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Refined Staging Classification of Cardiac Damage Associated with Aortic Stenosis and Outcomes after Transcatheter Aortic Valve Implantation

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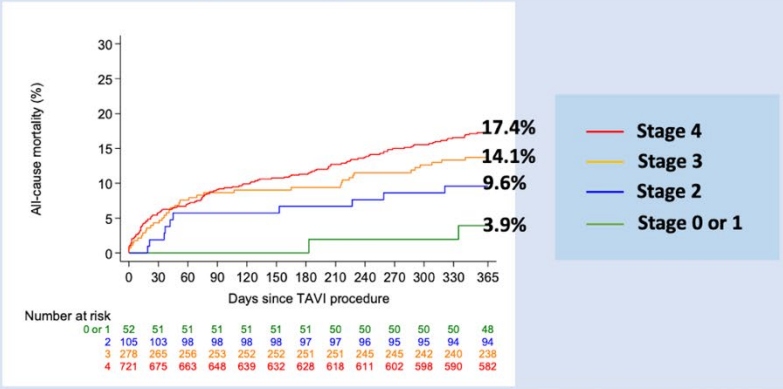
Graphical Abstract

Updated Staging Classification According to Extent of Cardiac Injury

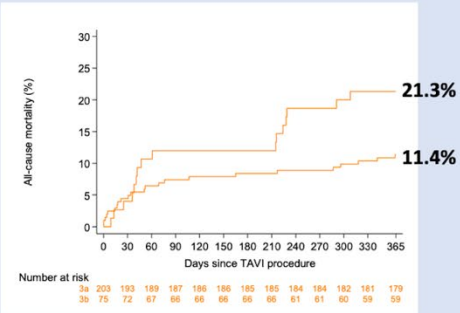
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Injury	LV Injury	LA/Mitral Injury	Pulmonary Vasculature/Tricuspid Injury	RV Injury/Low-flow state
Criteria		LV hypertrophy*1 LVEF <60% LV diastolic dysfunction ≥grade II*1	LA dilatation*1 Presence of atrial fibrillation Moderate/severe mitral regurgitation	Pulmonary hypertension*2 Moderate/severe tricuspid regurgitation	RV dysfunction*1 Moderate-to-severe low-flow*3
Prevalence	14 (1.2%)	38 (3.3%)	105 (9.1%)	278 (24.0%)	721 (62.4%)

All-Cause Mortality According to the Stages



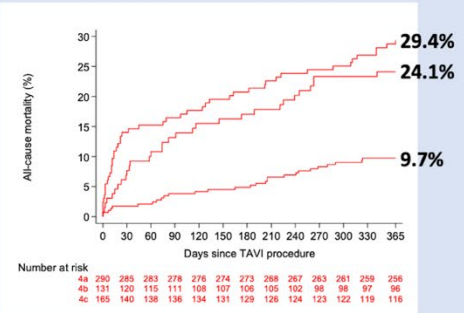
All-Cause Mortality According to the Sub-groups of Stage 3 and 4

Stage 3



Stage 3a: ≤Moderate pulmonary hypertension (systolic PAP <60mmHg)
Stage 3b: Severe pulmonary hypertension (systolic PAP ≥60mmHg)

Stage 4



Stage 4a: Moderate-to-severe low-flow state
Stage 4b: RV dysfunction
Stage 4c: RV dysfunction and moderate-to-severe low-flow state

ABSTRACT

Aims: A new staging classification of aortic stenosis (AS) characterizing the extent of cardiac damage was established and validated in patients undergoing transcatheter aortic valve implantation (TAVI). We aimed to validate an updated classification system in patients undergoing TAVI.

Methods and Results: In a prospective TAVI registry, AS patients were categorized into the following stages: no cardiac damage (Stage 0), left ventricular damage (Stage 1), left atrial or mitral valve damage (Stage 2), pulmonary vasculature or tricuspid valve damage (Stage 3), or right ventricular (RV) damage or low-flow state (Stage 4). Stage 3 was sub-divided into Stage 3a (≤moderate pulmonary hypertension) and Stage 3b (severe pulmonary hypertension). Stage 4 was sub-divided into Stage 4a (low-flow without RV dysfunction), Stage 4b (RV dysfunction without low-flow), and Stage 4c (RV dysfunction with low-flow). The primary endpoint was all-cause death at 1 year. Among 1,156 eligible patients, 14 were classified as Stage 0, 38 as Stage 1, 105 as Stage 2, 278 as Stage 3, and 721 as Stage 4. There was a stepwise increase in mortality according to advancing stages of cardiac damage: 3.9% (Stage 0-1), 9.6% (Stage 2), 14.1% (Stage 3), and 17.4% (Stage 4) (p=0.002). After multivariable adjustment, only Stage 3b, Stage 4b, and Stage 4c conferred a significantly increased risk of mortality compared to Stage 0-1.

Conclusion: More than one third of patients had advanced cardiac damage (severe pulmonary hypertension or RV dysfunction) before TAVI, associating with a 5- to 7-fold increased risk of mortality at 1 year.

Clinical Trial Registration: https://www.clinicaltrials.gov. NCT01368250.

Keywords: transcatheter aortic valve implantation; aortic stenosis; cardiac damage; staging; prognosis.

