Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy

Vollema, E.M.

Part I

RISK STRATIFICATION AND TIMING OF INTERVENTION

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STAGING CARDIAC DAMAGE IN PATIENTS WITH SYMPTOMATIC AORTIC VALVE STENOSIS

E. Mara Vollema*, Mohammed R. Amanullah*, Arnold C.T. Ng,
Pieter van der Bijl, Francesca Prevedello, Yoong Kong Sin,
Edgard A. Prihadi, Nina Ajmone Marsan, Zee Pin Ding,
Philippe Généreux, Philippe Pibarot, Martin B. Leon, Jagat Narula,
See Hooi Ewe, Victoria Delgado, Jeroen J. Bax

*Drs. Vollema and drs. Amanullah contributed equally to this manuscript.

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ABSTRACT

BACKGROUND

In severe aortic stenosis (AS), patients often show extra-aortic valvular injury. Recently, a new staging system for severe AS has been proposed based on the extent of cardiac damage.

OBJECTIVES

The present study evaluated the prevalence and prognostic impact of these different stages of cardiac damage in a large, real-world, multicenter cohort of symptomatic severe AS patients.

METHODS

From the ongoing registries from 2 academic institutions, a total of 1189 symptomatic severe AS patients were selected and retrospectively analysed. According to the extent of cardiac damage on echocardiography, patients were classified as Stage 0 (no cardiac damage), Stage 1 (left ventricular damage), Stage 2 (mitral valve or left atrial damage), Stage 3 (tricuspid valve or pulmonary artery vasculature damage) or Stage 4 (right ventricular damage). Patients were followed for all-cause mortality and combined endpoint (all-cause mortality, stroke and cardiac-related hospitalization).

RESULTS

On the basis of the proposed classification, 8% of patients were classified as Stage 0, 24% as Stage 1, 49% as Stage 2, 7% as Stage 3 and 12% as Stage 4. On multivariable analysis, cardiac damage was independently associated with all-cause mortality and combined outcome, although this was mainly determined by Stages 3 and 4.

CONCLUSIONS

In this large multicenter cohort of symptomatic severe AS patients, stage of cardiac injury as classified by a novel staging system was independently associated with all-cause mortality and combined endpoint, although this seemed to be predominantly driven by tricuspid valve or pulmonary artery vasculature damage (Stage 3) and right ventricular dysfunction (Stage 4).

Introduction

In aortic stenosis (AS), referral for aortic valve replacement (AVR) is currently driven by the severity of AS and by the presence of AS related symptoms or signs of left ventricular (LV) systolic dysfunction (defined as a LV ejection fraction <50%) [1, 2]. Severity of AS is primarily quantified on echocardiography using hemodynamic parameters of the aortic valve specifically, that is, mean transvalvular pressure gradient, peak aortic jet velocity and aortic valve area [3]. However, the clinical outcomes of severe AS patients are not influenced by the stenotic aortic valve only. Changes in the LV structure and function as well as hemodynamic consequences beyond the left ventricle such as significant mitral [4, 5] and tricuspid regurgitation [5, 6] and right ventricular (RV) dysfunction [7, 8] have been associated with poor outcomes in severe AS patients undergoing AVR. Recently, a new staging system for severe AS has been proposed based on the extent of anatomic and functional cardiac damage [9]. Généreux et al. [9] demonstrated the strong predictive value of a proposed model to stage severe AS patients who were included for the PARTNER II (Placement of AoRTic TraNscathetER Valves) trial. The generalization of this staging model to an unselected symptomatic severe AS population has not been tested. Therefore, the present study aimed at evaluating the prevalence of the different stages of extra-aortic valvular cardiac damage and its impact on prognosis in a large, real-world, multicenter cohort of symptomatic severe AS patients.

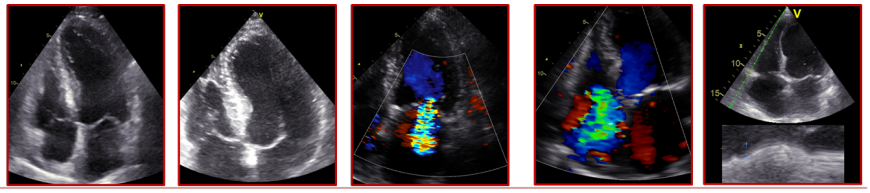
Methods

Patient population and data collection

From the ongoing registries of patients with aortic valve disease from 2 academic institutions (Leiden University Medical Center, Leiden, The Netherlands and National Heart Centre, Singapore, Singapore) between 1999 and 2017, a total of 1189 symptomatic severe AS patients were selected upon available echocardiographic data at baseline (defined as the first available echocardiogram with symptomatic severe AS). Severe AS was defined according to current guidelines as a mean aortic valve gradient ≥40 mmHg and/or aortic valve area <1.0 cm^2 (or an indexed aortic valve area <0.6 cm^2/m^2) and/or a peak aortic jet velocity ≥4 m/s [1–3]. At each participating center, echocardiographic measurements were performed by experienced observers. Patients 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 and the need for patient written informed consent was waived due to the retrospective nature of the study.

Transthoracic echocardiography

Using commercially available ultrasound systems, 2-dimensional, colour, pulsed and continuous wave Doppler images were obtained from the apical and parasternal views according to current recommendations with the patient at rest in left lateral decubitus position [10]. From the apical 3- or 5-chamber views, continuous wave Doppler recordings were obtained to estimate peak aortic jet velocity [3]. Mean and peak transvalvular



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	Left ventricular damage	Left atrial or mitral damage	Pulmonary vasculature or tricuspid damage	Right ventricular damage
Echocardiographic criteria		LV mass index ♂ >115 g/m² ♀ > 95 g/m² LV ejection fraction <50% E/e' ratio >14	Left atrial volume index >34 ml/m² Presence of atrial fibrillation Moderate/severe mitral regurgitation	Systolic pulmonary arterial pressure ≥60 mmHg Moderate/severe tricuspid regurgitation	TAPSE <16 mm

Figure 1: Stages of cardiac damage in severe AS. Proposed staging classification based on the extent of echocardiographic signs of extra-aortic valvular cardiac damage. AS, aortic stenosis; LA, left atrial; LV, left ventricular; TAPSE, tricuspid annular plane systolic excursion.

pressure gradients were calculated using the Bernoulli equation [3]. Aortic valve area (AVA) was calculated according to the continuity equation using velocity time integrals of the LV outflow tract and aortic valve and indexed for body surface area (indexed AVA) [3]. In the parasternal long-axis view, LV dimensions were assessed and LV mass was calculated by Devereux's formula and indexed for body surface area (LV mass index) [10]. LV end-diastolic and end-systolic volumes were evaluated in the apical 2- and 4-chamber views and the LV ejection fraction was calculated according to the Simpson's biplane method [10]. Using the biplane method of disks, left atrial volumes were measured at end-systole in the apical 2- and 4-chamber views and indexed for body surface area (left atrial [LA] volume index) [10]. 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 [11]. 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 [11]. Severity of mitral and tricuspid regurgitation was graded according to a multi-parametric approach, as recommended [12]. The 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 [10, 13]. For the evaluation of RV systolic function, anatomical M-mode was applied on the focused apical 4-chamber view of the right ventricle to measure tricuspid annular plane systolic excursion (TAPSE) [10].

