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Prognostic impact of cardiac damage staging classification in each aortic stenosis subtype undergoing TAVI

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KEYWORDS

- imaging modalities
- TAVI
- transthoracic echocardiogram

Abstract

Background: The prognostic value of cardiac damage staging classifications across the haemodynamic spectrum of severe aortic stenosis (AS) remains unknown.

Aims: We aimed to investigate the prognostic impact of cardiac damage staging classifications in patients with high-gradient AS (HG-AS) and low-gradient AS (LG-AS) undergoing transcatheter aortic valve implantation (TAVI).

Methods: In a prospective TAVI registry, five-year mortality was evaluated for early stages of cardiac damage (stage 0, 1, or 2) and advanced stages of cardiac damage (stage 3 or 4) in patients with HG-AS, classical low-flow (LF) LG-AS, LF LG-AS with preserved ejection fraction (pEF), and normal-flow (NF) LG-AS.

Results: Among 2,090 patients undergoing TAVI, 1,045 patients had HG-AS, 337 patients had classical LF LG-AS, 394 patients had LF LG-AS with pEF, and 314 patients had NF LG-AS. The majority of patients with classical LF LG-AS exhibited advanced cardiac damage (73.6%), followed by LF LG-AS with pEF (55.6%), NF LG-AS (51.6%), and HG-AS (50.6%). Patients with advanced stage cardiac damage had significantly higher mortality after TAVI than those with early stage cardiac damage in all subtypes of AS (adjusted hazard ratio [$HR_{adjusted}$] 1.66, 95% confidence interval [CI]: 1.34-2.06 for HG-AS; $HR_{adjusted}$ 1.49, 95% CI: 1.02-2.16 for classical LF LG-AS; $HR_{adjusted}$ 1.69, 95% CI: 1.22-2.35 for LF LG-AS with pEF; and $HR_{adjusted}$ 1.52, 95% CI: 1.04-2.32 for NF LG-AS).

Conclusions: Cardiac damage staging classifications stratified mortality after TAVI irrespective of AS subtype.

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Abbreviations

AS	aortic stenosis
EF	ejection fraction
HG	high gradient
LF	low flow
LG	low gradient
LV	left ventricular
LVEF	left ventricular ejection fraction
NF	normal flow
TAVI	transcatheter aortic valve implantation

Introduction

Aortic stenosis (AS) is the prevailing valvular heart disease in high-income countries with ageing populations[1]. High-gradient AS (HG-AS) can be assumed to be severe irrespective of left ventricular (LV) function and flow condition, and current guidelines recommend aortic valve intervention for symptomatic HG-AS[2,3]. Low-gradient AS (LG-AS) is a unique entity, accounting for nearly 40% of patients with symptomatic, severe AS. The low-gradient state may represent a more advanced stage of severe AS than HG-AS due to impaired LV function or altered LV morphology caused by long-standing outflow obstruction; however, it may also be caused by other cardiac factors such as coronary artery disease, multivalvular heart disease, and atrial fibrillation (AF), resulting in a considerable heterogeneity of this entity[4]. Although current guidelines indicate that aortic valve replacement therapy is recommended or reasonable in patients with LG-AS and evidence of true stenosis[2,3], the available evidence does not provide guidance on the indications nor the timing at an individual level for this heterogenic group of patients. As a result, patients with LG-AS are less likely to undergo aortic valve replacement therapy when compared to those with HG-AS, despite their poor prognosis[5].

Recently, Généreux et al proposed a new staging classification to semiquantitatively assess the extent of extra-aortic valve cardiac damage[6]. Several studies demonstrated a strong prognostic impact of the staging classification in patients undergoing transcatheter aortic valve implantation (TAVI)[7-10], and the concept may provide further insights into the indications and appropriate timing of TAVI for each AS subtype. In the present study, we aimed to investigate the extent of extra-aortic valve cardiac damage and its prognostic impact in patients with HG-AS and LG-AS who underwent TAVI.

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Methods

STUDY DESIGN AND POPULATION

Between August 2007 and June 2022, consecutive AS patients undergoing TAVI at Bern University Hospital (Bern, Switzerland) were enrolled into an institutional prospective registry. The registry is part of the nationwide SwissTAVI Registry (ClinicalTrials.gov: NCT01368250)[11]. For the purpose of the present study, we excluded 1,405 patients with incomplete or unavailable baseline echocardiographic images to assess cardiac damage according to the staging classification proposed by Généreux and colleagues. After dividing patients into HG-AS and LG-AS groups, LG-AS was categorised into 3 subtypes according to LV systolic function and flow status. During this process, 19 patients without information on stroke volume index (SVI) and 1 patient with missing data on LV ejection fraction (LVEF) were excluded. The registry is approved by the Bern cantonal ethics committee, and patients provided written informed consent for participation.

CARDIAC DAMAGE STAGING CLASSIFICATION

The presence and extent of cardiac damage were evaluated prior to TAVI based on the modified staging scheme[6,9,12]. Patients were classified into the following stages: Stage 0 – no extra-aortic valve cardiac damage; Stage 1 – LV damage (LVEF <60%, LV mass index >95 g/m^2 in women or >115 g/m^2 in men, or LV diastolic dysfunction ≥grade II); Stage 2 – left atrial (LA) or mitral valve damage (LA volume index >34 ml/m^2, mitral regurgitation ≥moderate, or presence of AF); Stage 3 – pulmonary vasculature or tricuspid valve damage (systolic pulmonary artery pressure [PAP] ≥60 mmHg, mean PAP ≥25 mmHg, or tricuspid regurgitation ≥moderate); and Stage 4 – right ventricular (RV) damage. PAP was obtained from either right heart catheterisation or echocardiographic measurements[12]. Patients were hierarchically classified into the most advanced stage if at least one of the criteria was met within that stage. Based on the considerable difference in prognostic impact[13], we grouped these five stages into early stage disease (stage 0, 1, and 2) and advanced stage disease (stage 3 and 4) as previously validated[14].

