, detected on baseline echocardiographic examination.

PROGNOSTIC VALUE OF PROPOSED CLASSIFICATION OF THE EXTENT OF ASSOCIATED CARDIAC ABNORMALITIES. The correlates of all-cause mortality and the combined endpoint on univariable and multivariable Cox regression analyses are shown in Table 5 for the entire population. On multivariable analysis, age, NYHA functional class ≥III, renal function, diabetes, peak aortic jet velocity, surgical or transcatheter AVR and the presence of extra-aortic valvular cardiac abnormalities remained independently associated with all-cause mortality. Importantly, when considering the extent of extra-aortic cardiac involvement as a categorical variable on multivariable analysis, only Group 2 (HR: 1.46; 95% CI: 1.02 to 2.08; $p = 0.041$), Group 3 (HR: 2.28; 95% CI: 1.49 to 3.47; $p < 0.001$), and Group 4 (HR: 2.35; 95% CI: 1.50 to 3.69; $p < 0.001$) cardiac abnormalities were independently associated with all-cause mortality (Harrell's $c = 0.76$). For the combined endpoint, age, male gender, previous myocardial infarction, chronic obstructive pulmonary disease, NYHA functional class ≥III, renal function, diabetes, peak aortic-jet velocity, and the presence of extra-aortic valvular cardiac abnormalities were independent associates of all-cause mortality and hospitalization for stroke, heart failure and myocardial infarction, or unstable angina on multivariable Cox regression analyses. Of note, only Group 3 (HR: 1.92; 95% CI: 1.30 to 2.83; $p = 0.001$), and Grade 4 (HR: 1.91; 95% CI: 1.25 to 2.91; $p < 0.001$) were independently associated with combined adverse cardiovascular events (Harrell's $c = 0.72$).

Using multivariable Cox regression analyses for patients with moderate AS on medical therapy and censored at the time of surgical or transcatheter AVR,

FIGURE 3 Survival Analyses Censored at the Time of Aortic Valve Replacement According to the Extent of Extra-Aortic Valvular Cardiac Abnormalities in Patients With Moderate Aortic Stenosis



Kaplan-Meier estimates for the cumulative event rates of all-cause mortality **(A)** and the combined endpoint **(B),** according to the presence of the extent of extra-aortic valvular cardiac abnormalities in patients with moderate aortic stenosis censored at the time of aortic valve replacement.

