

Staging Cardiac Damage in Patients With Asymptomatic Aortic Valve Stenosis



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ABSTRACT

BACKGROUND The optimal timing of intervention in patients with asymptomatic severe aortic stenosis (AS) remains controversial.

OBJECTIVES This multicenter study sought to test and validate the prognostic value of the staging of cardiac damage in patients with asymptomatic moderate to severe AS.

METHODS This study retrospectively analyzed the clinical, Doppler echocardiographic, and outcome data that were prospectively collected in 735 asymptomatic patients (71 ± 14 years of age; 60% men) with at least moderate AS (aortic valve area <1.5 cm²) and preserved left ventricular ejection fraction (≥50%) followed in the heart valve clinics of 4 high-volume centers. Patients were classified according to the following staging classification: no cardiac damage associated with the valve stenosis (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 damage or subclinical heart failure (Stage 4). The primary endpoint was all-cause mortality.

RESULTS At baseline, 89 (12%) patients were classified in Stage 0, 200 (27%) in Stage 1, 341 (46%) in Stage 2, and 105 (14%) in Stage 3 or 4. Median follow-up was 2.6 years (interquartile range: 1.1 to 5.2 years). There was a stepwise increase in mortality rates according to staging: 13% in Stage 0, 25% in Stage 1, 44% in Stage 2, and 58% in Stages 3 to 4 (p < 0.0001). The staging was significantly associated with excess mortality in multivariable analysis adjusted for aortic valve replacement as a time-dependent variable (hazard ratio: 1.31 per each increase in stage; 95% CI: 1.06 to 1.61; p = 0.01), and showed incremental value to several clinical variables (net reclassification index = 0.34; p = 0.003).

CONCLUSIONS The new staging system characterizing the extra-aortic valve cardiac damage provides incremental prognostic value in patients with asymptomatic moderate to severe AS. This staging classification may be helpful to identify asymptomatic AS patients who may benefit from elective aortic valve replacement.

(J Am Coll Cardiol 2019;74:550-63) © 2019 by the American College of Cardiology Foundation.

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Calcific aortic stenosis (AS) is the most prevalent valvular heart disease in high-income countries, and the burden of the disease is expected to increase dramatically in the next 20 years with the aging of the population (1). Aortic valve replacement (AVR), either surgical or transcatheter, remains the sole effective treatment for severe AS (2,3). Current guidelines recommend AVR in patients with hemodynamically severe AS and symptoms related to the severity of valve stenosis or left ventricular (LV) systolic dysfunction defined by a LV ejection fraction (LVEF) <50% (2,3). However, management of patients with severe asymptomatic AS and normal LVEF remains controversial (4,5). American guidelines recommend (Class IIa) AVR in patients with very severe (peak aortic jet velocity [V_{peak}] >5 m/s) or rapid AS progression and with low surgical risk (6). Ongoing randomized trials are comparing “watchful waiting” versus early AVR strategies in patients with asymptomatic severe AS (7).

Recently, Généreux et al. (8) proposed a new staging classification characterizing the extent of extra-aortic valve cardiac damage and reported that this staging system has strong prognostic implication in patients with severe symptomatic AS undergoing AVR. We hypothesized that this cardiac damage staging may enhance risk stratification in asymptomatic moderate to severe AS. The objective of this international multicenter study was to assess the prognostic value of the cardiac damage staging classification in patients with asymptomatic moderate to severe AS.

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METHODS

STUDY GROUP. The registry included anonymized data of patients evaluated at heart valve clinics, as defined by the European Society of Cardiology Working Group in Valvular Heart Diseases (9), of 4 high-volume centers. This registry included the data of 1,655 consecutive patients with moderate to severe AS, defined as aortic valve area <1.5 cm², who were