DEFINITION OF AS SUBTYPES

HG-AS was defined as an aortic valve area (AVA) ≤1.0 cm^2 and aortic mean gradient (MG) ≥40 mmHg. Classical low-flow (LF) LG-AS was defined as an AVA <1 cm^2, LVEF <50%, MG <40 mmHg, and SVI <35 ml/m^2. LF LG-AS with preserved ejection fraction (EF) was defined as an AVA <1 cm^2, LVEF ≥50%, MG <40 mmHg, and SVI <35 ml/m^2. Normal-flow (NF) LG-AS was defined as an AVA <1 cm^2, LVEF ≥50%, MG <40 mmHg, and SVI >35 ml/m^2. Aortic-valvular complex calcification was assessed using the end-systolic phase of computed tomography by a dedicated core lab, and the device landing zone calcium volume was quantified in the contrast images using a predefined Hounsfield unit threshold of 850, as previously validated[15]. Dobutamine stress echocardiography, which can be useful in the diagnosis of LG-AS, was not routinely performed.

ECHOCARDIOGRAPHY

Comprehensive transthoracic echocardiography was performed by a board-certified cardiologist and echocardiography specialist within 3 months before TAVI in accordance with the current American Society of Echocardiography guidelines[16]. Acquired images were independently re-evaluated by experienced imaging specialists in the Bern imaging core laboratory (Bern, Switzerland). Stroke volume was derived from the cross-sectional area of the LV outflow tract multiplied by the time-velocity integral of flow by pulsed-wave Doppler at that location. RV

function was assessed as previously described, and RV dysfunction was documented in the presence of at least two of the following parameters: tricuspid annular plane systolic excursion <1.7 cm, tricuspid annular peak systolic velocity (S') <9.5 cm/s and fractional area change <35%[17].

DATA COLLECTION AND CLINICAL ENDPOINTS

Baseline clinical, procedural, and follow-up data were prospectively recorded in a dedicated database held at the Clinical Trials Unit of the University of Bern, Switzerland. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee based on the Valve Academic Research Consortium definitions applicable at the time of the procedure[18-20]. The primary outcome of interest in the present study was all-cause mortality after TAVI.

STATISTICAL ANALYSIS

Categorical variables are represented as frequencies and percentages, and the differences between groups were evaluated with the Veni test or Fisher's exact test. Continuous variables are presented as mean values±standard deviation and compared between groups using the F-test in an analysis of variance (ANOVA) or Kruskal-Wallis test in combination with pairwise Wilcoxon test with correction for multiple testing, as appropriate. Risk ratios with 95% confidence intervals (CIs) from Poisson regressions were provided where appropriate. Time-to-event curves were constructed using the Kaplan-Meier method; a comparison of cumulative event rates between these groups was performed by log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% CIs for the clinical outcomes. Age, sex, and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), baseline LVEF, baseline New York Heart Association (NYHA) Functional Class III or IV, estimated glomerular filtration rate, and the year of TAVI (the study period was divided into tertiles [1st: up to 20 May 2014; 2nd: 20 May 2014 to 12 August 2017; 3rd: 12 August 2017 to 30 June 2022]) were selected and introduced as covariates in multivariable Cox proportional hazards models. SPSS software version 23.0 (IBM) was used for statistical analysis. All statistical tests were 2-sided, and p-values<0.05 were considered significant.

Results

STUDY POPULATION AND BASELINE CHARACTERISTICS

Among 3,586 consecutive patients undergoing TAVI between August 2007 and June 2022, 2,090 patients were included in the present analysis. Of these, 1,045 patients (50.0%) had HG-AS, 337 patients (16.1%) had classical LF LG-AS, 394 patients (18.9%) had LF LG-AS with preserved EF, and 314 patients (15.0%) had NF LG-AS **(Figure 1)**. Baseline characteristics according to each AS subtype are shown in **Table 1**. The prevalence of cardiac damage stage across different subtypes of AS is summarised in **Figure 2** and the **Central illustration**. An advanced stage of cardiac damage was most prevalent among patients with classical LF LG-AS (73.6%), followed by LF LG-AS with preserved EF (55.6%), NF LG-AS (51.6%), and HG-AS (50.6%).

In patients with HG-AS, approximately half (50.6%) had advanced cardiac damage. Patients with advanced stage cardiac damage had a higher surgical risk (STS-PROM: 6.2±4.7% vs 4.7±3.1%; p<0.001), worse heart failure symptoms (NYHA Functional Class III or IV: 68.6% vs 61.2%; p=0.012), and a lower LVEF (53±14% vs 61±10%; p<0.001) than those with early stage cardiac damage. Chronic kidney disease, AF, previous myocardial infarction, previous cardiac surgery, and previous permanent pacemaker implantation were more common in patients with advanced compared to early stage cardiac damage (73.5% vs 64.3%; p=0.001; 35.3% vs 24.0%; p<0.001; 14.2% vs 8.7%;