Continued on the next page

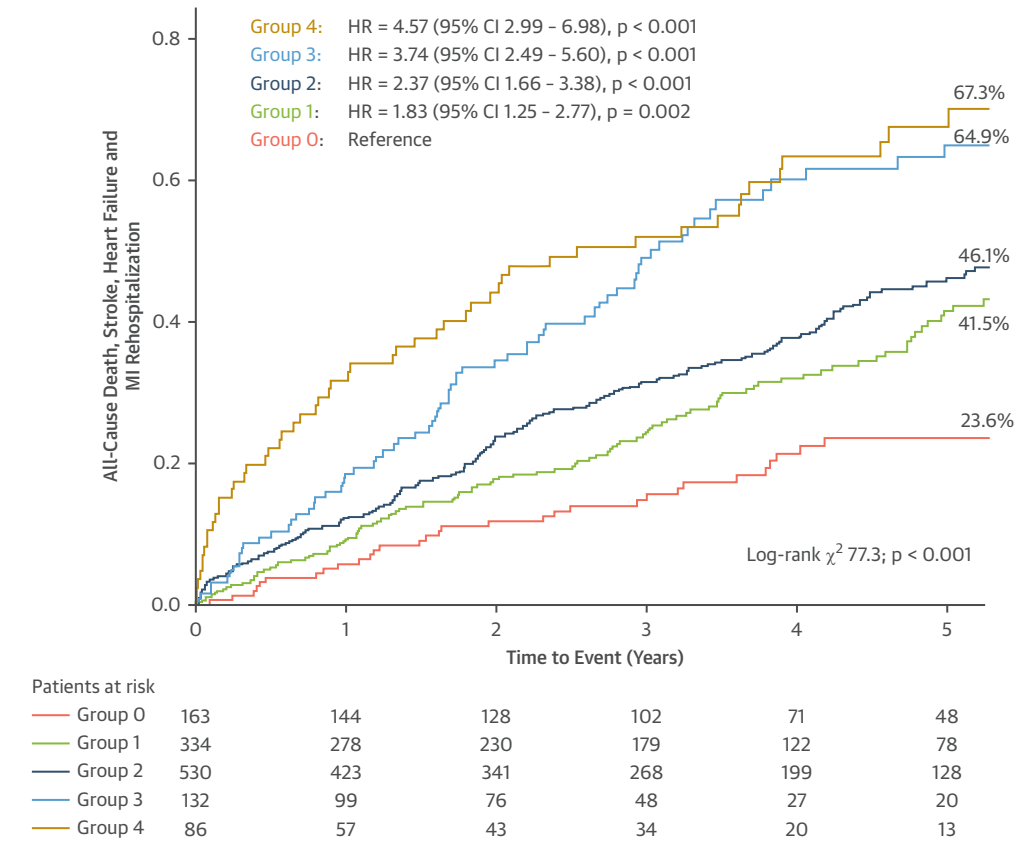
the presence of extra-aortic valvular cardiac abnormalities was also independently associated with all-cause mortality (Harrell's c = 0.76) and the combined endpoint (Harrell's c = 0.75) (Supplemental Table 1). Importantly, this effect was mainly caused by the presence of more extensive cardiac abnormalities, with ≥Group 3 and ≥Group 2 involvement associated with all-cause mortality, as well as combined outcome, respectively (Supplemental Table 1).

DISCUSSION

The current study demonstrated that in a real-world experience of patients with moderate AS, extra-aortic valvular cardiac abnormalities involving the LV (in Group 1), to the LA or mitral valve (in Group 2), to the pulmonary vasculature or tricuspid valve (in Group 3), and to the RV (in Group 4) is common (**Central Illustration**). When present in patients with moderate AS, the extent of extra-aortic valvular cardiac involvement (by proposed classification criteria ≥Group 2) is independently associated with all-cause mortality, as well as a combined outcome of all-cause mortality and adverse cardiovascular events (hospitalization for stroke, heart failure, and myocardial infarction or unstable angina).

PREVALENCE OF EXTRA-AORTIC VALVULAR CARDIAC ABNORMALITIES. Aortic stenosis can lead to extra-aortic valvular cardiac remodeling in the long term,

FIGURE 3 Continued



caused by chronic pressure overload, with subsequent increase in LV filling pressures, associated with an increase in the incidence of cardiac arrhythmias: in particular, atrial fibrillation (17–19). In fact, chronically elevated LA pressure may lead to a rise in pulmonary artery pressure and, eventually, significant tricuspid regurgitation and RV dilatation and dysfunction (20,21). Previous studies have indicated that these structural changes, when present individually or in combination in patients with severe AS, are associated with adverse outcomes (22,23).

The current results show that extra-aortic valvular cardiac abnormalities are already present (beyond the aortic-valve dysfunction) in moderate AS, with prevalence as high as 87% in our population. Interestingly, the extent of cardiac abnormalities is not so different from patients with severe AS, with a reported prevalence of 13% to 24% in Group 1, 49% to 51% in Group 2, 7% to 25% in Group 3, and 9% to 12% in Group 4 in those with symptomatic severe AS, using similar classification criteria (7,8), This is not surprising, as in AS (being a progressive valvular disease), gradual changes in the LV may have occurred over time as a response to the hemodynamic stress of an increased LV afterload, even before the valve lesion becomes severe. In addition, the presence of comorbidities, such as hypertension, coronary artery disease, and diabetes (24), which are also prevalent in patients with AS, may further aggravate cardiac remodeling. Of note, significantly more concomitant comorbidities were observed in patients with more extensive cardiac involvement in the current study. Although only one-third of the entire population experienced symptoms at the time of first diagnosis of moderate AS, these observations may explain why there was a higher proportion of symptomatic patients observed with greater extent of extravalvular cardiac abnormalities.