DEFINITIONS STAGING CLASSIFICATION

The presence and extent of extra-aortic valvular cardiac damage was evaluated on baseline transthoracic echocardiography (i.e., the first available echocardiogram with symptomatic severe AS) and accordingly, patients were classified into 5 independent stages as proposed by Généreux et al. [9] (Figure 1): Stage 0 – no signs of cardiac damage; Stage 1 – LV damage (LV ejection fraction <50%, LV mass index >95 g/m^2 for women or >115 g/m^2 for men or E/e' >14) [10, 11], Stage 2 – mitral valve or LA damage (LA volume index >34 ml/m^2 or mitral regurgitation (MR) ≥ grade 3 or presence of atrial fibrillation at

the moment of echocardiography) [10, 12], Stage 3 – tricuspid valve or pulmonary artery vasculature damage (systolic pulmonary artery pressure ≥60 mmHg or tricuspid regurgitation (TR) ≥ grade 3) [12] or Stage 4 – RV damage (TAPSE <16 mm) [13]. Patients were classified according to the criteria of the worst (i.e., highest) stage present.

Clinical endpoints and follow-up

All patients were followed-up for the occurrence of surgical or transcatheter AVR, all-cause mortality, stroke and hospitalization for cardiac cause. The primary outcome was all-cause mortality, as ascertained by review of hospital records linked to the governmental death registry database. The secondary outcome was a composite of all-cause mortality, stroke (major or minor) and cardiac-related hospitalization, occurring between baseline echocardiography and last follow-up.

Statistical analysis

Continuous data are presented as mean±SD or median (interquartile range [IQR]), as appropriate. Categorical data are presented as frequencies and percentages. Patients were divided according to stage of cardiac damage. For comparison of continuous variables between groups, the analysis of variance 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 χ^2 test. The Kaplan-Meier method was used to calculate survival and event rates for the different stages of cardiac damage, comparison of cumulative event rates between these groups was performed by log-rank test. For the secondary outcome, patients were censored at the occurrence of the first event. To evaluate the association of the staging classification and other clinical and echocardiographic parameters with the primary and secondary endpoints, univariable Cox proportional hazards analyses were performed. From this analysis, 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 a time-dependent covariate. For both uni- and multivariable analyses, hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. SPSS software version 23.0 (IBM, Armonk, New York) was used for statistical analyses. A 2-sided P value <0.05 was considered statistically significant.

Results

Patient characteristics

Baseline clinical characteristics for the overall study population (mean age 73±11 years, 53% male) are listed in Table 1. The majority of patients had cardiovascular risk factors: hypertension and hypercholesterolemia were present in 72% and 66% of the population, respectively, and almost one-half of the patients (47%) had coronary artery disease. As per design of the study, all patients were symptomatic and one-third (33%) had New York Heart Association (NYHA) functional class III or IV symptoms. Patients were divided by the presence and extent of extra-aortic valvular cardiac damage seen on echocardiography (Figure 1): 8% (97) of patients were classified as Stage 0 (no cardiac damage), 24% (282) as Stage 1 (LV damage), 49% (588) as Stage 2 (mitral valve or LA damage), 7% (82) as

Table 1: Clinical characteristics of total patient population and according to stage of cardiac damage.

Variables	Total population (N = 1189)	Stage 0 (N = 97)	Stage 1 (N = 282)	Stage 2 (N = 588)	Stage 3 (N = 82)	Stage 4 (N = 140)	*P* value*
Age (years)	73.4±10.8	72.7±9.9	71.6±11.4	73.8±10.7	75.0±10.3	75.3±10.2†	**0.004**
Male gender, *N* (%)	624 (53)	65 (67)	139 (49)	301 (51)	34 (42)	85 (61)	**0.002**
Body mass index (kg/m^2)	25.5±4.6	26.1±4.7	25.5±4.2	25.6±4.9	24.6±4.6‡	24.8±4.4	0.098
Body surface area (m^2)	1.74±0.24	1.79±0.24	1.76±0.23	1.74±0.25	1.68±0.24	1.75±0.25	**0.048**
Hypertension, *N* (%)	857 (72)	67 (69)	210 (75)	430 (73)	56 (68)	94 (67)	0.429
Hypercholesterolemia, *N* (%)	790 (66)	67 (69)	185 (66)	397 (68)	49 (60)	92 (66)	0.668
Diabetes mellitus, *N* (%)	317 (27)	30 (31)	80 (28)	144 (25)	18 (22)	45 (32)	0.069
Coronary artery disease, *N* (%)	563 (47)	42 (43)	131 (47)	267 (45)	30 (37)	93 (66)	**<0.001**
Previous MI, *N* (%)	189 (16)	12 (12)	36 (13)	85 (15)	14 (17)	42 (30)	**<0.001**
History of smoking, *N* (%)	330 (28)	36 (37)	82 (29)	158 (27)	20 (24)	34 (24)	0.198
COPD, *N* (%)	129 (11)	11 (11)	31 (11)	49 (8)	17 (21)	21 (15)	**0.005**
History of atrial fibrillation, *N* (%)	354 (30)	8 (8)	35 (12)	184 (31)	45 (55)	82 (59)	**<0.001**
NYHA class ≥III, *N* (%)	393 (33)	27 (31)	67 (26)	189 (35)	44 (55)	66 (49)	**<0.001**
Symptoms, *N* (%)							
Angina	358 (30)	33 (34)	98 (35)	175 (30)	18 (22)	34 (24)	0.072
Dyspnea	956 (81)	72 (74)	207 (74)	473 (81)	77 (94)	127 (91)	**<0.001**
Syncope	103 (9)	9 (9)	37 (13)	53 (9)	0 (0)	4 (3)	**<0.001**
Estimated GFR (ml/min/1.73 m^2)	61.8±24.9	69.1±22.0	64.7±24.5	62.8±24.7	49.3±24.3†‡§	53.9±25.5†‡§	**<0.001**
Systolic BP (mmHg)	135.6±24.0	139.6±21.9	137.1±24.3	136.9±23.8	129.6±26.5	128.1±22.1†‡§	**<0.001**
Diastolic BP (mmHg)	71.0±13.0	73.4±13.3	73.0±12.5	70.0±12.8†	70.1±13.7	70.2±13.5	**0.007**
Medication, *N* (%):							
Beta blocker	644 (54)	41 (42)	152 (54)	325 (55)	42 (51)	84 (60)	0.090
ACE inhibitor/ARB	548 (46)	45 (46)	128 (45)	275 (47)	37 (45)	63 (45)	0.992
Aspirin/thienopyridines	556 (47)	46 (47)	144 (51)	262 (45)	37 (45)	67 (48)	0.491
Oral anticoagulant	263 (22)	12 (12)	26 (9)	127 (22)	33 (40)	65 (46)	**<0.001**
Statin	757 (64)	67 (69)	186 (66)	367 (62)	46 (56)	91 (65)	0.354
Calcium channel blocker	359 (30)	27 (29)	89 (32)	190 (32)	20 (24)	33 (24)	0.200
Diuretic agents	515 (43)	25 (26)	100 (36)	252 (43)	59 (72)	79 (56)	**<0.001**

Continuous variables are presented as mean±SD or median [interquartile range]. Categorical variables are expressed as number (percentage). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; MI, myocardial infarction; NYHA, New York Heart Association. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. † $P<0.05$ vs. Stage 1 with Bonferroni's post hoc analysis. ‡ $P<0.05$ vs. Stage 0 with Bonferroni's post hoc analysis. § $P<0.05$ vs. Stage 2 with Bonferroni's post hoc analysis.

Table 2: Echocardiographic characteristics of total patient population and according to stage of cardiac damage.