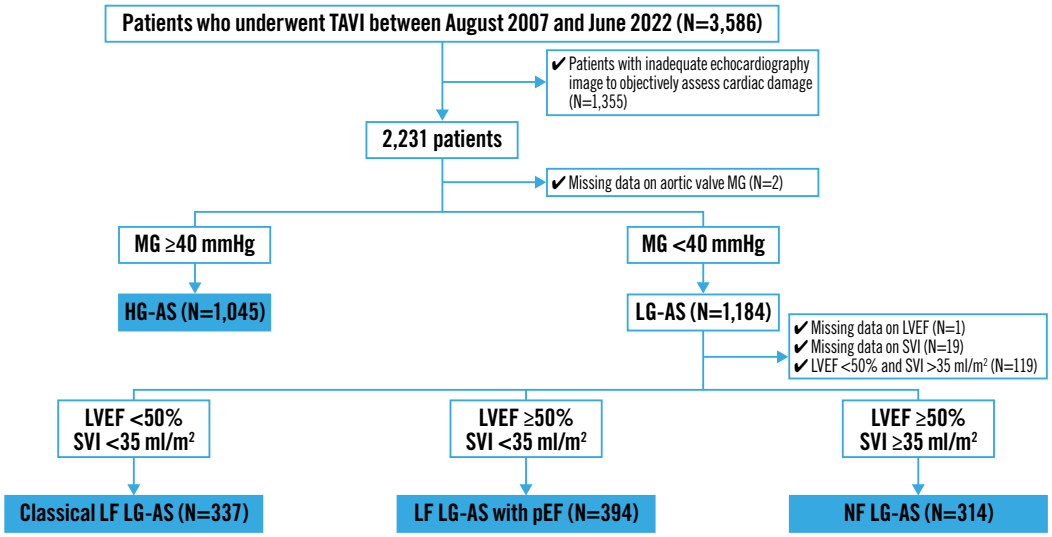

Figure 1. *Study flowchart. AS: aortic stenosis; HG: high gradient; LF: low flow; LG: low gradient; LVEF: left ventricular ejection fraction; MG: mean gradient; NF: normal flow; pEF: preserved ejection fraction; SVI: stroke volume index; TAVI: transcatheter aortic valve implantation*

Table 1. Baseline characteristics according to AS subtypes.

	HG-AS	Classical LF LG-AS	LF LG-AS with pEF	NF LG-AS	*p*-value
	N=1,045	N=337	N=394	N=314	
Age, years	82.4±5.9[bd]	81.0±7.5[a]	82.0±6.6	81.5±6.3[a]	0.073
Female	565 (54.1)[b]	109 (32.3)[acd]	220 (55.8)[b]	155 (49.4)[b]	<0.001
Body mass index, kg/m²	26.4±5.5[c]	25.8±5.2[c]	27.0±5.7[abd]	25.9±5.1[c]	0.018
STS-PROM, %	5.4±4.1[b]	7.0±5.3[acd]	5.1±3.2[b]	5.1±3.5[b]	<0.001
NYHA III or IV	679 (65.0)[b]	262 (78.0)[acd]	273 (69.3)[b]	197 (62.7)[b]	<0.001
Concomitant diseases					
Hypertension	882 (84.4)[d]	289 (85.8)	342 (86.8)	280 (89.2)[a]	0.177
Diabetes mellitus	256 (24.5)[b]	113 (33.5)[ad]	116 (29.4)	76 (24.2)[b]	0.004
CKD (eGFR <60 ml/min/1.73 m²)	720 (69.0)	238 (70.6)	267 (67.8)	219 (70.0)	0.847
eGFR, ml/min/1.73 m²	52.5±21.7[b]	50.2±22.1[ac]	53.1±21.6[b]	50.6±22.5	0.088
COPD	114 (10.9)[c]	47 (14.0)	61 (15.5)[a]	43 (13.7)	0.088
Coronary artery disease	580 (55.5)[bd]	231 (68.5)[ac]	240 (60.9)[b]	194 (61.8)[a]	<0.001
Atrial fibrillation	311 (29.8)[bc]	161 (47.8)[ad]	167 (42.4)[ad]	104 (33.1)[bc]	<0.001
Previous history					
Previous myocardial infarction	120 (11.5)[b]	97 (28.8)[acd]	51 (12.9)[b]	40 (12.7)[b]	<0.001
Previous cardiac surgery	109 (10.4)[bcd]	81 (24.0)[ac]	64 (16.2)[ab]	57 (18.2)[a]	<0.001
Previous stroke	115 (11.0)[b]	52 (15.4)[a]	49 (12.4)	44 (14.0)	0.141
Previous permanent pacemaker implantation	63 (6.0)[bc]	49 (14.5)[ad]	42 (10.7)[a]	28 (8.9)[b]	<0.001
Peripheral artery disease	138 (13.2)[b]	61 (18.1)[a]	57 (14.5)	43 (13.7)	0.165
Echocardiography					
Aortic valve area, cm²	0.63±0.23[bcd]	0.76±0.28[ad]	0.77±0.26[ad]	0.85±0.30[abc]	<0.001
Mean aortic valve pressure gradient, mmHg	53±13[bcd]	24±9[acd]	27±8[ab]	28±9[ab]	<0.001
Left ventricular ejection fraction, %	57±13[bcd]	32±11[acd]	61±7[abd]	63±7[abc]	<0.001
Left ventricular mass index, g/m²	139±44[bcd]	147±51[acd]	121±41[ab]	124±41[ab]	<0.001
Left atrial volume index, ml/m²	43±16[bcd]	49±23[acd]	42±17[ab]	42±24[ab]	<0.001
Mitral regurgitation ≥moderate	217 (21.0)[b]	141 (42.7)[acd]	80 (20.6)[b]	59 (19.2)[b]	<0.001
Tricuspid regurgitation ≥moderate	161 (15.6)[bc]	90 (27.4)[ad]	84 (21.6)[a]	52 (16.7)[b]	<0.001
Systolic pulmonary artery pressure, mmHg	46±18[bd]	49±19[acd]	46±18[bd]	43±16[abc]	<0.001
Tricuspid annular plane systolic excursion, mm	21±5[bc]	17±6[acd]	19±5[abd]	21±5[bc]	<0.001
Stroke volume index, ml/m²	34±12[bcd]	25±6[acd]	26±6[abd]	45±12[abc]	<0.001
Computed tomography					
Aortic valvular complex calcification, mm³	442.4±423.8[bcd]	213.3±229.9[a]	206.3±273.2[a]	200.3±203.6[a]	<0.001
Right heart catheterisation					
Mean pulmonary artery pressure, mmHg	31±12[bd]	34±12[acd]	30±12[bd]	28±9[abc]	<0.001