Introduction

The optimal timing of intervention in patients with aortic stenosis (AS) has recently become subject to increased scrutiny. Given the low periprocedural risks of aortic valve replacement in contemporary practice, earlier intervention has been drawing increasing attention[1-4]. Although there is no guideline recommendation for early aortic valve replacement in AS patients in a gray zone ranging from moderate AS to asymptomatic severe AS[5, 6], recent observational studies suggested adverse prognosis with conservative management in these patients[7, 8]. Thus, integrating structural and functional cardiac changes into the systematic staging of AS may refine the traditional AS classification based on aortic valve area and clinical symptoms.

Généreux and colleagues proposed an objective staging system to quantify downstream cardiac damage in patients with aortic stenosis[9]. Progressive stages of cardiac damage were independently associated with an incremental risk of death after valvular replacement. The prognostic implications of the staging classification has been validated in several independent cohorts[10-14]. However, during the validation process, the staging system has been iteratively optimized to integrate current evidence (**Supplementary Table 1**)[15]. Therefore, the objective of the present study was to evaluate the prognostic value of the updated cardiac damage staging system [15] in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods

Study population

All consecutive AS patients who underwent TAVI at Bern University Hospital, Bern, Switzerland, were enrolled into a prospective institutional registry, which is a part of the nationwide Swiss TAVI registry (registered at clinicaltrials.gov with NCT01368250)[16]. Patients were excluded if a non-CE marked device was used or if no transcatheter heart valve was implanted. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Bern cantonal

ethics committee. All patients gave an informed consent to participate in this study. CTU Bern, an independent institution of Bern University, was responsible for central data monitoring and statistical analysis.

Cardiac damage staging classification

The presence and extent of extra-aortic valvular cardiac damage was evaluated on echocardiography and right heart catheterization before TAVI. According to the most recent staging classification[15], patients were categorized into the following stages: Stage 0 - no cardiac damage; Stage 1- left ventricle (LV) damage (LV ejection fraction <60%, LV mass index >95g/m^2 for women, >115g/m^2 for men, or LV diastolic dysfunction ≥grade II); Stage 2 - left atrial (LA) or mitral valve damage (LA volume index >34ml/m^2, mitral regurgitation ≥moderate, or presence of atrial fibrillation); Stage 3 - pulmonary vasculature or tricuspid valve damage (systolic pulmonary artery pressure (PAP) ≥60mmHg, mean PAP ≥25mmHg, or tricuspid regurgitation ≥moderate); Stage 4 – right ventricular (RV) damage or low-flow state (RV dysfunction or moderate-to-severe low-flow defined as stroke volume index (SVi) <30ml/m^2) (**Supplementary Table 1**). Stage 3 was sub-divided into Stage 3a (≤moderate pulmonary hypertension: systolic PAP <60mmHg) and Stage 3b (severe pulmonary hypertension: systolic PAP ≥60mmHg). Stage 4 was sub-divided into Stage 4a (low-flow state without RV dysfunction), Stage 4b (RV dysfunction without low-flow state), and Stage 4c (RV dysfunction with low-flow state).

All baseline echocardiographic studies were performed by a board-certified cardiologist and an echocardiography-specialist within 3 months before TAVI. Acquired images were Core laboratory re-evaluated by dedicated and experienced imaging specialists. LV diastolic dysfunction and RV dysfunction were assessed in accordance with current American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines[17, 18]. Details of the assessment methods have been previously published[19, 20]. PAP and SVi were obtained either by invasive or echocardiographic measurements. Patients were hierarchically classified into the most advanced stage

if at least one of the criteria was met within that stage, and patients who could not be classified in any of the stages were excluded from the present analysis[9].

Follow-up and endpoint assessment

Clinical follow-up was scheduled at 1 year, and the data was obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events during the follow-up were reviewed by an independent clinical event committee and adjudicated according to the Valve Academic Research Consortium (VARC-2) criteria[21]. The primary endpoint of the study was all-cause death at 1 year. Secondary endpoints included cardiovascular death and functional status as assessed by New York Heart Association (NYHA) class at 1 year.

Statistical analysis

Categorical data are presented as frequencies and percentages, and the differences between groups were evaluated using the chi-square test or Fisher's exact test. Continuous variables are expressed as mean values ± standard deviation (SD), and were compared between groups using the analysis of variance test. Cumulative incidence curves were constructed using the Kaplan-Meier method. Comparison of cumulative event rates between groups was performed by Cox's regression. In case of zero events in one group of interest, a continuity corrected risk ratio (RR) and 95% confidence intervals (CI) with p-value from Fisher's exact test is reported. For a comparison of more than two groups, hazard ratios (HR) with 95% CI and p values for a linear trend were provided. Multivariable adjustment was performed with pre-defined baseline variables including age, diabetes, cerebrovascular events, peripheral artery disease, hypertension, NYHA class III or IV, cardiogenic shock, and STS-PROM (Society of Thoracic Surgeons Predicted Risk of Mortality), in view of the presumed association with survival outcome. Throughout the present study, a *p*-value of <0.05 was considered significant. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Study population

Among 1,619 consecutive patients undergoing TAVI between August 2007 and June 2018, 1,156 patients had adequate echocardiographic and invasive measurements to objectively stage the extent of cardiac damage associated with AS. The prevalence of the individual cardiac stages and their respective components are provided in **Table 1**. According to the staging scheme, 721 (62.4%) patients were classified as Stage 4, 278 (24.0%) as Stage 3, 105 (9.1%) as Stage 2, 38 (3.3%) as Stage 1, and 14 (1.2%) as Stage 0. Patient flow is shown in **Figure 1**.