PROGNOSTIC SIGNIFICANCE OF THE PROPOSED CLASSIFICATION OF THE EXTENT OF ASSOCIATED CARDIAC ABNORMALITIES IN MODERATE AS. Importantly, the mortality increased with increasing

TABLE 5 Univariable and Multivariable Cox Proportional Hazard Analyses for All-Cause Mortality and Combined Endpoint of All-Cause Mortality and Rehospitalization for Stroke, Heart Failure, and MI

	Univariable Analysis		Multivariable Analysis	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
All-cause mortality				
Age (per 1-yr increase)	1.042 (1.034–1.051)	<0.001	1.030 (1.022–1.039)	<0.001
Male gender (yes/no)	1.090 (0.924–1.285)	0.309	1.183 (0.989–1.415)	0.066
Coronary artery disease (yes/no)	1.155 (0.979–1.362)	0.088	0.940 (0.784–1.127)	0.504
Previous myocardial infarction (yes/no)	1.801 (1.481–2.191)	<0.001	1.121 (0.905–1.389)	0.295
Chronic obstructive pulmonary disease (yes/no)	1.467 (1.082–1.991)	0.014	1.250 (0.906–1.723)	0.174
Atrial fibrillation (yes/no)	1.212 (1.002–1.468)	0.048	0.975 (0.782–1.215)	0.818
NYHA functional class ≥III (yes/no)	2.652 (2.148–3.274)	<0.001	1.667 (1.329–2.091)	<0.001
eGFR (per 1 ml/min/1.73 m^2 increase)	0.978 (0.975–0.980)	<0.001	0.981 (0.978–0.984)	<0.001
Systolic blood pressure (per 1 mm Hg increase)	0.994 (0.991–0.998)	0.004	0.997 (0.993–1.001)	0.109
Hypertension (yes/no)	1.677 (1.340–2.098)	<0.001	0.838 (0.648–1.085)	0.180
Diabetes mellitus (yes/no)	1.645 (1.390–1.946)	<0.001	1.299 (1.082–1.560)	0.005
Diuretics (yes/no)	1.364 (1.152–1.616)	<0.001	0.889 (0.738–1.071)	0.217
Ca-antagonist (yes/no)	1.286 (1.089–1.518)	0.003	0.994 (0.828–1.193)	0.946
Peak aortic jet velocity (per 1 m/s increase)	0.534 (0.449–0.635)	<0.001	0.767 (0.637–0.922)	0.005
AVA (per 0.1 cm^2 increase)	0.499 (0.285–0.874)	0.015	0.622 (0.336–1.150)	0.130
Surgical or transcatheter AVR (yes/no)	0.601 (0.472–0.766)	<0.001	0.731 (0.565–0.948)	0.018
Group according to the extent of extra-aortic valvular cardiac abnormalities				
Group 0 vs. Group 1	1.777 (1.251–2.525)	0.001	1.282 (0.889–1.848)	0.184
Group 0 vs. Group 2	2.159 (1.546–3.015)	<0.001	1.455 (1.016–2.084)	0.041
Group 0 vs. Group 3	3.425 (2.336–5.022)	<0.001	2.278 (1.494–3.473)	<0.001
Group 0 vs. Group 4	4.464 (2.977–6.692)	<0.001	2.352 (1.498–3.692)	<0.001
Combined endpoint				
Age (per 1 yr increase)	1.036 (1.029–1.044)	<0.001	1.024 (1.016–1.033)	<0.001
Male (yes/no)	1.199 (1.024–1.404)	0.025	1.236 (1.042–1.465)	0.015
Coronary artery disease (yes/no)	1.312 (1.120–1.537)	0.001	1.059 (0.891–1.258)	0.518
Previous myocardial infarction (yes/no)	1.933 (1.605–2.327)	<0.001	1.253 (1.023–1.535)	0.029
Chronic obstructive pulmonary disease (yes/no)	1.584 (1.189–2.110)	0.002	1.419 (1.062–1.898)	0.018
Atrial fibrillation (yes/no)	1.305 (1.089–1.563)	0.004	1.076 (0.873–1.327)	0.492
NYHA functional class ≥III (yes/no)	2.664 (2.171–3.268)	<0.001	1.718 (1.379–2.140)	<0.001
eGFR (per 1 ml/min/1.73m^2 increase)	0.980 (0.978–0.983)	<0.001	0.984 (0.981–0.987)	<0.001
Systolic blood pressure (per 1 mm Hg increase)	0.994 (0.991–0.998)	0.002	0.996 (0.993–1.000)	0.053
Hypertension (yes/no)	1.624 (1.316–2.005)	<0.001	0.882 (0.690–1.128)	0.318
Diabetes mellitus (yes/no)	1.643 (1.398–1.930)	<0.001	1.276 (1.073–1.519)	0.006
Diuretics (yes/no)	1.333 (1.133–1.568)	0.001	0.888 (0.744–1.060)	0.189
ACE or ARB (yes/no)	1.194 (1.019–1.398)	0.028	1.012 (0.855–1.198)	0.889
Ca-antagonist (yes/no)	1.320 (1.126–1.547)	0.001	1.092 (0.917–1.300)	0.321
Peak aortic jet velocity (per 1 m/s increase)	0.560 (0.475–0.660)	<0.001	0.792 (0.663–0.945)	0.010
AVA (per 0.1 cm^2 increase)	0.666 (0.392–1.131)	0.133	0.745 (0.420–1.322)	0.314
Surgical or transcatheter AVR (yes/no)	0.828 (0.663–1.034)	0.096	0.907 (0.712–1.154)	0.426
Group according to the extent of extra-aortic valvular cardiac abnormalities				
Group 0 vs. Group 1	1.549 (1.129–2.126)	0.007	1.160 (0.833–1.614)	0.380
Group 0 vs. Group 2	1.938 (1.437–2.613)	<0.001	1.354 (0.979–1.873)	0.067
Group 0 vs. Group 3	2.808 (1.975–3.993)	<0.001	1.915 (1.296–2.828)	0.001
Group 0 vs. Group 4	3.494 (2.397–5.093)	<0.001	1.907 (1.250–2.908)	0.003