Data are presented as n (%) or mean±standard deviation. [a]p-value<0.05 versus HG-AS. [b]p-value<0.05 versus classical LF LG-AS. [c]p-value<0.05 versus LF LG-AS with pEF. [d]p-value <0.05 versus NF LG-AS. AS: aortic stenosis; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; HG: high gradient; LF: low flow; LG: low gradient; NF: normal flow; NYHA: New York Heart Association; pEF: preserved ejection fraction; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

p=0.006; 12.5% vs 8.3%; p=0.028; and 7.6% vs 4.5%; p=0.035, respectively) **(Supplementary Table 1)**.

The majority of patients with classical LF LG-AS (73.6%) had advanced cardiac damage. Patients in this subgroup with advanced cardiac damage were comparable in terms of surgical risk and comorbidities to patients with early stage cardiac damage, except for the presence of AF (51.2% vs 38.2%; p=0.035). LVEF was lower in patients with advanced cardiac damage compared with those with early cardiac damage (31±12% vs 35±10%; p=0.004) **(Supplementary Table 2)**.

LF LG-AS with preserved EF patients had advanced cardiac damage in 55.6% of cases. Patients in this particular group were found to have higher surgical risk (STS-PROM: 5.5±3.5% vs 4.7±2.6%; p=0.009), higher prevalence of AF (55.3% vs 26.3%; p<0.001), and a lower LVEF (60±7% vs 63±7%; p<0.001) compared to those with early stage cardiac damage **(Supplementary Table 3)**.

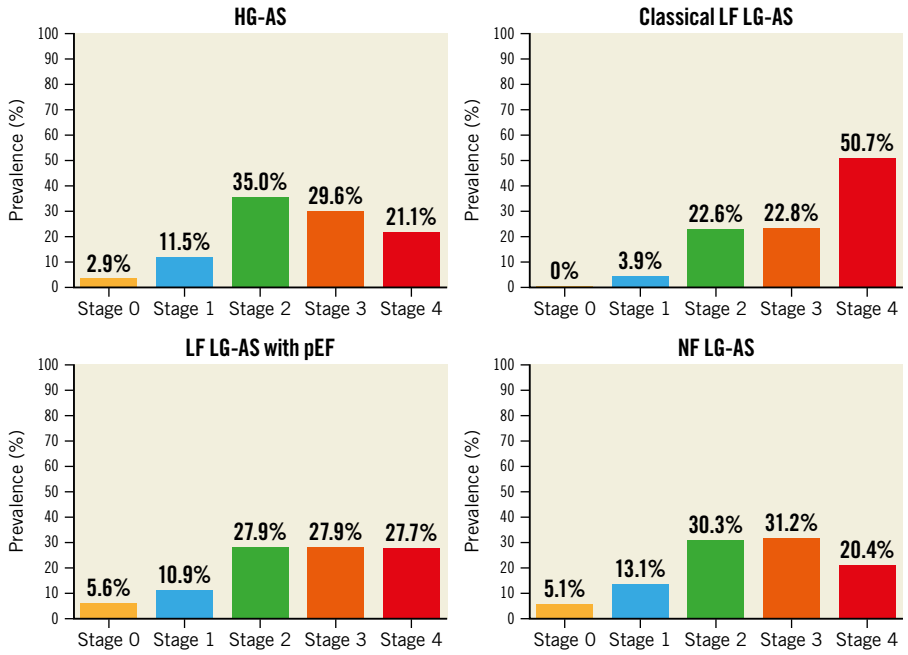

Figure 2. *Distribution of cardiac damage stage according to AS subtype. AS: aortic stenosis; HG: high gradient; LF: low flow; LG: low gradient; NF: normal flow; pEF: preserved ejection fraction*

In NF LG-AS patients, 162 (51.6%) were in an advanced stage of cardiac damage. They had worse heart failure symptoms (NYHA Functional Class III or IV: 69.1% vs 55.9%; p=0.016) and a lower LVEF (62±7% vs 64±7%; p=0.040) compared to patients with early stage cardiac damage. Along the same line, hypertension (93.8% vs 84.2%; p=0.006), coronary artery disease (68.5% vs 54.6%; p=0.011), and a history of cardiac surgery (22.8% vs 13.2%; p=0.026) were more common in patients with advanced stage cardiac damage than those with early stage damage **(Supplementary Table 4)**.

The prevalence of AF was higher in the advanced stages than in the early stages of cardiac damage across all AS subtypes.