Baseline clinical characteristics according to the stages of cardiac damage are presented in **Table 2**. The mean age in the total population (50.1% female) was 82.1 ± 6.2 years and the mean STS PROM was 6.00 ± 4.20. Patients in more advanced stages were more likely to be female, had an increased surgical risk (STS-PROM), and were more commonly symptomatic (NYHA III or IV). Echocardiographic parameters and invasive measurements are summarized in **Supplementary Table 2**.

Clinical outcome

Clinical follow-up at 1 year was complete in 1,139 patients (98.5%); 14 patients refused follow-up, 2 patients were not traceable, and follow-up was not performed in 1 patient. Clinical outcomes at 1 year according to the stages of cardiac damage are summarized in **Table 3**. All-cause death and cardiovascular death gradually increased with advancing stages of cardiac damage (HR 1.40, 95% CI 1.13-1.73, p=0.002 and HR 1.55, 95% CI 1.17-2.05, p=0.002, respectively, for linear trend) (**Figure 2**). There was also a stepwise increase in NYHA III or IV at 1 year according to progressive stages of cardiac damage: 0% in Stage 0, 8.1% in Stage 1, 9.8% in Stage 2, 10.9% in Stage 3, 15.0% in Stage 4 (Odds ratio 1.36, 95% CI 1.06-1.75, p=0.017 for linear trend).

As European guidelines for the management of valvular heart disease have been updated in August 2012, we performed a sensitivity analysis using a cohort who underwent TAVI after September 2012. The prevalence of each cardiac stage was comparable to that of the overall cohort: Stage 4 (62.8%), Stage 3 (22.8%), Stage 2 (9.3%), Stage 1 (3.2%), and Stage 0 (2.0%). The trends for all-cause and cardiovascular death were consistent in the sensitivity analysis cohort (p=0.030 and p=0.011, respectively, for linear trend) (**Supplementary Table 3**).

Stratification of stage 3 according to pulmonary artery pressure

Among 278 patients in Stage 3, 75 patients (27.0%) had severe pulmonary hypertension (systolic PAP ≥60 mmHg) and were categorized as Stage 3b, and the remaining 203 patients (73.0%) (mean PAP ≥25mmHg or tricuspid regurgitation ≥moderate, and systolic PAP ≤60mmHg) were categorized as Stage 3a. Clinical outcomes at 1year according to the sub-categories of Stage 3 are presented in **Table 3**. As shown in **Figure 3**, patients in Stage 3b had significantly higher incidence of all-cause death (21.3% vs. 11.4%, HR 1.95, 95% CI 1.03-3.69, p=0.040) and numerically higher incidence of cardiovascular death (14.9% vs. 7.1%, HR 2.19, 95% CI 0.99-4.81, p=0.052) as compared to patients in Stage 3a at 1 year.

Stratification of stage 4 according to RV function and flow state

Among 721 patients in Stage 4, 165 patients (22.9%) had both RV dysfunction and low-flow state and were categorized as Stage 4c, 131 patients (18.2%) had only RV dysfunction and were categorized as Stage 4b, 290 patients (40.2%) had only low-flow state and were categorized as Stage 4a, and 135 patients (18.7%) were not categorized because of incomplete data to assess subcategories. Clinical outcomes at 1year according to the sub-categories of Stage 4 are presented in **Table 3**. We found a stepwise increase in all-cause death (9.7% vs. 24.1% vs. 29.4%, HR 1.82, 95% CI 1.46-2.26, p<0.001 for linear trend) and cardiovascular death (5.3% vs. 19.8% vs. 23.3%, HR 2.07, 95% CI 1.59-2.71, p<0.001 for linear trend) at 1 year according to the sub-categories of Stage 4

(Figure 3). Cumulative event rates for the uncategorized patients are presented in Supplementary Table 4.

Prognostic value of the updated staging system of cardiac damage associated with AS

Univariate and multivariate survival analysis for each cardiac stage as compared to Stage 0 to 1 are summarized in Table 4. After adjustment for age, diabetes, cerebrovascular events, peripheral artery disease, hypertension, NYHA class III or IV, cardiogenic shock, and STS-PROM, patients in Stage 3b, Stage 4b, and Stage 4c had a significantly increased risk of all-cause death at 1 year (HR 4.65; 95% CI 1.06-20.37; p=0.042, HR 5.41; 95% CI 1.29-22.72; p=0.021, and HR 6.91; 95% CI 1.67-28.55; p=0.008, respectively), while patients in Stage 2, Stage 3a, and Stage 4a had a comparable risk (HR 2.77; 95% CI 0.65-11.80; p=0.273, HR 2.77; 95% CI 0.65-11.80; p=0.167, and HR 2.11; 95% CI 0.50-8.90; p=0.307, respectively) compared to those in Stage 0 to 1. Univariate analysis for cardiovascular death showed a similar trend as for all-cause death.

Discussion

Prognosis in patients with aortic stenosis is determined by downstream cardiac damage associated with AS rather than valve-related factors. In the present study, we evaluated the prognostic value of the updated staging classification of cardiac damage [15] in a prospective cohort of consecutive patients undergoing TAVI. We found a stepwise increase in all-cause and cardiovascular death for each increment in cardiac stage category. Furthermore, after stratification of stages 3 (pulmonary vasculature/tricuspid injury) and 4 (RV injury, flow state), Stage 3b (severe pulmonary hypertension with/without tricuspid regurgitation), Stage 4b (RV dysfunction) and Stage 4c (RV dysfunction with low-flow state) conferred a significantly increased risk of mortality as compared to Stage 0-1. In contrast, the risk of mortality among patients in Stage 2 (LA or mitral valve damage), Stage 3a (mild

or moderate pulmonary hypertension with/without tricuspid regurgitation), and Stage 4a (low-flow state without RV dysfunction), was comparable to the risk of patients in Stage 0 to 1 (no cardiac damage or LV damage).