AVA = aortic valve area; AVR = aortic valve replacement; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction or unstable angina; NYHA = New York Heart Association).

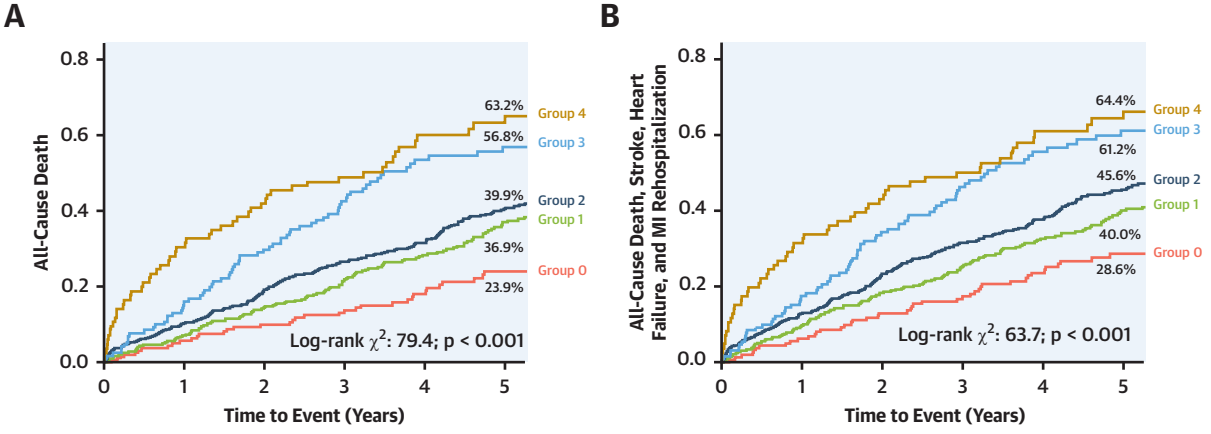
extent of cardiac abnormalities detected on echocardiography in patients with moderate AS in the current study. Compared with previous studies of unselected patients with moderate AS, the 5-year mortality rate was 56% (5), whereas in another study that included 305 patients with moderate AS and LVEF <50%, the reported 4-year all-cause mortality rate was 36%, with an up to 48% event rate for combined deaths and admissions for heart failure (6). Hence, it is a novel finding that the current proposed classification