CLINICAL OUTCOMES

At a median follow-up of 1,095 (interquartile range 365-1,825) days after TAVI, mortality was highest in patients with classical LF LG-AS (63.0%), followed by LF LG-AS with preserved EF (53.1%), HG-AS (46.1%), and NF LG-AS (41.1%), reflecting the respective proportions of advanced cardiac damage **(Figure 3)**. Adjusted HRs of all-cause and cardiovascular mortality in patients with advanced compared to early stage cardiac damage in each subtype of AS are summarised in the **Central illustration** and **Table 2**. The presence of advanced cardiac damage was independently associated with higher all-cause mortality, regardless of the AS subtype ($HR_{adjusted}$ 1.66, 95% CI: 1.34-2.06; p<0.001 for HG-AS; $HR_{adjusted}$ 1.49; 95% CI: 1.02-2.16; p=0.043 for classical LF LG-AS; $HR_{adjusted}$ 1.69; 95% CI: 1.22-2.35; p=0.002 for LF LG-AS with preserved LVEF; and $HR_{adjusted}$ 1.52; 95% CI: 1.04-2.32; p=0.042 for NF LG-AS, respectively). A detailed analysis differentiating four cardiac stages (stage 0 or 1, stage 2, stage 3, and stage 4) in each AS subtype is shown in **Figure 4** and **Supplementary Table 5**.

Discussion

The main findings of the current study are as follows: 1) the majority of patients with classical LF LG-AS had evidence of advanced cardiac damage, followed by LF LG-AS with preserved EF, NF LG-AS, and HG-AS in descending order. 2) Mortality in both early and advanced stages was highest in patients with classical LF LG-AS, followed by LF LG-AS with preserved EF, HG-AS, and NF LG-AS. 3) Advanced cardiac damage conferred an increased mortality risk after TAVI irrespective of the AS subtype.

The cardiac damage staging classification characterising the extent of extra-aortic valve cardiac damage, as proposed by Généreux and colleagues, has important prognostic implications in patients undergoing TAVI[6]. The prognostic model was validated and refined in several populations, including symptomatic and asymptomatic AS patients[7-10]. In these studies, patients with LG-AS represented 20-30% of the total population, and this proportion increased with progressive stages of advanced cardiac damage. Recently, Snir et al reported that advanced cardiac damage was observed in 34.0% of classical LF LG-AS patients, 22.5% of LF LG-AS patients with preserved EF, 15.5% of NF LG-AS patients, and 14.0% of HG-AS patients[21]. Consistent with these results, the present study demonstrated that an advanced stage of cardiac damage was most common in classical LF LG-AS (73.6%), followed by LF LG-AS with preserved EF (55.6%), NF LG-AS (51.6%), and HG-AS (50.6%). The marked prevalence of advanced cardiac damage in our study, compared to the previous study, may be attributed, at least in part, to differences in the

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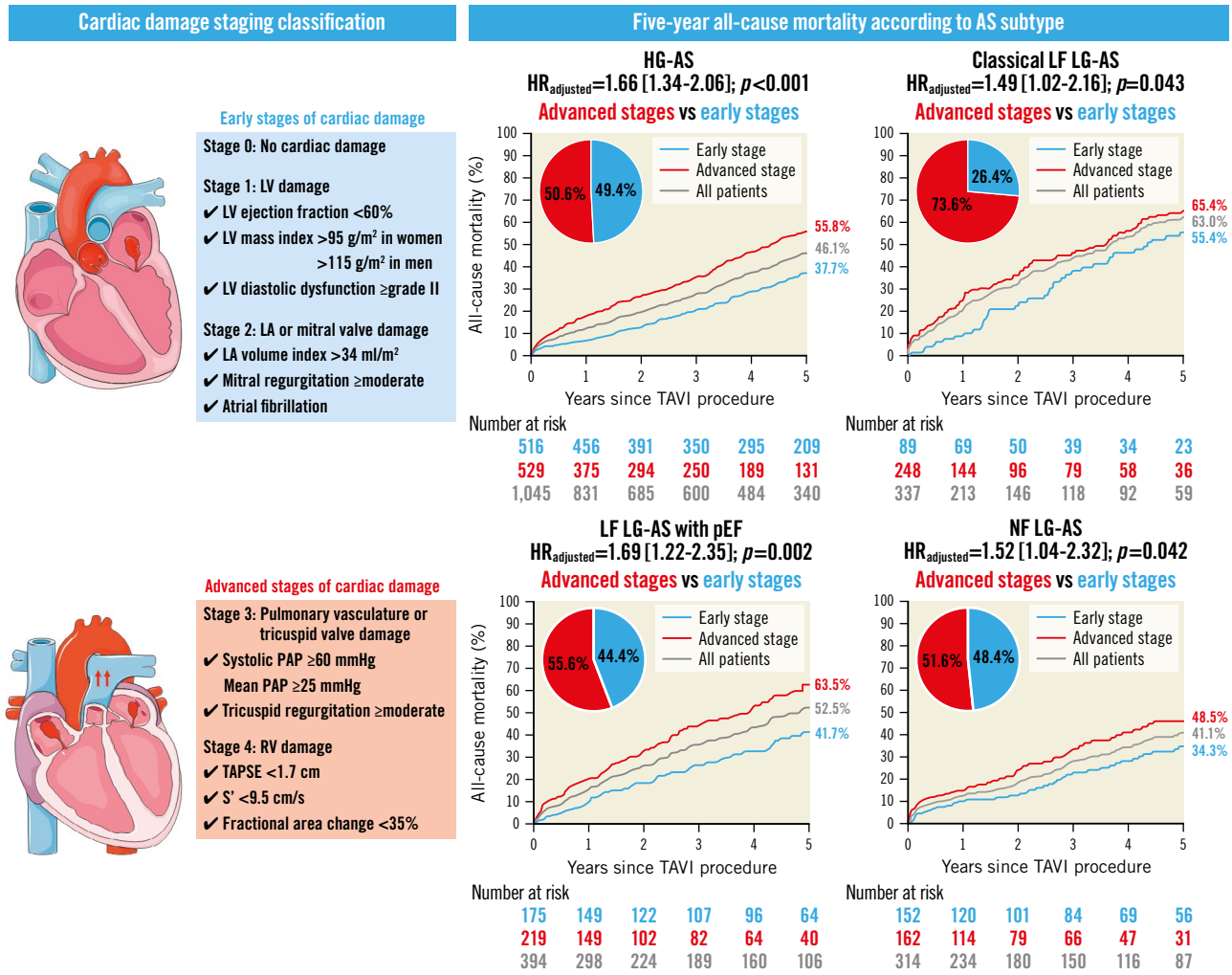
CENTRAL **ILLUSTRATION** 5-year all-cause mortality according to cardiac damage staging classification in each AS subtype.