Since its original description [9], the proposed staging system of cardiac damage has undergone iterative refinement. Parameters and criteria for each stage have been modified based on recent evidence (**Supplementary Table 1**)[19, 20, 22-30]: In the definition of Stage 4, a moderate to severe low-flow state as defined by reduced SVi (<30 ml/m^2) has been added to the criteria[11, 23]. RV dysfunction was initially defined as moderate-to-severe RV dysfunction by visual assessment; however, multiparametric quantitative assessment has been introduced as a superior approach in accordance with current echocardiographic guidelines[17, 20, 24]. In the definition of Stage 3, mean PAP ≥25mmHg has been added to the criterion of pulmonary hypertension[15, 26]. In the definition of Stage 2, a multiparametric approach in accordance with current echocardiographic guidelines has been suggested for the assessment of LV diastolic dysfunction rather than relying on a single parameter (E/e' >14)[19]. Finally, in the definition of Stage 1, the cut-off value of the LVEF for subclinical LV systolic dysfunction has been raised from <50% to <60% for better sensitivity[11, 28-30]. Although impaired LV global longitudinal strain has also been suggested for an additional criterion for subclinical LV systolic dysfunction[11, 13], it has not been systematically evaluated in our cohort and therefore was excluded from the staging definition in the present study. In this updated version of the staging classification, a significantly higher proportion of patients (85%) undergoing TAVI were categorized into advanced cardiac stages (Stage 3 or 4) compared to the previous derivation and validation studies[9-13]. Thereby, only 5% of patients were categorized into early cardiac stages (Stage 0 or 1) with timely aortic valve intervention before downstream cardiac damage occurred. Further detailed evaluation for patients categorized into the advanced cardiac stages may allow us to identify more patients in earlier cardiac stages who may benefit more from aortic valve intervention.

A low-flow state has been associated with an increased risk of cardiac events in AS patients in

several studies, and thus, proposed as a marker of subclinical heart failure representing an advanced cardiac stage (Stage 4)[11, 22, 23, 27]. The validation study conducted in asymptomatic AS patients suggested that adding the SVi criteria improved the discrimination between Stage 2 and Stage 3 to 4 with respect to the prediction of outcomes[11]. In the present analysis, while patients having a low-flow state in combination with RV dysfunction had the highest risk of mortality at 1 year, those with a low-flow state in the absence of RV dysfunction had a similar risk of mortality as patients in Stage 2. This observation may suggest that patients with subclinical heart failure without RV dysfunction may particularly benefit from aortic valve intervention compared to the other entities in Stage 4.

Pulmonary hypertension as the criterion of Stage 3 has been originally defined by systolic PAP ≥60mmHg in previous studies[9-13]. Recently, mean PAP ≥25mmHg has been added to the definition of pulmonary hypertension in Stage 3 based on recent findings of studies conducted in TAVI cohorts[15, 25, 26]. In a study including 1,400 patients undergoing TAVI, pulmonary hypertension defined as mean PAP ≥25 mmHg was associated with increased risk of mortality, irrespective of pre-capillary or post-capillary etiology of pulmonary hypertension[26]. This modification has lowered the threshold for pulmonary hypertension as compared to the previous definition using only systolic PAP ≥60mmHg. In the stratified analysis of Stage 3, patients with mild or moderate pulmonary hypertension (mean PAP ≥25mmHg but systolic PAP≤60mmHg) or tricuspid regurgitation in the absence of severe pulmonary hypertension (systolic PAP ≥60 mmHg) had significantly lower risk of mortality as compared to those with severe pulmonary hypertension. Furthermore, the risk in Stage 3a was comparable to that of Stage 2, suggesting that mild or moderate pulmonary hypertension and tricuspid regurgitation represents an earlier stage of cardiac damage (comparable to Stage 2).

Thus, the present study suggests that the established cardiac damage staging system needs to be further refined to better discriminate between patients at an earlier stage of disease that may benefit more from aortic valve intervention and those at a late stage of disease that may benefit less. While the presence of RV dysfunction or severe pulmonary hypertension strongly indicates an advanced stage

of AS with poorer prognosis after TAVI, a moderate-to-severe low flow state, mild to moderate pulmonary hypertension, and tricuspid regurgitation may be markers of a rather earlier stage, similar to LA or mitral valve damage (**Figure 4**). Clinical outcomes according to the refined cardiac stages are shown in **Supplementary Table 5**. Intriguingly, a significant proportion of patients (>45%) underwent TAVI only after the development of advanced cardiac damage associated with AS (severe pulmonary hypertension or RV dysfunction), while only a very small proportion of patients (<5%) had no or minimal cardiac damage at the time of TAVI. The presence of the advanced cardiac stage not only suggests the need for careful follow-up after TAVI but also should be considered in the decision-making process before TAVI in elderly patients with multiple comorbidities where palliative care is an option. Whether the integration of the cardiac damage staging system into the traditional AS classification improves the timely referral and intervention for AS patients in a gray zone (moderate AS and asymptomatic severe AS) needs to be investigated in future studies.