Variables	Total population (N = 1189)	Stage 0 (N = 97)	Stage 1 (N = 282)	Stage 2 (N = 588)	Stage 3 (N = 82)	Stage 4 (N = 140)	*P* value*
Heart rate at TTE (bpm)	74.7±14.8	76.4±13.2	72.2±12.5	73.6±14.4	81.0±18.7†‡	79.6±16.9†‡	**<0.001**
Valve morphology, *N* (%):							**<0.001**
Tricuspid	1049 (88)	76 (78)	228 (81)	535 (91)	77 (94)	133 (95)	
Bicuspid	140 (12)	21 (22)	54 (19)	53 (9)	5 (6)	7 (5)	
Atrial fibrillation at TTE, *N* (%)	165 (14)	0 (0)	0 (0)	81 (14)	28 (34)	56 (40)	**<0.001**
LV end-diastolic diameter (mm)	48.2±8.0	41.4±5.3	47.4±6.9§	48.8±8.1§	50.2±8.0†§	50.9±8.2†‡§	**<0.001**
LV end-systolic diameter (mm)	33.4±9.6	26.8±6.0	32.1±8.2§	33.2±9.4§	36.4±10.2†‡§	39.4±10.8†‡§	**<0.001**
Septal wall thickness (mm)	12.5±2.4	11.4±1.5	12.3±1.9§	12.9±2.6†§	12.2±2.3	12.3±2.5‡§	**<0.001**
Posterior wall thickness (mm)	11.9±2.2	10.9±1.4	11.7±1.8§	12.2±2.3§	11.8±2.0§	11.5±2.3‡	**<0.001**
LV mass index (g/m^2)	132.6±39.7	87.7±14.5	124.5±30.0§	140.7±42.4†§	142.3±36.6†§	138.2±34.9†§	**<0.001**
LV end-diastolic volume (ml)	107.3±46.8	79.4±25.2	97.4±41.8§	111.9±49.3†§	113.1±45.5§	123.6±46.1†§	**<0.001**
LV end-systolic volume (ml)	54.7±40.0	31.1±14.1	46.5±34.1§	55.6±40.9†§	64.9±40.3†§	77.5±45.3†‡§	**<0.001**
LV ejection fraction (%)	54.2±14.3	62.9±7.0	57.8±12.0§	55.1±13.4†§	46.9±14.9†‡§	41.6±16.1†‡§‖	**<0.001**
LV ejection fraction <50%	339 (29)	0 (0)	52 (18)	156 (27)	39 (48)	92 (66)	**<0.001**
Peak E-wave velocity (cm/s)	96.2±43.0	68.5±16.7	78.0±27.8	100.2±42.1†§	132.5±51.3†‡§	115.0±51.5†‡§‖	**<0.001**
E' (cm/s)	5.3±2.0	6.5±2.3	4.7±1.5§	5.4±2.0†§	5.7±1.9†	5.3±2.1§	**<0.001**
E/e' ratio	19.3±10.2	10.8±2.2	18.0±8.0§	19.8±10.3§	24.2±11.4†‡§	23.3±12.7†‡§	**<0.001**
Left atrial volume index (ml/m^2)	44.5±23.1	24.8±5.9	26.1±6.1	50.8±19.1†§	60.4±34.3†‡§	57.9±28.2†‡§	**<0.001**
Significant MR, *N* (%)	68 (6)	0 (0)	0 (0)	35 (6)	14 (17)	19 (14)	**<0.001**
Systolic PAP (mmHg)	36.5±14.0	26.9±8.7	30.4±8.5	34.9±10.0†§	61.4±14.6†‡§	42.8±16.6†‡§‖	**<0.001**
Significant TR, *N* (%)	65 (6)	0 (0)	0 (0)	0 (0)	39 (48)	26 (19)	**<0.001**
TAPSE (mm)	20.8±4.4	22.2±3.3	21.9±3.5	21.8±3.6	20.1±3.6†‡§	13.3±1.9†‡§‖	**<0.001**
Mean AV gradient (mmHg)	43.1±15.5	41.9±12.5	43.9±14.4	46.0±16.0	38.2±14.1†‡	33.5±14.3†‡§	**<0.001**
Peak aortic jet velocity (m/s)	4.1±0.7	4.1±0.6	4.1±0.6	4.2±0.7	3.9±0.7†‡	3.6±0.7†‡§‖	**<0.001**
AVA (cm^2)	0.78±0.18	0.84±0.19	0.78±0.17§	0.78±0.18	0.75±0.20§	0.73±0.17‡§	**<0.001**
Indexed AVA (cm^2/m^2)	0.45±0.11	0.47±0.11	0.45±0.10	0.46±0.12	0.45±0.12	0.43±0.12§	**0.021**
Low-flow low-gradient AS, *N* (%)	224 (19)	15 (16)	39 (14)	81 (14)	24 (29)	65 (46)	**<0.001**

Continuous variables are presented as mean±SD. Categorical variables are expressed as number (percentage). AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; Bpm, beats per minute; LV, left ventricular; MR, mitral regurgitation; PAP, pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram. **P* values depict differences between stages of cardiac damage and are calculated by ANOVA and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by χ^2 test for categorical data. † $P<0.05$ vs. Stage 1 with Bonferroni's post hoc analysis. ‡ $P<0.05$ vs. Stage 2 with Bonferroni's post hoc analysis. § $P<0.05$ vs. Stage 0 with Bonferroni's post hoc analysis. ‖ $P<0.05$ vs. Stage 3 with Bonferroni's post hoc analysis.

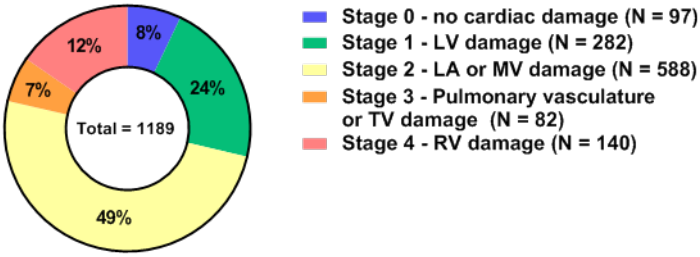


Figure 2: Distribution of stages of cardiac damage in total population. LA, left atrial; LV, left ventricular; MV, mitral valve; RV, right ventricular; TV, tricuspid valve.

Stage 3 (tricuspid valve or pulmonary artery vasculature damage) and 12% (140) as Stage 4 (RV damage) (Figure 2). Compared to patients in less advanced stages, the patients in the higher stages were older, had more severe symptoms (NYHA functional class ≥III), worse kidney function and more frequently had a history of coronary artery disease, previous myocardial infarction and atrial fibrillation. In addition, these patients more often used oral anticoagulation and diuretic agents.

Baseline echocardiographic parameters for the overall study population and per separate stage of cardiac damage are presented in Table 2. The mean LV ejection fraction was 54±14%, LV mass index 133±40 g/m^2, mean aortic valve gradient 43±16 mmHg, peak aortic jet velocity 4.1±0.7 m/s and AVA 0.78±0.18 cm^2. Interestingly, patients in Stage 3 and 4 showed a lower mean aortic valve gradient and peak aortic jet velocity, corresponding with a higher percentage of low-flow low-gradient severe AS (29% in Stage 3 and 46% in Stage 4 compared with ≤16% in less advanced stages; P<0.001). Patients in more advanced stages had lower LV ejection fraction and more often had an LV ejection fraction <50%, had higher E/e' ratios and LA volume indices and more often had significant mitral and tricuspid regurgitation compared with patients in lower stages. The incidences of the individual staging components of cardiac damage in the total study population are presented in Table 3.

LONG-TERM OUTCOMES

During follow-up, 917 patients (77%) underwent AVR within a median time of 67 (IQR: 5 to 197) days, of whom 47% received a transcatheter AVR and 53% a surgical AVR. During a median follow-up of 42 (IQR: 20 to 77) months, 472 patients (40%) died and over a median time of 35 (IQR: 14 to 67) months, 617 patients (52%) reached the combined endpoint (all-cause mortality, stroke and cardiac-related hospitalization). The clinical outcomes during follow-up per stage of cardiac damage are presented in Table 4.