AS: aortic stenosis; HG: high gradient; HR: hazard ratio; LA: left atrial; LF: low flow; LG: low gradient; LV: left ventricular; NF: normal flow; PAP: pulmonary artery pressure; pEF: preserved ejection fraction; RV: right ventricular; S': tricuspid annular peak systolic velocity; TAPSE: tricuspid annular plane systolic excursion; TAVI: transcatheter aortic valve implantation

studied populations. Whereas the previous study was based on a national echo database in which only 20% of patients underwent aortic valve intervention, our study focused on elderly patients with symptomatic severe AS undergoing TAVI. Moreover, using an echocardiographic guideline-based definition of RV dysfunction may have enhanced the sensitivity in identifying patients with advanced cardiac damage in the present study[7].

Previous studies have shown that patients with advanced cardiac stage were likely to be at higher surgical risk and have a higher prevalence of comorbidities[7-10]. In the present study, this observation was corroborated across the haemodynamic spectrum of AS. Furthermore, there was a higher proportion of women in advanced stages of cardiac damage across all AS subtypes, corroborating previous observations that women with AS tend to be underdiagnosed and undertreated[22]. We found that an advanced stage of cardiac damage conferred an approximately 1.5-fold increased risk of mortality across all AS subtypes, thus, underscoring the importance of timely aortic valve intervention before the development of secondary cardiac damage. However, a higher mortality was observed in classical LF LG-AS patients compared to other AS subtypes, even in the early stages.

Myocardial fibrosis, as indicated by the presence of late gadolinium enhancement, was more frequently observed in classical LF LG-AS[23], implying that it is the most advanced AS phenotype; this is supported by our finding that more than 70% of patients with classical LF LG-AS are in an advanced stage of cardiac damage. However, considering that patients with classical LF LG-AS had larger AVA than those patients with HG-AS in the present study, this subtype is not necessarily a late presentation of AS. In classical LF LG-AS, the LF haemodynamic state is usually caused

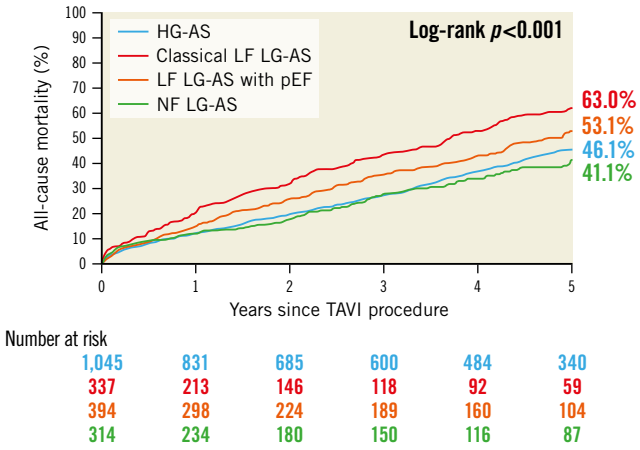


Figure 3. *Five-year all-cause mortality according to AS subtype. AS: aortic stenosis; HG: high gradient; LF: low flow; LG: low gradient; NF: normal flow; pEF: preserved ejection fraction; TAVI: transcatheter aortic valve implantation*

by impaired LV function due to afterload mismatch by chronic AS or concomitant cardiomyopathy, frequently as a result of coronary artery disease[4]. Indeed, in the present study, patients with classical LF LG-AS were more likely to be male and had the highest frequency of cardiovascular disease, chronic obstructive pulmonary disease, history of myocardial infarction and cardiac surgery, which may contribute to impaired LV systolic function. In the analysis from the PARTNER 2 trials, a lower proportion of patients with advanced cardiac damage had cumulative damage from earlier stages[6]. Nevertheless, this group showed that persistent cardiac damage after aortic intervention was associated with a worse prognosis[24]. These findings suggest that the development of cardiac damage is also driven by comorbid and/or underlying disease and highlight the importance of targeted-treatment strategies for the underlying disease in patients with severe AS referred for aortic valve intervention.

In contrast, patients with NF LG-AS featured the least extent of cardiac damage and experienced lower all-cause mortality

Table 2. Clinical outcomes according to cardiac damage in each AS subtype.