Study Limitations

This retrospective analysis of a large prospective TAVI registry has several limitations inherent to its study design. First, the results of the present analysis reflect the experience of a single center. Further, as is in previous studies, 29% of patients were excluded from the analysis due to missing data in echocardiographic or invasive measurements. These limitations may have introduced some degree of selection bias. Second, the present cohort included only TAVI patients. The advanced stage of cardiac damage may often times have contributed to the decision to perform TAVI rather than SAVR. Thus, our data comprises only a modest number of patients in early stages of cardiac damage. Due to the small number of patients with no or minimal cardiac damage (Stage 0 to 1), the present study may have been underpowered to detect the smaller effect sizes of earlier cardiac stages. Finally, as mentioned in the previous studies, the observed cardiac changes may or may not be a direct consequence of AS. However, even if cardiac damage is not entirely due to AS, the patient is at higher risk of adverse events and potentially benefits from afterload reduction by an early aortic valve

intervention.

Conclusion

In this prospective registry, a significant proportion of patients with AS had evidence of advanced cardiac damage (severe pulmonary hypertension or RV dysfunction) at the time of TAVI, associated with a 5- to 7-fold increased risk of mortality at 1 year. Future studies are needed to investigate whether integrating the cardiac damage staging system into the current decision-making process reduces the proportion of patients presenting at an advanced stage and improves clinical outcomes after TAVI.

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Figures

Figure 1. Patient flow

TAVI = transcatheter aortic valve replacement; RV = right ventricle; SVi = stroke volume index; LV = left ventricular; LVEF = left ventricular ejection fraction.

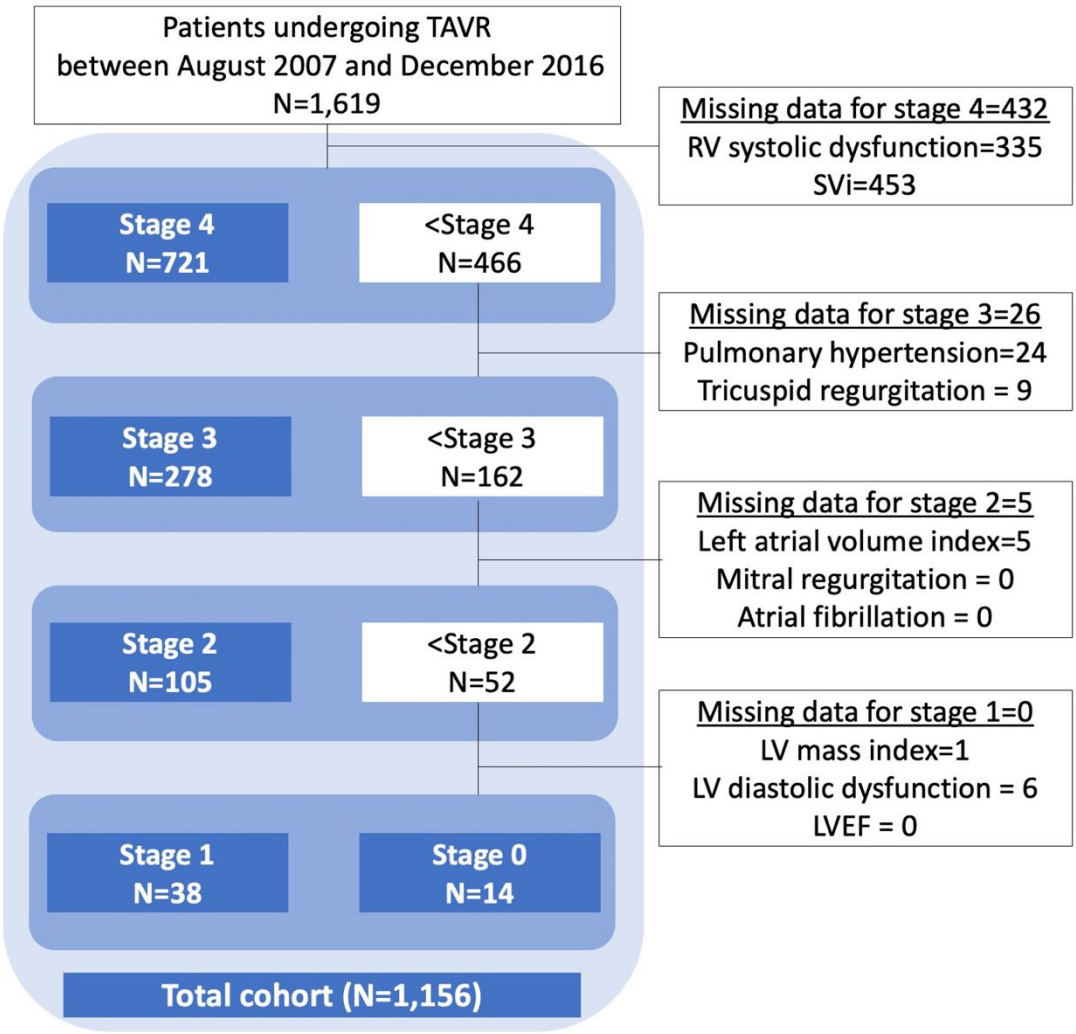


Figure 2. All-cause and cardiovascular death according to the updated staging classification of cardiac damage associated with AS

Kaplan-Meier curves for all-cause death (A) and cardiovascular death (B) according to the update staging classification.