prospectively recruited and followed between February 1998 and July 2017. Exclusion criteria were a history of rheumatic valve disease, endocarditis, more than mild aortic regurgitation or mitral stenosis, LVEF <50%, pregnant or breast-feeding women, and previous valve repair or replacement. Patients presenting with symptoms at baseline, including exertional dyspnea, angina, presyncope, or syncope, were excluded. However, patients with mild symptoms (New York Heart Association [NYHA] functional class II) not considered, by their treating cardiologist, to be related to AS were included. The assessment of patients' symptomatic status was carefully performed by experienced teams of physicians and nurses from specialized heart valve clinics using comprehensive questionnaire and physical examination. Exercise testing was performed in patients with equivocal history or symptoms, as recommended in the guidelines (2). The study group thus included 735 asymptomatic patients (Online Figure 1). The clinical and Doppler echocardiographic data were collected prospectively in the context of heart valve clinics and were retrospectively analyzed. The methods for the definitions and measurements of clinical and Doppler echocardiographic data are described in the Online Appendix. The Institutional Review Board of each participating center approved the study protocol.

CARDIAC DAMAGE STAGING CLASSIFICATION. On the basis of a cardiac damage staging scheme recently proposed by Généreux et al. (8), the following staging classification was first tested: Stage 0, no extra-aortic valve cardiac damage; Stage 1, LV damage as defined by the presence of LV hypertrophy (LV mass index >95 g/m² in women and >115 g/m² in men) (10), and/or elevated LV filling pressures (E/e' ratio >14) (11), and/or ≥mild LV systolic dysfunction (LVEF <60%) (12-15); Stage 2, left atrial (LA) and/or mitral valve damage as defined by the presence of LA enlargement (LA volume >34 ml/m²), and/or atrial

ABBREVIATIONS AND ACRONYMS

AS	= aortic stenosis
AVR	= aortic valve replacement
CI	= confidence interval
GLS	= global longitudinal strain
HR	= hazard ratio
IQR	= interquartile range
LA	= left atrial
LV	= left ventricular
LVEF	= left ventricular ejection fraction
NRI	= net reclassification index
NYHA	= New York Heart Association
RV	= right ventricular
SV	= stroke volume

received speaker fees from Edwards Lifesciences, Medtronic, Tryton Medical, Cardinal Health, Abbott Vascular, and Cardiovascular Systems; has received consulting fees from Boston Scientific, Cardiovascular Systems, Edwards Lifesciences, and Pi-Cardia; has received an institutional research grant from Boston Scientific; has been a proctor for Edwards Lifesciences; has served on the Advisory Boards of Boston Scientific and Cardinal Health; is a principal investigator on the EARLY TAVR trial; and has equity in SIG.NUM, SoundBite Medical Solutions, Saranas, and Pi-Cardia. Dr. Pibarot holds the Canada Research Chair in Valvular Heart Diseases from CIHR; and has received funding from Edwards Lifesciences and Medtronic for echocardiography core laboratory analyses in the field of transcatheter aortic valve replacement with no direct personal compensation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Roberto M. Lang, MD, served as Guest Associate Editor for this paper.

Manuscript received February 12, 2019; revised manuscript received April 11, 2019, accepted April 12, 2019.

TABLE 1 Prevalence of Cardiac Damage Stages and Their Individual Components According to the Original and Modified Staging Scheme