CENTRAL ILLUSTRATION **Prevalence and Clinical Outcomes of the Extent of Echocardiographic Signs of Extra-Aortic Valvular Cardiac Abnormalities in Patients With Moderate Aortic Stenosis**

Extra-Aortic Valvular Cardiac Abnormalities

	Group 0	Group 1	Group 2	Group 3	Group 4
Involvement	No Extra-Valvular	Left Ventricular	Left Atrial or Mitral	Pulmonary or Tricuspid	Right Ventricular
Prevalence	13.1%	26.8%	42.6%	10.6%	6.9%
Echo-cardiographic criteria		LV mass index ♂ >115 g/m^2 ♀ >95 g/m^2 LV ejection fraction <50% E/e' ratio >14	Left atrial volume index >34 ml/m^2 Atrial fibrillation Moderate or severe mitral regurgitation	Systolic pulmonary arterial pressure >60 mm Hg Moderate or severe tricuspid regurgitation	TAPSE <16 mm

Outcomes According to Extent of Cardiac Involvement



Amanullah, M.R. et al. J Am Coll Cardiol Img. 2021;14(9):1724–1737.

(Top) The prevalence of the presence of the extent of extra-aortic valvular cardiac abnormalities according to the proposed classification based on echocardiography at the time of moderate aortic stenosis. **(Bottom)** For both all-cause mortality **(left)** and the combined endpoint of all-cause mortality and rehospitalization for stroke, heart failure, and myocardial infarction or unstable angina **(right)**, the greater extent of cardiac involvement showed significantly higher cumulative 5-year event rates.

algorithm incorporating the extent of concomitant cardiac abnormalities is able to identify those at higher risk of all-cause mortality or adverse cardiac outcomes, even in nonsevere AS. For example, a 1.5-fold increase in risk of all-cause mortality would be anticipated if concomitant LV abnormalities were present at the time of moderate AS, compared with patients with moderate AS alone. On the other hand, the presence of ≥ moderate tricuspid regurgitation or pulmonary hypertension or concomitant RV dysfunction would increase the risk of dying by 2.3-fold in patients with moderate AS, adjusted for baseline characteristics including AVR as time-dependent variable. Interestingly, Tastet et al. (9) did not observe a significant association between the presence of extra-aortic valvular cardiac abnormalities and all-cause mortality or cardiovascular death in a subgroup of 285 patients with asymptomatic moderate AS. Given that a relatively smaller population of moderate AS was included in their study, it might have accounted for the lack of power to detect a difference. In contrast, the current study included a larger population with moderate AS and demonstrated that the proposed extra-aortic valvular cardiac involvement classification criteria could identify patients with worse prognosis in terms of both long-term all-cause mortality and combined endpoint (death and rehospitalization for cardiovascular events).