SURVIVAL ANALYSIS

Kaplan-Meier curve analysis showed that patients with more advanced stages of cardiac damage had significantly higher 5-year cumulative event rates (Figure 3 *panel A*) (log-rank χ^2 93.4; P<0.001). Particularly for Stage ≥2, significantly higher 5-year cumulative event rates were noted compared to Stage 0 (P<0.02 for all) and Stage 1 (P<0.01

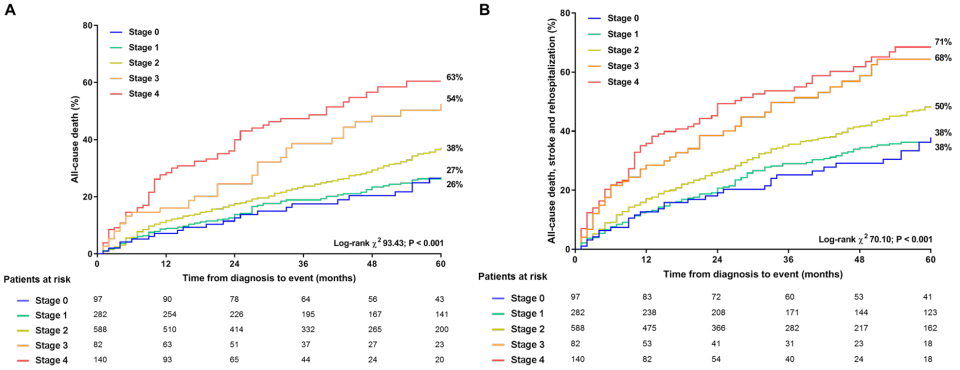


Figure 3: Survival analyses according to stage of cardiac damage for total population. Kaplan-Meier estimates for the cumulative event rates of all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage.

Table 3: Incidence of the individual staging components of cardiac damage in total population.

Stage 0 – no damage	**97/1189**
Stage 1 – left ventricular damage	**282/1189**
Increased LV mass index (>95 for women or >115 g/m^2 for men), *N* (%)	882 (74)
LV ejection fraction <50%, *N* (%)	339 (29)
E/e' ratio >14, *N* (%)	625 (53)
Stage 2 – left atrial or mitral valve damage	**588/1189**
Indexed left atrial volume >34 ml/m^2, *N* (%)	757 (64)
Moderate or severe mitral regurgitation (≥ grade 3), *N* (%)	68 (6)
Presence of atrial fibrillation at time echocardiography, *N* (%)	165 (14)
Stage 3 – pulmonary vasculature or tricuspid valve damage	**82/1189**
Systolic pulmonary artery pressure ≥60 mmHg, *N* (%)	74 (6)
Moderate or severe tricuspid regurgitation (≥grade 3), *N* (%)	65 (6)
Stage 4 – right ventricular damage	**140/1189**
Tricuspid annular plane systolic excursion <16 mm, *N* (%)	140 (12)

LV, left ventricular.

Table 4: Clinical outcomes during follow-up per stage of cardiac damage.

	Stage 0 (N = 97)	**Stage 1 (N = 282)**	**Stage 2 (N = 588)**	**Stage 3 (N = 82)**	**Stage 4 (N = 140)**	***P* value***
Surgical or transcatheter AVR, % (*N*)	80% (78)	84% (238)	77% (452)	66% (54)	68% (95)	**<0.001**
All-cause death, % (*N*)	27% (26)	32% (90)	39% (229)	55% (45)	59% (82)	**<0.001**
1 year	7% (7)	10% (28)	13% (78)	23% (19)	34% (47)	
Any stroke, % (*N*)	12% (11)	9% (25)	10% (58)	12% (10)	17% (24)	0.104
Major stroke	6	11	37	5	11	
Minor stroke	5	14	21	5	13	
Cardiac-related hospitalization, % (*N*)	12% (12)	16% (46)	22% (131)	24% (20)	18% (25)	0.055
Combined endpoint (all-cause death, any stroke and cardiac-related rehospitalisation), % (*N*)	40% (39)	46% (128)	52% (303)	66% (54)	66% (93)	**<0.001**

AVR, aortic valve replacement. **P* values are calculated by χ^2 test.

Table 5: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in the total study population.

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.033 (1.024-1.043)	**<0.001**	1.020 (1.009-1.031)	**<0.001**
Male gender (yes/no)	0.926 (0.773-1.110)	0.406	1.027 (0.837-1.261)	0.802
Coronary artery disease (yes/no)	1.386 (1.157-1.662)	**<0.001**	0.933 (0.741-1.173)	0.551
Previous MI (yes/no)	2.092 (1.684-2.597)	**<0.001**	1.698 (1.285-2.244)	**<0.001**
COPD (yes/no)	1.134 (0.841-1.529)	0.409		
History of atrial fibrillation (yes/no)	1.531 (1.264-1.854)	**<0.001**	1.016 (0.812-1.270)	0.892
NYHA class ≥III (yes/no)	1.541 (1.267-1.874)	**<0.001**	1.205 (0.976-1.487)	0.083
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.976 (0.972-0.979)	**<0.001**	0.981 (0.977-0.985)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.995 (0.991-0.999)	**0.012**	0.996 (0.992-1.000)	0.059
Diuretic agents (yes/no)	1.332 (1.111-1.596)	**0.002**	1.041 (0.844-1.284)	0.709
Peak aortic jet velocity (per 1 m/s increase)	0.678 (0.595-0.772)	**<0.001**	0.952 (0.817-1.110)	0.531
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.005 (0.997-1.014)	0.197	2.001 (0.793-5.046)	0.142
Surgical or transcatheter AVR (yes/no)	0.395 (0.323-0.483)	**<0.001**	0.498 (0.397-0.625)	**<0.001**
Stage of cardiac damage (per 1 stage increase)	1.481 (1.358-1.616)	**<0.001**	1.283 (0.158-1.422)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.111 (0.718-1.720)	0.635	1.126 (0.682-1.858)	0.644
Stage 0 vs. Stage 2	1.611 (1.074-2.417)	**0.021**	1.486 (0.930-2.374)	0.098
Stage 0 vs. Stage 3	2.736 (1.688-4.435)	**<0.001**	1.975 (1.125-3.469)	**0.018**
Stage 0 vs. Stage 4	3.847 (2.470-5.991)	**<0.001**	2.472 (1.471-4.155)	**0.001**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 5: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in the total study population (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.026 (1.018-1.034)	**<0.001**	1.013 (1.004-1.022)	**0.007**
Male gender (yes/no)	0.991 (0.845-1.161)	0.911	1.013 (0.850-1.207)	0.887
Coronary artery disease (yes/no)	1.419 (1.210-1.663)	**<0.001**	1.000 (0.822-1.217)	1.000
Previous MI (yes/no)	1.862 (1.531-2.266)	**<0.001**	1.474 (1.156-1.880)	**0.002**
COPD (yes/no)	1.116 (0.859-1.448)	0.411		
History of atrial fibrillation (yes/no)	1.447 (1.221-1.714)	**<0.001**	1.095 (0.899-1.333)	0.368
NYHA class ≥III (yes/no)	1.379 (1.162-1.638)	**<0.001**	1.110 (0.923-1.335)	0.268
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.982 (0.979-0.985)	**<0.001**	0.986 (0.983-0.990)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.993-0.999)	**0.018**	0.997 (0.944-1.001)	0.165
Diuretic agents (yes/no)	1.420 (1.211-1.664)	**<0.001**	1.124 (0.938-1.346)	0.206
Peak aortic jet velocity (per 1 m/s increase)	0.729 (0.650-0.817)	**<0.001**	0.937 (0.821-1.069)	0.333
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.000 (0.993-1.007)	0.938	1.664 (0.743-3.726)	0.216
Surgical or transcatheter AVR (yes/no)	0.677 (0.564-0.813)	**<0.001**	0.798 (0.651-0.979)	**0.031**
Stage of cardiac damage (per 1 stage increase)	1.355 (1.256-1.462)	**<0.001**	1.191 (1.091-1.299)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.117 (0.780-1.598)	0.547	1.157 (0.777-1.724)	0.474
Stage 0 vs. Stage 2	1.508 (1.080-2.106)	**0.016**	1.456 (1.002-2.118)	**0.049**
Stage 0 vs. Stage 3	2.356 (1.560-3.559)	**<0.001**	1.764 (1.104-2.819)	**0.018**
Stage 0 vs. Stage 4	2.901 (1.993-4.223)	**<0.001**	1.947 (1.268-2.988)	**0.002**