	HG-AS	Classical LF LG-AS	LF LG-AS with pEF	NF LG-AS
All-cause mortality at 1 year				
Early stage	35 (7.1)	7 (9.5)	17 (10.2)	15 (11.1)
	reference	reference	reference	reference
Advanced stage	89 (19.3)	57 (28.6)	42 (22.2)	23 (16.9)
	HR 2.39 [1.57-3.66]	HR 3.24 [1.46-7.19]	HR 1.65 [0.90-3.01]	HR 1.31 [0.67-2.58]
	p<0.001	*p*=0.004	*p*=0.105	*p*=0.432
Cardiovascular mortality at 1 year				
Early stage	21 (4.3)	4 (5.4)	11 (6.6)	5 (3.7)
	reference	reference	reference	reference
Advanced stage	59 (12.8)	44 (22.1)	31 (16.4)	14 (10.3)
	HR 2.47 [1.43-4.27]	HR 4.21 [1.49-11.86]	HR 1.78 [0.85-3.73]	HR 2.40 [0.84-6.87]
	p=0.001	*p*=0.007	*p*=0.129	*p*=0.102
All-cause mortality at 5 years				
Early stage	164 (37.7)	37 (55.4)	63 (41.7)	41 (34.3)
	reference	reference	reference	reference
Advanced stage	233 (55.8)	114 (65.4)	106 (63.5)	55 (48.5)
	HR 1.66 [1.34-2.06]	HR 1.49 [1.02-2.16]	HR 1.69 [1.22-2.35]	HR 1.52 [1.04-2.32]
	p<0.001	*p*=0.043	*p*=0.002	*p*=0.042
Cardiovascular mortality at 5 years				
Early stage	103 (26.7)	26 (42.7)	44 (32.7)	25 (24.4)
	reference	reference	reference	reference
Advanced stage	166 (45.4)	91 (58.4)	74 (51.6)	38 (37.6)
	HR 1.90 [1.45-2.47]	HR 1.60 [1.02-2.50]	HR 1.71 [1.15-2.53]	HR 1.59 [0.93-2.68]
	p<0.001	*p*=0.040	*p*=0.008	*p*=0.105

Data are presented as n (%) or HR with 95% CI. HR was adjusted by age, sex, Society of Thoracic Surgeons Predicted Risk of Mortality, left ventricular ejection fraction, New York Heart Association Class III or IV, estimated glomerular filtration rate, and the year of transcatheter aortic valve implantation. AS: aortic stenosis; CI: confidence interval; HG: high gradient; HR: hazard ratio; LF: low flow; LG: low gradient; NF: normal flow; pEF: preserved ejection fraction

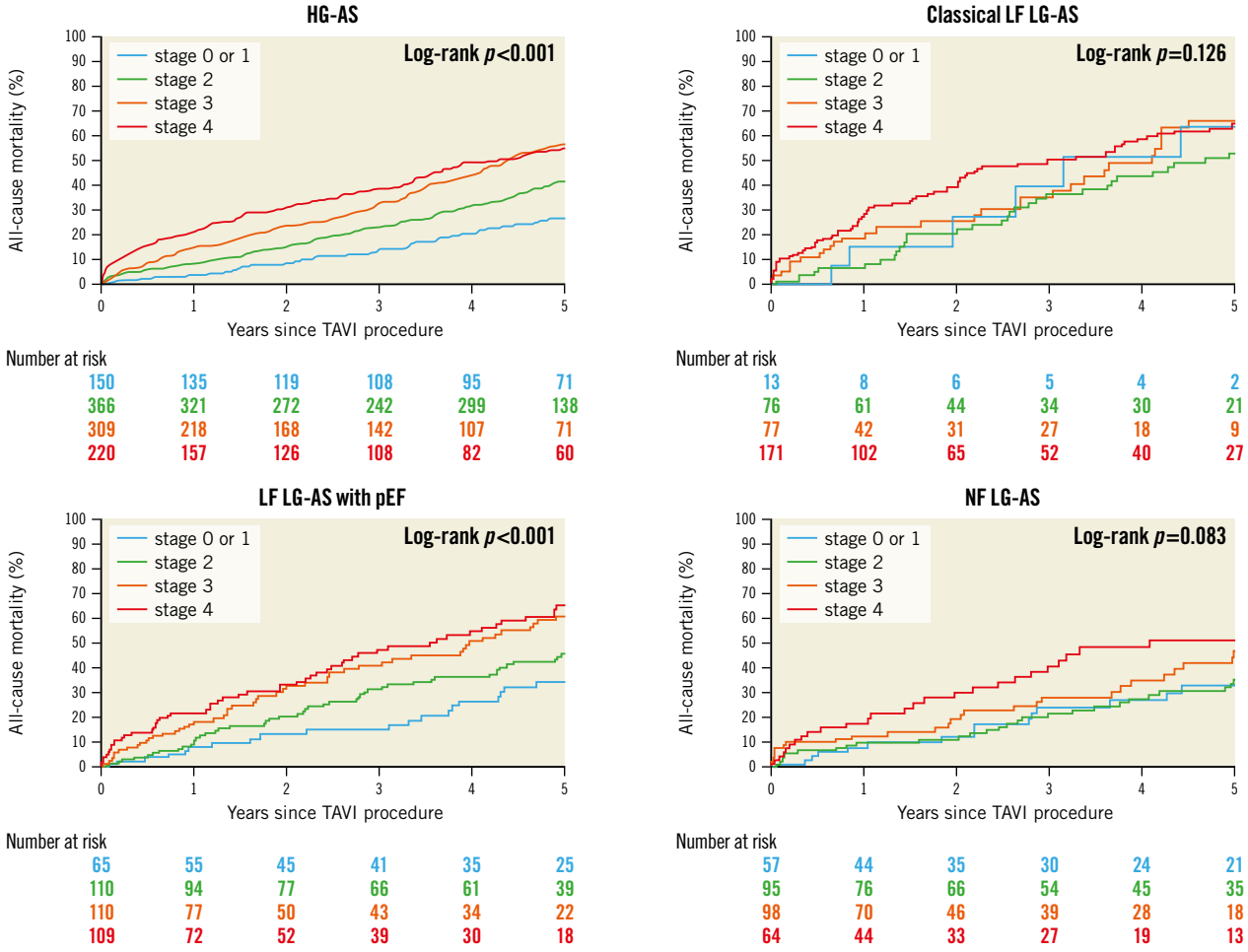


Figure 4. *Five-year all-cause mortality according to four cardiac damage stages. AS: aortic stenosis; HG: high gradient; LF: low flow; LG: low gradient; NF: normal flow; pEF: preserved ejection fraction; TAVI: transcatheter aortic valve implantation*