Interestingly, only a smaller proportion (13%) of patients in advanced Group 4 of cardiac abnormalities underwent AVR compared with less extensive cardiac involvement (>30% in Groups 0 to 2 and 22% in Group 3), despite being more symptomatic at baseline. This

is presumably related to late or nonreferral for AVR because of perceived high risk for valve surgery because of multiple comorbidities. Alternatively, patients could have died before AVR or AS might not have been considered as severe enough to warrant AVR when the aortic valve area was >1.0 cm^2. This was supported by the observation that there was higher use of diuretics, beta blockers, and angiotensin converting enzyme inhibitors and shorter survival in this group of patients. Recently, Gomez-Doblas et al. (25) observed that the presence of significant mitral regurgitation was independently associated with the decision to treat conservatively in patients with severe AS.

Current guidelines recommend monitoring patients with moderate AS every 1 to 2 years, based on expert consensus, because of the lack of large-scale observational studies to determine the frequency of monitoring and its impact on long-term outcomes (10). In the current study, the time to event, in terms of all-cause mortality or combined endpoint, was significantly shorter in patients with more extensive concomitant cardiac abnormalities detected on echocardiography. This study highlights the importance of assessment of the global hemodynamic impact caused by valvular AS and other comorbidities and provides a better risk-stratification tool for patients with moderate AS. It is unclear, at this point, if early intervention for patients with Group 2 to 4 would have improved survival, and this awaits evaluation in future prospective studies.

STUDY LIMITATIONS. The limitations are related to the retrospective, observational design of the study. However, all the patients who met the echocardiographic definition of moderate AS were included, representing patient data from daily clinical practice. Referral bias and selection for AVR may be present, although these are screened by the multidisciplinary heart team in the respective centers, as per guidelines recommendation (26,27). In addition, the analysis of additional comorbidity index, imaging data, and biomarkers is limited in the current study because of its retrospective nature. However, these parameters could be useful for future prospective study in the prognostic and prediction model in patients with moderate AS. Finally, classification of the extent of extra-aortic valvular cardiac abnormalities by grouping may not necessarily represent increasing levels of severity in a linear manner and that abnormalities can also occur in combination. A more sophisticated statistical technique, such as the latent class analysis, could potentially be explored in the future.

CONCLUSIONS

In this large multicenter study of patients with moderate AS, addition of classification scheme, based on the extent of extra-aortic valvular cardiac involvement, could help to identify the patients at risk for all-cause mortality and the combined outcome of all-cause mortality and adverse cardiovascular events (hospitalization for stroke, heart failure, and myocardial infarction or unstable angina). Risk stratification using this approach may help to identify those patients with moderate AS who are at increased risk of adverse events and may benefit from close monitoring.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Department of Cardiology, Heart Lung Center, Leiden University Medical Center has received grants from Biotronik, Medtronic, Boston Scientific, GE Healthcare, and Edwards Lifesciences. Dr. Marsan has received speaker fees from Abbott and Philips Ultrasound. Dr. Ding has received speaker fees from Philips. Dr. Ewe has received speaker fees from Edwards Lifesciences and Abbott Vascular. Dr. Delgado has received speaker fees from Abbott Vascular. Dr. Bax has received speaker fees from Abbott Vascular and Boehringer Ingelheim. Dr. Pio has received funding from European Society of Cardiology in the form of an ESC Training Grant (reference of application number: T-2018-17405). Dr. Genereux has received speaker fees from Edwards Lifesciences, Cordis, and Medtronic; has served as consultant for Abiomed, Boston Scientific, Cardiovascular System Inc., Cordis, Edwards Lifesciences, Medtronic, Opsens, Soundbite Medical Solutions Inc., Pi-Cardia, Saranas, Siemens, Shockwave Medical Inc., SIG.NUM, Teleflex, and 4C Medical; and holds shares in Soundbite Medical Solutions Inc., SIG.NUM, Pi-Cardia, and Puzzle Medical. Dr. Leon is an early physician founder of Mitralign and has an equity relationship (<1% of the company). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Extra-aortic valvular cardiac abnormalities, as assessed by echocardiography, in patients with moderate aortic stenosis is associated with increased risk of all-cause mortality as well as combined adverse cardiovascular events.