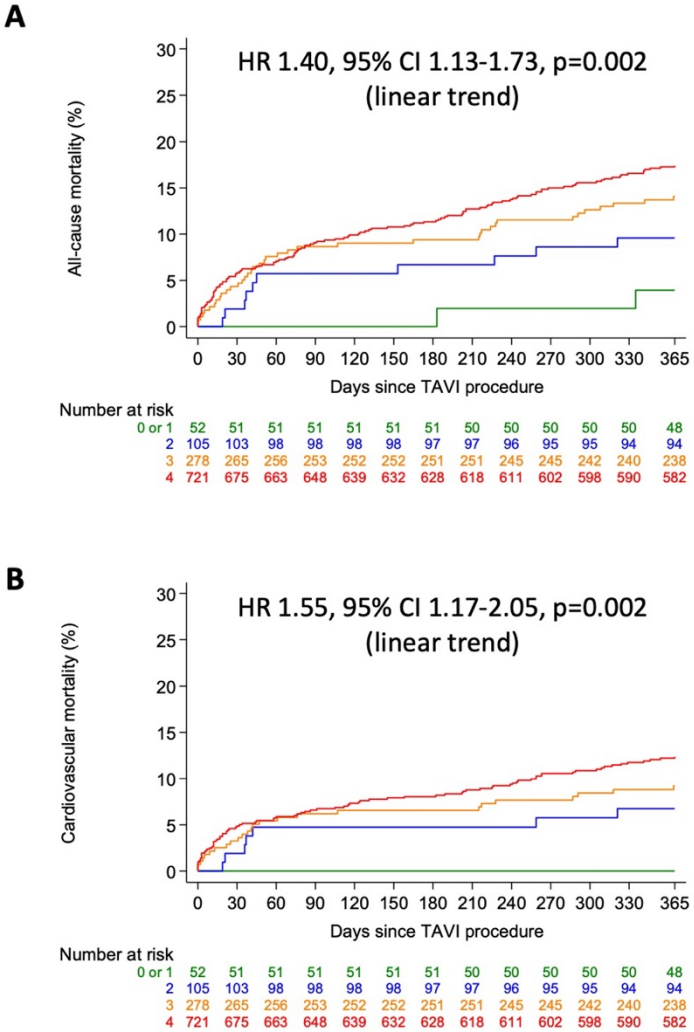


Figure 3. All-cause and cardiovascular death according to sub-categories of Stage 3 and 4

(A, B) Kaplan-Meier curves for all-cause death and cardiovascular death according to sub-categories of Stage 3.

(C, D) Kaplan-Meier curves for all-cause death and cardiovascular death according to sub-categories of Stage 4.

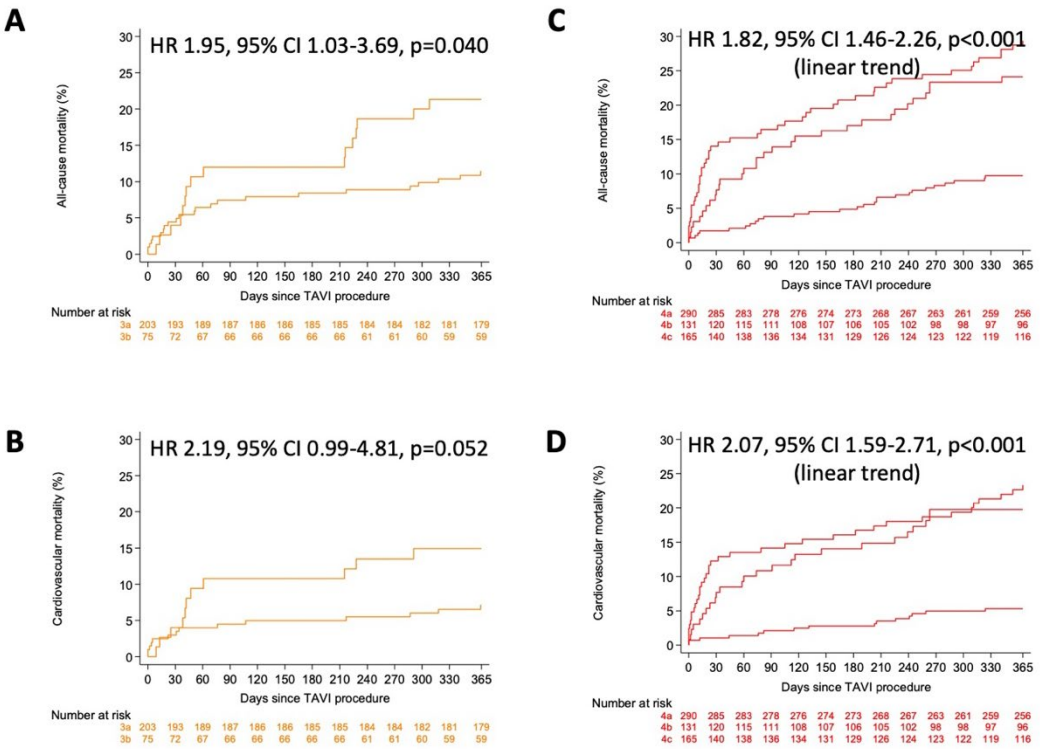
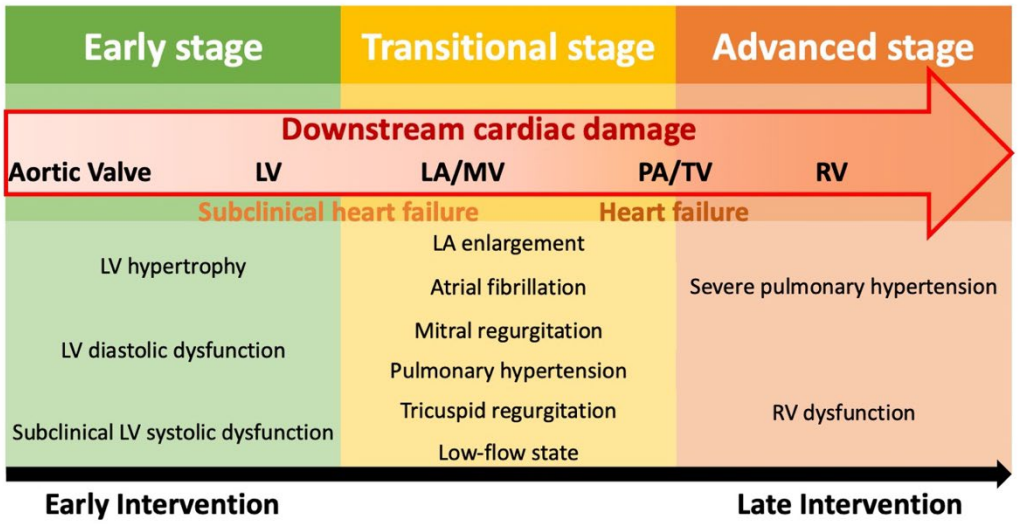