compared with other AS subtypes, thus, supporting the notion that NF LG-AS represents only moderate to borderline severe AS[3,25-27]. Nevertheless, a recent study in 1,245 individuals reported that 17.5% of patients with moderate AS exhibited advanced cardiac damage and demonstrated a stepwise increase in long-term mortality according to cardiac damage stage[28]. Our findings corroborate these results by showing a significantly higher mortality in patients with advanced stages of cardiac damage compared to those in an earlier stage. Interestingly, however, patients with NF LG-AS had lower mortality than other AS subtypes, despite features of advanced cardiac damage. A previous study suggested that a proportion of patients exhibit regression of cardiac damage following TAVI[24]. It can therefore be hypothesised that advanced cardiac damage is reversible in patients with NF LG-AS and may improve after TAVI. An ongoing clinical trial will provide further insight into the clinical benefit of early intervention in patients with less severe AS and delineate the importance of cardiac damage in this population (PROGRESS; ClinicalTrials.gov: NCT04889872).

Limitations

The present analysis is a retrospective, observational, single-centre study with inherent limitations. First, more than 40% of the patients were excluded because of inadequate echocardiography for assessment of cardiac damage classification and AS subtype, which may have resulted in some degree of selection bias. As shown in **Supplementary Table 6**, patients included in the present analyses were older, had a higher surgical risk and a higher prevalence of comorbidities compared with those excluded from the present analysis. Second, as we did not routinely perform dobutamine stress echocardiography in patients with classical LF LG-AS, patients with pseudo-severe AS may have been included in this study. Furthermore, this study may have included some patients with moderate AS in the NF LG-AS group (AVA 0.85±0.30 cm²). However, all patients underwent intervention after thorough clinical assessment and interdisciplinary discussion within the Heart Team. Third, due to the small number of patients in each AS subtype, especially early stages, this study may have been underpowered to detect the smaller effect sizes of earlier cardiac damage stages. Furthermore, grouping cardiac damage into early and advanced stages is arbitrary. Finally, we did not investigate follow-up echocardiography after TAVI. Further studies on the evolution of cardiac damage and its impact on clinical outcomes in each AS subtype are needed.

Conclusions

Staging classifications of AS according to extra-aortic valve cardiac damage successfully stratified mortality after TAVI in all AS subtypes. It is essential to identify AS patients at an early stage of secondary cardiac damage and perform TAVI before progression to more advanced stages, irrespective of AS subtype. However, in patients with classical LF LG-AS, a conservative control group is mandatory for comparison to ultimately quantify the net benefit of TAVI in accordance with the staging classification of the extra-aortic valve cardiac damage.

Impact on daily practice

The staging system provided prognostic value across all AS subtypes. However, higher mortality was observed in classical LF LG-AS patients compared to other AS subtypes, even in the early stages. In this particular population, the risks and benefits of TAVI should be carefully weighed.

Conflict of interest statement

S. Windecker reports research and educational grants to the institution from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Bayer AG, Biotronik, Boston Scientific, Cardinal Health, CardioValve (Venus Medtech), CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer, Regeneron, Sanofi-Aventis, Sinomed, Terumo, and V-Wave. S. Windecker serves as an unpaid advisory board member and/or unpaid member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, AstraZeneca, Bristol-Myers Squibb, Boston Scientific, Biotronik, CardioValve (Venus Medtech), Edwards Lifesciences, MED Alliance, Medtronic, Novartis, Polares, Sinomed, V-Wave, and Xeltis, but has not received personal payments from pharmaceutical companies or device manufacturers. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding from industry without impact on his personal remuneration. S. Windecker is an unpaid member of the Pfizer Research Award selection committee in Switzerland and of the Women as One Awards Committee. He is a member of the Clinical Study Group of the Deutsches Zentrum für Herz-Kreislauf-Forschung and of the Advisory Board of the Australian Victorian Heart Institute. He is Chairperson of the ESC Congress Program Committee and Deputy Editor of JACC Cardiovascular Interventions. T. Pilgrim reports research grants to the institution from Edwards Lifesciences and Biotronik; and personal fees from Biotronik, Medtronic, Abbott, Edwards Lifesciences, and HighLife SAS. S. Stortecky reports research grants to the institution from Edwards Lifesciences, Medtronic, Abbott, and Boston Scientific; and personal fees from Boston Scientific, Teleflex, and BTG. F. Praz reports travel expenses from Abbott, Edwards Lifesciences, and Polares Medical. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Baseline characteristics of high-gradient aortic stenosis.

Supplementary Table 2. Baseline characteristics of classical low-flow low-gradient aortic stenosis.

Supplementary Table 3. Baseline characteristics of low-flow low-gradient aortic stenosis with preserved ejection fraction.

Supplementary Table 4. Baseline characteristics of normal-flow low-gradient aortic stenosis.

Supplementary Table 5. Clinical outcomes according to four cardiac stages in each AS subtype.

Supplementary Table 6. Comparison of baseline characteristics between included and excluded patients.

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