AVA, aortic valve area; AVR, aortic valve replacement; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

for all). Similarly, for the combined outcome, the more advanced stages showed significantly higher cumulative 5-year event rates (Figure 3 *panel B*)(log-rank χ^2 70.1; *P*<0.001), specifically for Stage ≥2 compared to Stage 0 (*P*<0.02 for all) and Stage 1 (*P*<0.01 for all). For the subgroup of patients treated with surgical or transcatheter AVR, patients with more advanced cardiac damage showed higher cumulative events rates for both total and post-operative only all-cause mortality and combined outcome (Supplementary Figure 5 and 6, respectively).

Prognostic value of proposed staging classification

The correlates of all-cause mortality and the combined endpoint on univariable and multivariable Cox regression analyses are shown in Table 5. On multivariable analysis, age, previous myocardial infarction, renal function, surgical or transcatheter AVR, and stage of cardiac damage were independently associated with all-cause mortality. For each increase in stage, a 28% higher risk for all-cause mortality was observed (95% CI: 1.158-1.422, *P*<0.001). When evaluating each separate stage of cardiac damage, only Stage 3 (HR: 1.975, 95% CI: 1.125-3.469; *P*=0.018) and Stage 4 (HR: 2.472, 95% CI: 1.471-4.155; *P*=0.001) were independently associated with all-cause mortality. For the combined endpoint, age, previous myocardial infarction, renal function, surgical or transcatheter AVR and stage of cardiac damage were independent predictors on multivariable analysis. A 19% increase in risk for the combined outcome was observed for each increasing stage (95% CI: 1.091-1.299); P<0.001). However, only Stage 2 (HR: 1.456, 95% CI: 1.002-2.118; *P*=0.049), Stage 3 (HR: 1.764, 95% CI: 1.104-2.819; *P*=0.018) and Stage 4 (HR: 1.947, 95% CI: 1.268-2.988; *P*=0.002) were independently associated with all-cause mortality, stroke and cardiac-related hospitalization. In patients treated with surgical or transcatheter AVR, stage of cardiac damage was significantly associated with both total and postoperative only all-cause mortality and combined outcome, respectively, although only Stage 4 was independently associated with these outcomes when considering separate stages of cardiac damage (Supplementary Tables 6 and 7).

Discussion

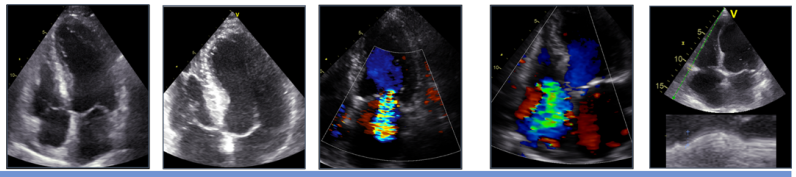
The present study demonstrated that, in a large real-world and multicenter cohort of symptomatic severe AS patients, extra-aortic valvular cardiac injury such as LA dilation, MR, and RV dysfunction is highly prevalent (Figure 4). Classified according to a newly proposed staging system, extra-aortic valvular cardiac damage is independently associated with all-cause mortality and a combined outcome of all-cause mortality, stroke and cardiac-related hospitalization, although this effect seems to be primarily driven by the Stages 3 (tricuspid valve or pulmonary artery vasculature damage) and 4 (RV damage).

Prevalence of cardiac damage in severe AS

In severe AS, chronic pressure overload imposed on the LV by progressive calcification and narrowing of the aortic valve induces a compensatory concentric hypertrophic response of the LV myocardium. After this initial adaptive response to normalize LV wall pressure and maintain cardiac output, ongoing development of LV hypertrophy will neg-

CENTRAL ILLUSTRATION Staging of Cardiac Damage in Severe AS: Clinical Outcomes in a Large Multicenter Cohort

Staging Classification According to Extent of Cardiac Damage



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	**Left ventricular damage**	**Left atrial or mitral valve damage**	**Pulmonary vasculature or tricuspid valve damage**	**Right ventricular damage**
Echocardiographic criteria		LV mass index ♂ >115 g/m² ♀ > 95 g/m² LV ejection fraction < 50% E/e' ratio > 14	Left atrial volume index > 34 ml/m² Presence of atrial fibrillation Moderate/severe mitral regurgitation	Systolic pulmonary arterial pressure ≥ 60 mmHg Moderate/severe tricuspid regurgitation	TAPSE < 16 mm
Prevalence in cohort	**8% (N = 97)**	**24% (N = 282)**	**49% (N = 588)**	**7% (N = 82)**	**12% (N = 140)**

Outcomes According to Stages of Cardiac Damage

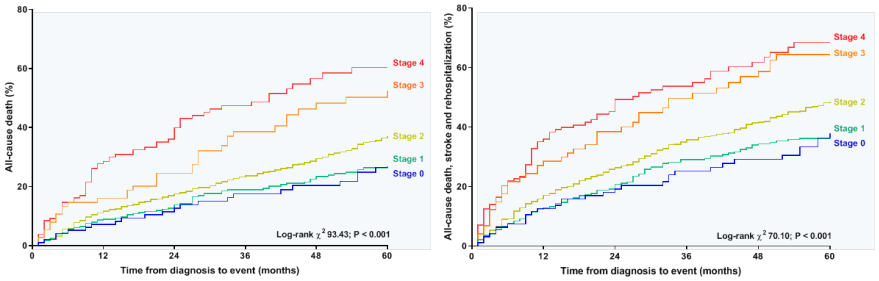


Figure 4: Clinical outcomes of stages of cardiac damage in a real-world multicenter severe symptomatic aortic stenosis cohort. **(Top)** After classification of patients with symptomatic severe AS according to the recently proposed staging system based on the presence and extent of extra-aortic valvular cardiac injury on echocardiography, a high prevalence of cardiac damage (e.g., left atrial enlargement and right ventricular dysfunction) was seen in the study population. **(Bottom)** For both all-cause mortality **(left)** and the combined outcome of all-cause mortality, stroke, and cardiac rehospitalization **(right)**, the more advanced stages (i.e., Stage ≥2) showed significantly higher cumulative 5-year event rates.

atively influence both LV systolic and diastolic function, and will eventually result in the formation of myocardial fibrosis [14]. At this time, most patients will be symptomatic [14]. Currently, AVR is indicated in patients with severe AS who are symptomatic or have reduced LV systolic function (i.e., LV ejection fraction <50%) [1, 2]. However, the hemodynamic effects of chronic pressure overload in severe AS are not limited to the LV only. Elevated LV filling pressures may lead to LA dilation, and this LA remodelling together with changes in LV geometry have been associated with an increased risk for the development of atrial fibrillation and MR [4, 15]. Rising LA pressure gradients will then contribute to an increase in pulmonary artery pressure, which may eventually lead to right atrial and ventricular remodelling, inducing TR and, ultimately, RV dysfunction [16].