Original Staging Scheme		Modified Staging Scheme	
Stages of cardiac damage		Stages of cardiac damage	
Stage 0: no cardiac damage	109/735 (14.8)	Stage 0: no cardiac damage	89/735 (12.1)
Stage 1: LV damage	195/735 (26.5)	Stage 1: LV damage	200/735 (27.2)
Stage 2: left atrial or mitral valve damage	368/735 (50.1)	Stage 2: left atrial or mitral valve damage	341/735 (46.4)
Stage 3: pulmonary vasculature or tricuspid valve damage	16/735 (2.2)	Stage 3: pulmonary vasculature or tricuspid valve damage	15/735 (2.0)
Stage 4: RV damage	47/735 (6.4)	Stage 4: RV damage or subclinical heart failure	90/735 (12.2)
Individual components of cardiac damage		Individual components of cardiac damage	
Stage 1: LV damage	531/735 (72.2)	Stage 1: LV damage	594/735 (80.8)
LV hypertrophy (>95 g/m ² women; >115 g/m ² men)	407/708 (57.5)	LV hypertrophy (>95 g/m ² women; >115 g/m ² men)	407/708 (57.5)
E/e' >14	189/544 (34.7)	LV diastolic dysfunction ≥ grade II*	348/730 (47.7)
LV ejection fraction <60%	206/735 (28.0)	LV subclinical systolic dysfunction†	226/735 (30.8)
		Impaired LV global longitudinal strain ≤15%	38/250 (15.2)
		LV ejection fraction <60%	206/735 (28.0)
Stage 2: Left atrial or mitral valve damage	416/735 (56.6)	Stage 2: Left atrial or mitral valve damage	416/735 (56.6)
Indexed left atrial volume >34 ml/m ²	367/705 (52.0)	Indexed left atrial volume >34 ml/m ²	367/705 (52.0)
Mitral regurgitation moderate or greater	9/727 (1.2)	Mitral regurgitation moderate or greater	9/727 (1.2)
Atrial fibrillation	152/732 (20.8)	Atrial fibrillation	152/732 (20.8)
Stage 3: Pulmonary vasculature or tricuspid valve damage	21/726 (2.9)	Stage 3: Pulmonary vasculature or tricuspid valve damage	21/726 (2.9)
Pulmonary hypertension (systolic PAP ≥60 mm Hg)	11/573 (1.9)	Pulmonary hypertension (systolic PAP ≥60 mm Hg)	11/573 (1.9)
Tricuspid regurgitation moderate or greater	10/704 (1.4)	Tricuspid regurgitation moderate or greater	10/704 (1.4)
Stage 4: RV damage	47/549 (8.6)	Stage 4: RV damage or subclinical heart failure	90/727 (12.4)
RV systolic dysfunction moderate or greater	47/549 (8.6)	RV systolic dysfunction moderate or greater	47/549 (8.6)
		Moderate to severe low-flow (stroke volume index <30 ml/m ²)	55/712 (7.7)

Values are n/N (%). *LV diastolic dysfunction defined according to American Society of Echocardiography guidelines (11). †LV subclinical systolic dysfunction defined as LV global longitudinal strain ≤15% or LV ejection fraction <60%.

LV = left ventricular; PAP = pulmonary arterial pressure; RV = right ventricular.

fibrillation, and/or ≥moderate mitral regurgitation; Stage 3, pulmonary vasculature and/or tricuspid valve damage as defined by the presence of systolic pulmonary hypertension (systolic pulmonary arterial pressure ≥60 mm Hg) and/or the presence of moderate or greater tricuspid regurgitation; Stage 4, RV damage as defined by the presence of moderate or greater right ventricular (RV) systolic dysfunction, which was determined by a multiparameter approach including semiquantitative assessment by visual examination and quantitative assessment using criteria of tricuspid annulus systolic velocity $S' < 9.5$ cm/s, and/or tricuspid annular plane systolic excursion <17 mm (10,16,17).

We also tested a “modified” staging scheme, in which impaired LV global longitudinal strain (LV GLS ≤15%) was included as an additional criterion in Stage 1 (18), the elevated LV filling pressures criterion (E/e' ratio >14) was replaced by grade ≥II of LV diastolic dysfunction (11), and moderate to severe low-flow state (defined as stroke volume [SV] index <30 ml/m²) was added as a supplemental criterion in Stage 4 (12,13,15,19–21); the other parameters and criteria in the other stages were unchanged compared with the original scheme.

In both staging schemes (original and modified), patients were hierarchically classified in a given stage