Figure 4. Progression of extra-aortic cardiac damage and timing of intervention

Late intervention for patients with advanced cardiac damage due to AS may result in adverse outcome, while premature intervention exposes patients to unnecessary peri-procedural risks, prosthetic valve degeneration and early need for re-intervention. Accurate risk stratification in patients with early to transitional cardiac stages is instrumental to determine the optimal timing of intervention.

LV = left ventricular; LA = left atrial; MV = mitral valve; PA = pulmonary artery; TV = tricuspid valve; RV = right ventricular.



Tables

Table 1. Prevalence of cardiac damage stages and their respective components.

Stages of Cardiac Damage	
Stage 4 (RV Damage/Low-flow state)	**721/1,156 (62.4%)**
Stage 3 (Pulmonary vasculature/Tricuspid valve Damage)	**278/1,156 (24.0%)**
Stage 2 (LA/Mitral valve Damage)	**105/1,156 (9.1%)**
Stage 1 (LV Damage)	**38/1,156 (3.3%)**
Stage 0 (No Cardiac Damage)	**14/1,156 (1.2%)**
Individual Components of Cardiac Damage	
Stage 4 (RV Damage/Low-flow state)	**721/1,156 (62.4%)**
RV systolic dysfunction	346/1071 (32.3%)
Moderate-to-severe low-flow (SVi <30ml/m^2)	493/1059 (46.6%)
Stage 3 (Pulmonary vasculature/Tricuspid valve Damage)	**773/1,111 (69.6%)**
Pulmonary hypertension (Systolic PAP ≥60mmHg or Mean PAP≥25mmHg)	722/1110 (65.0%)
Tricuspid regurgitation ≥moderate	149/1127 (13.2%)
Stage 2 (LA/Mitral valve Damage)	**869/1103 (78.8%)**
LA dilation (LAVi >34mL/m2)	712/1043 (68.3%)
Mitral regurgitaion ≥moderate	238/1125 (21.2%)
Atrial fibrillation	363/1156 (31.4%)
Stage 1 (LV Damage)	**947/1011 (93.7%)**

LV hypertrophy (LV mass index >115 g/m2 Male, >95 g/m2 Female)	746/928 (80.4%)
LV diastolic dysfunction Grade ≥2	321/672 (47.8%)
Subclinical LV systolic dysfunction (LVEF<60%)	516/1152 (44.8%)
RV = right ventricular; SVi = stroke volume index; LA = left atrial; LV = left ventricular; PAP = pulmonary artery pressure; LAVi = left atrial volume index; LVEF = left ventricular ejection fraction.	

Table 2. Baseline clinical characteristics according to stage of cardiac damage.