Multiple studies have demonstrated a high prevalence of extra-aortic valvular cardiac damage in severe AS patients. Atrial fibrillation has been reported in 8% to 13% of patients undergoing surgical AVR and in up to 51% of transcatheter AVR patients [15]. Both significant MR and TR are frequently observed, with reported rates ranging from 13% to 20% for MR [4, 17] and 11% to 27% for TR [6, 18–20]. Severe pulmonary hypertension has been reported in 10% of surgical AVR and in up to 36% of transcatheter AVR patients [21, 22]. For RV dysfunction, prevalence rates of 24% to 29% have been observed [7, 8, 23].

These percentages are largely consistent with the reported prevalence of cardiac damage by Généreux et al. [9] and by the present study. Interestingly, higher rates of low-flow low-gradient severe AS were seen in Stage 3 (tricuspid valve or pulmonary artery vasculature damage) and Stage 4 (RV damage) (29% and 46% vs. 14% to 16% in the less advanced stages, respectively), consistent with previous studies [7, 20, 24].

Prognostic relevance of cardiac damage in AS

Multiple studies have reported a negative prognostic impact of the individual cardiac damage components in severe AS patients, irrespective of the underlying etiology (either severe AS itself or concomitant comorbidities). Although the presence of LV damage (i.e., LV systolic or diastolic dysfunction or LV hypertrophy [Stage 1]) [25, 26] and of LA and mitral valve damage (i.e., significant MR, atrial fibrillation or LA enlargement [Stage 2]) [5, 15, 17, 27] have independently been associated with an increased risk for mortality, this effect was not observed in the present study when taking into account the whole extent of cardiac injury. This discrepancy may be attributed to the high prevalence of Stage 1 and Stage 2 in the current population and the stronger association between more advanced stages and clinical outcomes. Importantly, pulmonary artery vasculature or tricuspid valve damage (i.e., severe pulmonary hypertension or significant TR [Stage 3]) and RV dysfunction (Stage 4) were shown to be the strongest predictors for all-cause mortality in the present study, as shown previously in studies focusing on the effects of pulmonary hypertension [21], significant TR [6, 20], and RV dysfunction in severe AS patients [7, 8, 19].

Studies considering the collective prognostic effect of the different expressions of extra-aortic valvular cardiac injury are limited. In a cohort of 432 severe AS patients undergoing surgical AVR, Tan et al. [28] assessed the incremental predictive value of multiple pre-operatively assessed echocardiographic variables, including LV ejection fraction, E/e', LV mass index, LA volume index, MR and TR grade, systolic pulmonary artery pres-

sure, and several right atrial and ventricular functional parameters. After correcting for operative risk, only LV mass index, right atrial area index, mean gradient <40 mmHg, MR grade and LV end-diastolic volume index were independently predictive for 2-year all-cause mortality [28]. In the more recently proposed staging classification based on the anatomic and functional extent of cardiac damage, stages of cardiac injury were independently associated with an increased risk of 1-year mortality and adverse events in intermediate-risk severe AS patients undergoing either transcatheter or surgical AVR [9]. To our knowledge, the present study is the first to confirm the prognostic impact of this staging model in a large unselected real-world and multicenter cohort of symptomatic severe AS patients over longer term follow-up (median follow-up time 42 [IQR: 20 to 77] months) and to extend the earlier findings by demonstrating that the prognostic impact of this classification is mainly determined by the presence of significant TR or pulmonary artery hypertension (Stage 3) and RV dysfunction (Stage 4). Our results suggest that incorporation of the proposed staging system in future risk models, in particular the components of these advanced stages, could potentially aid in the risk stratification of severe AS patients, because these aspects are generally not included in current risk prediction models. Future prospective studies are needed to confirm the prognostic value of this staging classification and to determine its additional incremental value in the risk assessment of specific AS subpopulations.

LIMITATIONS

The present study has limitations inherent to its retrospective nature. The participating centers were referral centers for cardiac surgery and the decision for AVR was made at the discretion of the respective heart teams (as recommended by current guidelines [1, 2]); therefore selection and referral bias may be present. However, in this real-world, multicenter cohort, patients were included regardless of treatment or operative risk category. In the proposed staging classification, reduced LV ejection fraction (<50%) was included as criterium for Stage 1 (Figure 1) [9]. However, low LV ejection fraction is associated with a worse prognosis than atrial fibrillation (i.e., Stage 2) [29], potentially resulting in an underestimation of prognosis of patients in Stage 1. In the present study, subanalyses excluding Stage 1 patients with a LV ejection fraction <50% (Supplementary Figure 7 and Supplementary Table 8) showed similar results as the analyses using the proposed staging classification (Figure 3 and Table 5). The modest impact on prognosis of LV ejection fraction <50% in Stage 1 may be explained by the low prevalence of reduced LV ejection fraction in this stage versus increasing stages of cardiac damage (Table 2). Distinction between subtypes of significant TR (i.e., due to pulmonary hypertension or due to atrial fibrillation only) was beyond the scope of this paper; future studies will need to elucidate the role of different underlying pathophysiological mechanisms of TR on prognosis in severe AS patients. In the present study, only TAPSE was used to estimate RV systolic dysfunction. Consideration of other RV systolic function parameters could have resulted in a more accurate assessment of RV function, because TAPSE only takes into account the tricuspid lateral annulus displacement. However, TAPSE is easy to obtain, less dependent on image quality, and has been validated in large patient cohorts [13, 19]. Furthermore, TAPSE as a measure of RV dysfunction has been demonstrated to have prognostic implications in severe AS patients [7, 8, 19]. Future studies incorporating 3-

dimensional imaging techniques or RV free wall longitudinal strain for the assessment of RV systolic function in the proposed staging system might provide a more accurate evaluation of RV damage [30, 31].

Conclusions

In this large multicenter cohort of symptomatic severe AS patients, extra-aortic valvular cardiac injury was present in the majority of patients. Stage of cardiac damage as classified by a novel proposed staging system [9] was independently associated with all-cause mortality, although pulmonary artery hypertension and TR (Stage 3) and RV dysfunction (Stage 4) seemed to be the main determinants of this association. Incorporation of this proposed staging system into current risk stratification models, in particular the components of these advanced stages, may aid in the risk assessment of severe AS patients and their different subpopulations.

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SUPPLEMENTARY MATERIAL

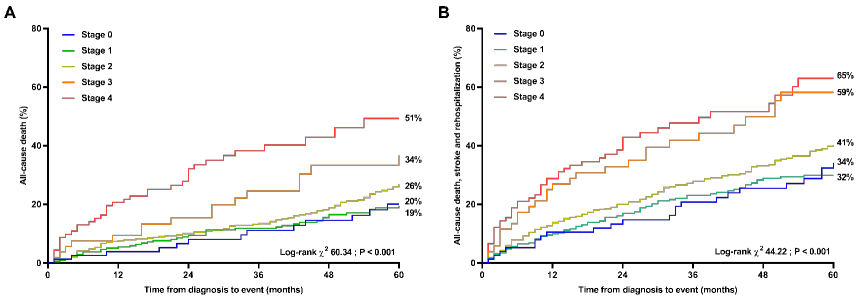

Figure 5: Survival analyses according to stage of cardiac damage for patients undergoing surgical or transcatheter aortic valve replacement. Kaplan-Meier estimates for the cumulative event rates of all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage.