TRANSLATIONAL OUTLOOK: Prospective studies are required to determine the prognostic value of incorporating this imaging classification scheme in patients with moderate aortic stenosis and to develop early therapeutic interventions to improve survival and outcome.

REFERENCES

1. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol*. 1988;61:123–130.

2. Ben-Dor I, Pichard AD, Gonzalez MA, et al. Correlates and causes of death in patients with severe symptomatic aortic stenosis who are not eligible to participate in a clinical trial of transcatheter aortic valve implantation. *Circulation*. 2010;122:S37–S42.

3. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2485–2491.

4. Rosenhek R, Klaar U, Schemper M, et al. Mild and moderate aortic stenosis: natural history and risk stratification by echocardiography. *Eur Heart J*. 2004;25:199–205.

5. Strange G, Stewart S, Celermajer D, et al. Poor long-term survival in patients with moderate aortic stenosis. *J Am Coll Cardiol*. 2019;74:1851–1863.

6. Gils LV, Clavel MA, Vollema EM, et al. Prognostic implications of moderate aortic stenosis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2017;69:2383–2392.

7. Genereux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017;38:3351–3358.

8. Vollema EM, Amanullah MR, Ng ACT, et al. Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:538–549.

9. Tastet L, Tribouilloy C, Maréchaux S, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563.

10. Nishimura R, Otto C, Bonow R, 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. *Circulation*. 2014;129:2440–2492.

11. 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. *Eur Heart J Cardiovasc Imaging*. 2017;18:254–275.

12. 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. *Eur Heart J Cardiovasc Imaging*. 2015;16:233–270.

13. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009;22:1–23.

14. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321–1360.

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. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713.

17. Tarantini G, Mojoli M, Urena M, Vahanian A. Atrial fibrillation in patients undergoing transcatheter aortic valve implantation: epidemiology, timing, predictors, and outcome. *Eur Heart J*. 2017;38:1285–1293.

18. Asami M, Lanz J, Stortecky S, et al. The impact of left ventricular diastolic dysfunction on clinical outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol Intv*. 2018;11:593–601.

19. Minamino-Muta E, Kato T, Morimoto T, et al. Impact of the left ventricular mass index on the outcomes of severe aortic stenosis. *Heart*. 2017;103:1992–1999.

20. Alushi B, Beckhoff F, Leistner D, et al. Pulmonary hypertension in patients with severe aortic stenosis: prognostic impact after transcatheter aortic valve replacement: pulmonary hypertension in patients undergoing TAVR. *J Am Coll Cardiol Img*. 2019;12:591–601.

21. Kammerlander A, Marzluf B, Graf A, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcome late after left heart valve procedure. *J Am Coll Cardiol*. 2014;64:2633–2642.

22. Zilberszac R, Gleiss A, Binder T, et al. Prognostic relevance of mitral and tricuspid regurgitation in patients with severe aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2018;19:985–992.

23. Amano M, Izumi C, Taniguchi T, et al. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2019;20:353–360.

24. Lv W, Li S, Zhao Z, et al. Diabetes mellitus is an independent prognostic factor for mid-term and long-term survival following transcatheter aortic valve implantation: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2018;27:159–168.

25. Gomez-Doblas JJ, Lopez-Garrido MA, Becerra-Munoz VM, et al. Significant mitral regurgitation worsens the prognosis and favours the decision of conservative treatment in octogenarians with severe symptomatic aortic stenosis. *Eur J Intern Med*. 2018;55:40–46.

26. Nishimura RA, Otto CM, Bonow RO, et al. AHA/ACC Focused update of 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 clinical practice guidelines. *Circulation*. 2017;135:e1159–e1195.

27. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines of the management of valvular heart disease. *Eur Heart J Cardiovasc Imaging*. 2017;38:2739–2791.

KEY WORDS aortic stenosis, classification, prognosis, valvular heart disease

APPENDIX For a supplemental table, please see the online version of this paper.