	Total population	Stage 0 or 1	Stage 2	Stage 3	Stage 4	p-value
	N = 1156	N = 52	N = 105	N = 278	N = 721	
Age (years)	82.1 ± 6.2	80.5 ± 6.0	82.4 ± 5.5	82.1 ± 6.0	82.1 ± 6.4	0.272
Gender (female)	579 (50.1%)	23 (44.2%)	41 (39.0%)	154 (55.4%)	361 (50.1%)	0.030
Body mass index (kg/m²)	26.2 ± 5.0	25.4 ± 4.0	26.2 ± 4.8	26.9 ± 5.2	26.0 ± 5.0	0.078
Body surface area (m²)	1.82 ± 0.23	1.80 ± 0.20	1.86 ± 0.22	1.83 ± 0.22	1.82 ± 0.23	0.285
STS PROM	6.00 ± 4.20	4.10 ± 2.41	4.93 ± 3.01	5.90 ± 4.37	6.33 ± 4.33	<0.001
NYHA III or IV	792 (68.6%)	29 (55.8%)	56 (53.3%)	185 (66.5%)	522 (72.5%)	<0.001
Concomitant diseases						
Hypertension	973 (84.2%)	44 (84.6%)	90 (85.7%)	245 (88.1%)	594 (82.4%)	0.158
Diabetes mellitus	297 (25.7%)	14 (26.9%)	27 (25.7%)	63 (22.7%)	193 (26.8%)	0.611
CKD (eGFR<60)	822 (71.2%)	35 (67.3%)	67 (63.8%)	195 (70.1%)	525 (73.0%)	0.213
Previous history						
Coronary artery disease	752 (65.1%)	34 (65.4%)	61 (58.1%)	191 (68.7%)	466 (64.6%)	0.270
History of MI	179 (15.5%)	4 (7.7%)	17 (16.2%)	34 (12.2%)	124 (17.2%)	0.095
History of PCI	324 (28.0%)	14 (26.9%)	28 (26.7%)	79 (28.4%)	203 (28.2%)	0.985
History of CABG	132 (11.4%)	5 (9.6%)	11 (10.5%)	31 (11.2%)	85 (11.8%)	0.945
History of atrial fibrillation	363 (31.4%)	0 (0.0%)	25 (23.8%)	71 (25.5%)	267 (37.0%)	<0.001
History of cerebrovascular event	130 (11.2%)	5 (9.6%)	12 (11.4%)	35 (12.6%)	78 (10.8%)	0.855
Peripheral artery disease	173 (15.0%)	7 (13.5%)	9 (8.6%)	51 (18.3%)	106 (14.7%)	0.112
COPD	159 (13.8%)	3 (5.9%)	17 (16.2%)	41 (14.8%)	98 (13.6%)	0.327

STS PROM = Society of Thoracic Surgeons Predicted Risk Of Mortality; NYHA = New York Heart Association; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease.

Table 3. Clinical outcomes at 1 year according to stage of cardiac damage and sub-groups of stage 3 and 4

	Stage 0	**Stage 1**	**Stage 2**	**Stage 3**	**Stage 4**	**Linear trend Hazard Ratio/Odds Ratio (95% CI)**	**p-value****
	N = 14	N = 38	N = 105	N = 278	N = 721		
Cardiac damage							
All-cause death (n, %)	1 (7.7)	1 (2.6)	10 (9.6)	39 (14.1)	124 (17.4)	1.40 (1.13-1.73)	0.002
Cardiovascular death (n, %)	0 (0.0)	0 (0.0)	7 (6.8)	25 (9.2)	86 (12.4)	1.55 (1.17-2.05)	0.002
NYHA III or IV (n, %)*	0/12 (0.0)	3/37 (8.1)	9/92 (9.8)	25/230 (10.9)	83/553 (15.0)	1.36 (1.06-1.75)	0.017

Subgroup of Stage 3				
	Stage 3a	**Stage 3b**	**Hazard Ratio (95% CI)**	**p-value**
	N = 203	N = 75		
All-cause death (n, %)	23 (11.4)	16 (21.3)	1.95 (1.03-3.69)	0.040
Cardiovascular death (n, %)	14 (7.1)	11 (14.9)	2.19 (0.99-4.81)	0.052
NYHA III or IV (n, %)*	19/173 (11.0)	6/57 (10.5)	0.95 (0.36-2.52)	0.924

Subgroup of Stage 4					
	Stage 4a	**Stage 4b**	**Stage 4c**	**Linear trend Hazard Ratio/Odds Ratio (95% CI)**	**p-value****
	N = 290	N = 131	N = 165		
All-cause death (n, %)	28 (9.7)	31 (24.1)	48 (29.4)	1.82 (1.46-2.26)	<0.001
Cardiovascular death (n, %)	15 (5.3)	25 (19.8)	37 (23.3)	2.07 (1.59-2.71)	<0.001
NYHA III or IV (n, %)*	34/245 (13.9)	16/91 (17.6)	18/106 (17.0)	1.14 (0.84-1.55)	0.395

The Kaplan-Meier estimated event rates and hazard ratios with 95% confidence intervals are provided.
*Numbers of patients with NYHA III or IV/numbers of patients assessed at 1 year and odds ratios with 95% confidence intervals are provided.
**p-values for a linear trend.

Table 4. Univariate and multivariate Cox Proportional Hazard Analyses

	Univariate analyses		Multivariate analyses	
	Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	Adjusted p-value
All-cause death at 1 year				
Stage 0-1	Reference		Reference	
Stage 2	3.08 (0.73-13.06)	0.227	2.77 (0.65-11.80)	0.273
Stage 3a	3.08 (0.73-13.06)	0.127	2.77 (0.65-11.80)	0.167
Stage 3b	6.03 (1.39-26.24)	0.017	4.65 (1.06-20.37)	0.042
Stage 4a	2.57 (0.61-10.78)	0.198	2.11 (0.50-8.90)	0.307
Stage 4b	6.99 (1.67-29.23)	0.008	5.41 (1.29-22.72)	0.021
Stage 4c	8.95 (2.18-36.83)	0.002	6.91 (1.67-28.55)	0.008
Cardiovascular death at 1 year				
Stage 0-1	Reference			
Stage 2	7.46 (0.43-128.13)	0.080		
Stage 3a	7.48 (0.45-123.35)	0.080		
Stage 3b	15.99 (0.96-265.44)	0.003		
Stage 4a	5.60 (0.34-92.16)	0.140		
Stage 4b	20.36 (1.26-328.35)	<0.001		
Stage 4c	23.79 (1.49-380.76)	<0.001		
Adjusted analyses are not provided for cardiovascular death due to no cardiovascular death in Stage 0-1. Crude analyses are continuity corrected risk ratios with 95% CI and p-values from Fisher's exact tests.				