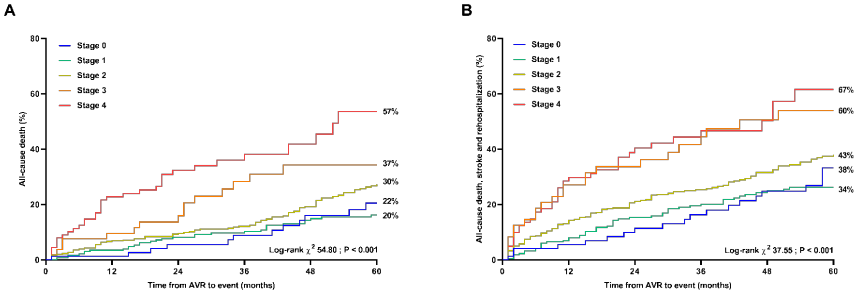

Figure 6: Survival analyses according to stage of cardiac damage for postoperative adverse events in patients undergoing surgical or transcatheter aortic valve replacement. Kaplan-Meier estimates for the cumulative event rates of postoperative all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage. AVR, aortic valve replacement.

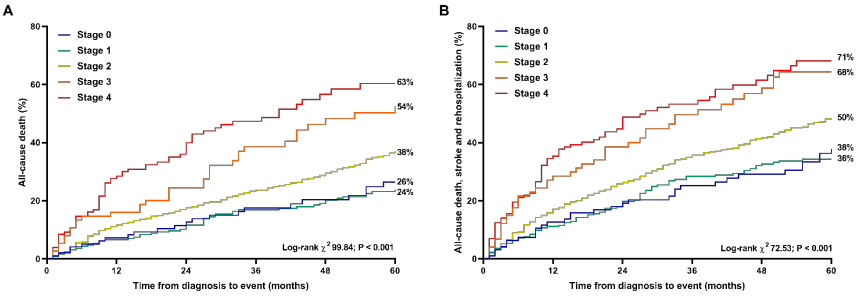

Figure 7: Survival analyses according to stage of cardiac damage for patients undergoing surgical or transcatheter AVR after exclusion of patients in Stage 1 with LV ejection fraction <50%. Kaplan-Meier estimates for the cumulative event rates of all-cause mortality (*panel A*) and the combined endpoint (*panel B*) according to stage of cardiac damage. AVR, aortic valve replacement; LV, left ventricular.

Table 6: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.038 (1.025-1.051)	**<0.001**	1.029 (1.014-1.043)	**<0.001**
Male gender (yes/no)	1.028 (0.806-1.310)	0.825	1.075 (0.821-1.407)	0.599
Coronary artery disease (yes/no)	1.708 (1.336-2.182)	**<0.001**	1.038 (0.772-1.396)	0.804
Previous MI (yes/no)	2.335 (1.749-3.117)	**<0.001**	1.604 (1.129-2.278)	**0.008**
COPD (yes/no)	1.222 (0.830-1.798)	0.310		
History of atrial fibrillation (yes/no)	1.301 (0.991-1.708)	0.058	0.870 (0.638-1.185)	0.377
NYHA class ≥III (yes/no)	1.806 (1.395-2.337)	**<0.001**	1.339 (1.017-1.763)	**0.038**
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.976 (0.971-0.981)	**<0.001**	0.982 (0.976-0.987)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.994 (0.989-0.999)	**0.019**	0.993 (0.988-0.999)	**0.017**
Diuretic agents (yes/no)	1.458 (1.145-1.857)	**0.002**	0.927 (0.704-1.221)	0.589
Peak aortic jet velocity (per 1 m/s increase)	0.642 (0.534-0.771)	**<0.001**	0.868 (0.705-1.068)	0.181
Indexed AVA (per 0.01 cm^2/m^2 increase)	0.974 (0.319-2.972)	0.963	2.901 (0.836-10.07)	0.093
Stage of cardiac damage (per 1 stage increase)	1.486 (1.319-1.675)	**<0.001**	1.320 (1.158-1.505)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.035 (0.603-1.777)	0.901	1.057 (0.598-1.868)	0.849
Stage 0 vs. Stage 2	1.387 (0.836-2.304)	0.206	1.386 (0.811-2.369)	0.233
Stage 0 vs. Stage 3	1.967 (1.022-3.785)	**0.043**	1.329 (0.654-2.698)	0.432
Stage 0 vs. Stage 4	4.005 (2.286-7.019)	**<0.001**	2.878 (1.571-5.271)	**0.001**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 6: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917) (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.028 (1.018-1.038)	**<0.001**	1.015 (1.004-1.027)	**0.007**
Male gender (yes/no)	1.071 (0.881-1.302)	0.492	1.038 (0.839-1.284)	0.733
Coronary artery disease (yes/no)	1.609 (1.322-1.959)	**<0.001**	1.104 (0.874-1.396)	0.406
Previous MI (yes/no)	2.022 (1.585-2.579)	**<0.001**	1.482 (1.110-1.978)	**0.008**
COPD (yes/no)	1.149 (0.840-1.572)	0.386		
History of atrial fibrillation (yes/no)	1.256 (1.07-1.567)	**0.043**	0.960 (0.748-1.232)	0.747
NYHA class ≥III (yes/no)	1.427 (1.156-1.761)	**0.001**	1.086 (0.867-1.360)	0.472
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.984 (0.980-0.988)	**<0.001**	0.990 (0.985-0.994)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.992-1.000)	0.059	0.997 (0.992-1.001)	0.187
Diuretic agents (yes/no)	1.544 (1.270-1.877)	**<0.001**	1.161 (0.932-1.445)	0.183
Peak aortic jet velocity (per 1 m/s increase)	0.713 (0.616-0.827)	**<0.001**	0.880 (0.747-1.036)	0.124
Indexed AVA (per 0.01 cm^2/m^2 increase)	0.694 (0.286-1.689)	0.421	1.541 (0.566-4.193)	0.397
Stage of cardiac damage (per 1 stage increase)	1.338 (1.215-1.473)	**<0.001**	1.211 (1.089-1.346)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.034 (0.686-1.558)	0.874	1.077 (0.700-1.658)	0.736
Stage 0 vs. Stage 2	1.316 (0.896-1.934)	0.161	1.287 (0.856-1.934)	0.225
Stage 0 vs. Stage 3	1.926 (1.160-3.195)	**0.011**	1.449 (0.839-2.503)	0.183
Stage 0 vs. Stage 4	2.788 (1.784-4.355)	**<0.001**	2.091 (1.292-3.385)	**0.003**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 7: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of postoperative all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.034 (1.021-1.047)	**<0.001**	1.026 (1.012-1.041)	**<0.001**
Male gender (yes/no)	1.029 (0.807-1.312)	0.816	1.103 (0.843-1.444)	0.474
Coronary artery disease (yes/no)	1.672 (1.308-2.136)	**<0.001**	1.063 (0.791-1.429)	0.686
Previous MI (yes/no)	2.179 (1.633-2.908)	**<0.001**	1.487 (1.047-2.113)	**0.027**
COPD (yes/no)	1.178 (0.800-1.735)	0.406		
History of atrial fibrillation (yes/no)	1.337 (1.018-1.756)	**0.037**	0.907 (0.665-1.236)	0.536
NYHA class ≥III (yes/no)	1.688 (1.304-2.184)	**<0.001**	1.268 (0.963-1.669)	0.091
Estimated GFR (per 1 ml/min/1.73m^2 increase)	0.977 (0.972-0.981)	**<0.001**	0.982 (0.976-0.988)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.994 (0.989-0.999)	**0.017**	0.994 (0.988-0.999)	**0.027**
Diuretic agents (yes/no)	1.411 (1.108-1.797)	**0.005**	0.933 (0.709-1.227)	0.620
Peak aortic jet velocity (per 1 m/s increase)	0.652 (0.544-0.782)	**<0.001**	0.886 (0.720-1.090)	0.252
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.484 (0.481-4.573)	0.492	4.093 (1.185-14.14)	**0.026**
Stage of cardiac damage (per 1 stage increase)	1.466 (1.303-1.651)	**<0.001**	1.319 (1.158-1.503)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.058 (0.616-1.816)	0.839	1.094 (0.619-1.934)	0.756
Stage 0 vs. Stage 2	1.446 (0.871-2.401)	0.154	1.458 (0.853-2.491)	0.168
Stage 0 vs. Stage 3	1.995 (1.037-3.840)	**0.039**	1.501 (0.740-3.046)	0.260
Stage 0 vs. Stage 4	3.874 (2.209-6.793)	**<0.001**	2.871 (1.563-5.273)	**0.001**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 7: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of postoperative all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization in patients undergoing surgical or transcatheter aortic valve replacement (N = 917) (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.023 (1.013-1.033)	**<0.001**	1.012 (1.001-1.023)	**0.029**
Male gender (yes/no)	1.073 (0.882-1.304)	0.483	1.061 (0.858-1.313)	0.586
Coronary artery disease (yes/no)	1.561 (1.282-1.899)	**<0.001**	1.124 (0.890-1.421)	0.327
Previous MI(yes/no)	1.868 (1.465-2.381)	**<0.001**	1.390 (1.040-1.856)	**0.026**
COPD (yes/no)	1.089 (0.796-1.490)	0.595		
History of atrial fibrillation (yes/no)	1.267 (1.015-1.580)	**0.036**	0.975 (0.759-1.251)	0.840
NYHA class ≥III (yes/no)	1.303 (1.056-1.609)	**0.014**	1.018 (0.813-1.275)	0.875
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.985 (0.981-0.989)	**<0.001**	0.990 (0.985-0.995)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.992-1.000)	0.057	0.997 (0.993-1.002)	0.232
Diuretic agents (yes/no)	1.465 (1.206-1.781)	**<0.001**	1.155 (0.929-1.437)	0.195
Peak aortic jet velocity (per 1 m/s increase)	0.732 (0.633-0.848)	**<0.001**	0.901 (0.765-1.062)	0.214
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.075 (0.438-2.638)	0.874	2.162 (0.795-5.883)	0.131
Stage of cardiac damage (per 1 stage increase)	1.310 (1.191-1.441)	**<0.001**	1.205 (1.085-1.340)	**0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.053 (0.699-1.587)	0.805	1.090 (0.708-1.677)	0.696
Stage 0 vs. Stage 2	1.353 (0.921-1.988)	0.123	1.325 (0.882-1.991)	0.176
Stage 0 vs. Stage 3	1.922 (1.158-3.189)	**0.012**	1.588 (0.921-2.738)	0.096
Stage 0 vs. Stage 4	2.595 (1.661-4.055)	**<0.001**	2.018 (1.244-3.274)	**0.004**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 8: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization after exclusion of patients in Stage 1 with a left ventricular ejection fraction <50% (N = 1137).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
All-cause mortality				
Age (per 1 year increase)	1.034 (1.024-1.043)	**<0.001**	1.021 (1.010-1.032)	**<0.001**
Male gender (yes/no)	0.910 (0.756-1.096)	0.321	1.017 (0.825-1.253)	0.874
Coronary artery disease (yes/no)	1.357 (1.127-1.634)	**0.001**	0.948 (0.750-1.198)	0.655
Previous MI (yes/no)	1.998 (1.595-2.504)	**<0.001**	1.592 (1.190-2.128)	**0.002**
COPD (yes/no)	1.183 (0.871-1.606)	0.281		
History of atrial fibrillation (yes/no)	1.592 (1.310-1.935)	**<0.001**	1.040 (0.827-1.307)	0.737
NYHA class ≥III (yes/no)	1.611 (1.317-1.969)	**<0.001**	1.262 (1.017-1.566)	**0.035**
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.976 (0.972-0.979)	**<0.001**	0.981 (0.977-0.985)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.995 (0.991-0.999)	**0.008**	0.996 (0.991-1.000)	0.055
Diuretic agents (yes/no)	1.307 (1.085-1.575)	**0.005**	1.010 (0.814-1.255)	0.926
Peak aortic jet velocity (per 1 m/s increase)	0.683 (0.596-0.782)	**<0.001**	0.974 (0.831-1.141)	0.743
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.814 (0.790-4.168)	0.160	2.441 (0.951-6.266)	0.063
Surgical or transcatheter AVR (yes/no)	0.398 (0.324-0.489)	**<0.001**	0.507 (0.402-0.640)	**<0.001**
Stage of cardiac damage (per 1 stage increase)	1.518 (1.388-1.661)	**<0.001**	1.302 (1.168-1.450)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	0.963 (0.611-1.517)	0.871	1.047 (0.622-1.762)	0.864
Stage 0 vs. Stage 2	1.612 (1.074-2.418)	0.021	1.481 (0.927-2.369)	0.101
Stage 0 vs. Stage 3	2.741 (1.691-4.444)	**<0.001**	1.965 (1.117-3.458)	**0.019**
Stage 0 vs. Stage 4	3.864 (2.481-6.019)	**<0.001**	2.518 (1.495-4.242)	**0.001**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.

Table 8: Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke and cardiac-related hospitalization after exclusion of patients in Stage 1 with a left ventricular ejection fraction <50% (N = 1137) (*continued*).

	Univariate analysis		**Multivariate analysis**	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Combined endpoint				
Age (per 1 year increase)	1.026 (1.018-1.034)	**<0.001**	1.014 (1.004-1.023)	**0.004**
Male gender (yes/no)	0.973 (0.827-1.143)	0.737	1.001 (0.837-1.197)	0.995
Coronary artery disease (yes/no)	1.391 (1.183-1.637)	**<0.001**	0.998 (0.817-1.220)	0.987
Previous MI (yes/no)	1.814 (1.481-2.223)	**<0.001**	1.423 (1.105-1.831)	**0.006**
COPD (yes/no)	1.139 (0.872-1.489)	0.339		
History of atrial fibrillation (yes/no)	1.475 (1.240-1.754)	**<0.001**	1.104 (0.903-1.349)	0.337
NYHA class ≥III (yes/no)	1.415 (1.186-1.688)	**<0.001**	1.153 (0.954-1.393)	0.140
Estimated GFR (per 1 ml/min/1.73 m^2 increase)	0.982 (0.978-0.985)	**<0.001**	0.986 (0.982-0.990)	**<0.001**
Systolic blood pressure (per 1 mmHg increase)	0.996 (0.992-0.999)	**0.012**	0.997 (0.993-1.001)	0.134
Diuretic agents (yes/no)	1.373 (1.166-1.616)	**<0.001**	1.076 (0.894-1.295)	0.439
Peak aortic jet velocity (per 1 m/s increase)	0.737 (0.655-0.830)	**<0.001**	0.957 (0.835-1.096)	0.523
Indexed AVA (per 0.01 cm^2/m^2 increase)	1.087 (0.528-2.240)	0.820	1.927 (0.848-4.381)	0.117
Surgical or transcatheter AVR (yes/no)	0.396 (0.333-0.471)	**<0.001**	0.807 (0.655-0.995)	**0.044**
Stage of cardiac damage (per 1 stage increase)	1.372 (1.269-1.483)	**<0.001**	1.199 (1.094-1.313)	**<0.001**
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.023 (0.707-1.482)	0.903	1.122 (0.744-1.693)	0.583
Stage 0 vs. Stage 2	1.510 (1.082-2.108)	**0.015**	1.459 (1.003-2.123)	**0.048**
Stage 0 vs. Stage 3	2.362 (1.564-3.567)	**<0.001**	1.776 (1.110-2.842)	**0.017**
Stage 0 vs. Stage 4	2.880 (1.977-4.195)	**<0.001**	1.973 (1.282-3.035)	**0.002**

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; NYHA, New York Heart Association.