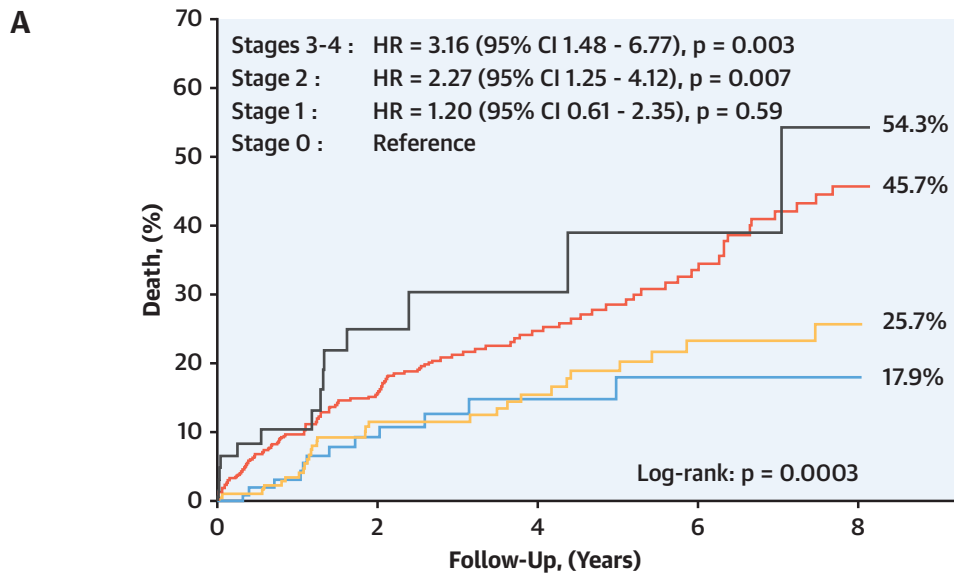
(worst stage) if at least 1 of the proposed criteria was met within that stage.

STUDY ENDPOINTS. The primary endpoint was overall death during the entire follow-up, regardless of whether the patient underwent AVR. Hence, the deaths included those that occurred in patients who did not undergo AVR and those that occurred after AVR. The secondary endpoints were cardiovascular death, regardless of treatment, and all-cause and cardiovascular mortality under medical treatment (i.e., analysis censored at time of AVR). Information on date and cause of death was obtained from review of medical records and/or death certificate.

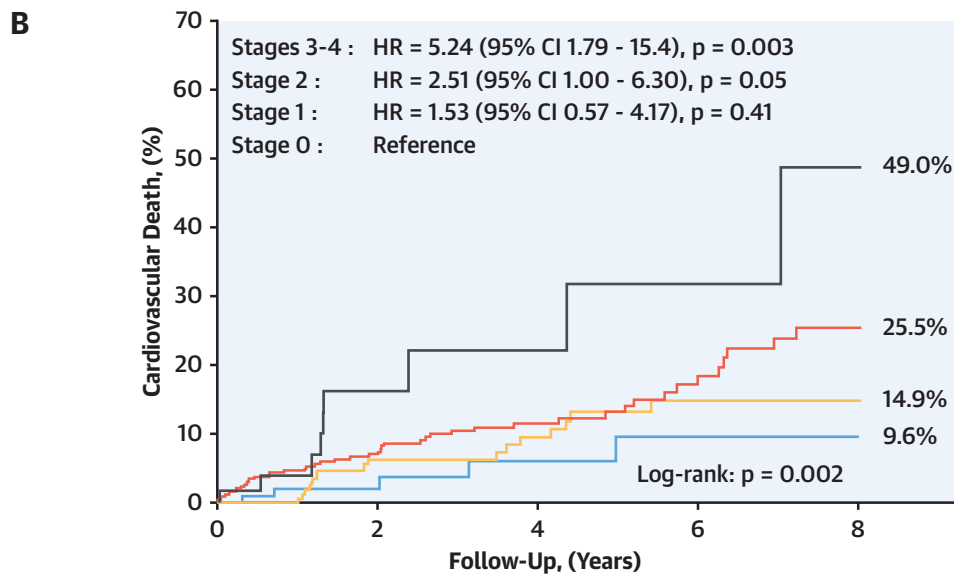
STATISTICAL ANALYSIS. Continuous data were expressed as mean ± SD or median (interquartile range [IQR]) and tested for the normality of distribution and homogeneity of variances with the Shapiro-Wilk and Levene tests, respectively. Comparison of continuous data were performed using Student's *t*-test or Wilcoxon-Mann-Whitney test as appropriate. Categorical data were expressed as percentages and compared with the chi-square test or Fisher exact test as appropriate.

Kaplan-Meier curves and log-rank tests of the time-to-event data were used to compare the survival

FIGURE 1 Survival Analysis According to the Original Cardiac Damage Staging Classification

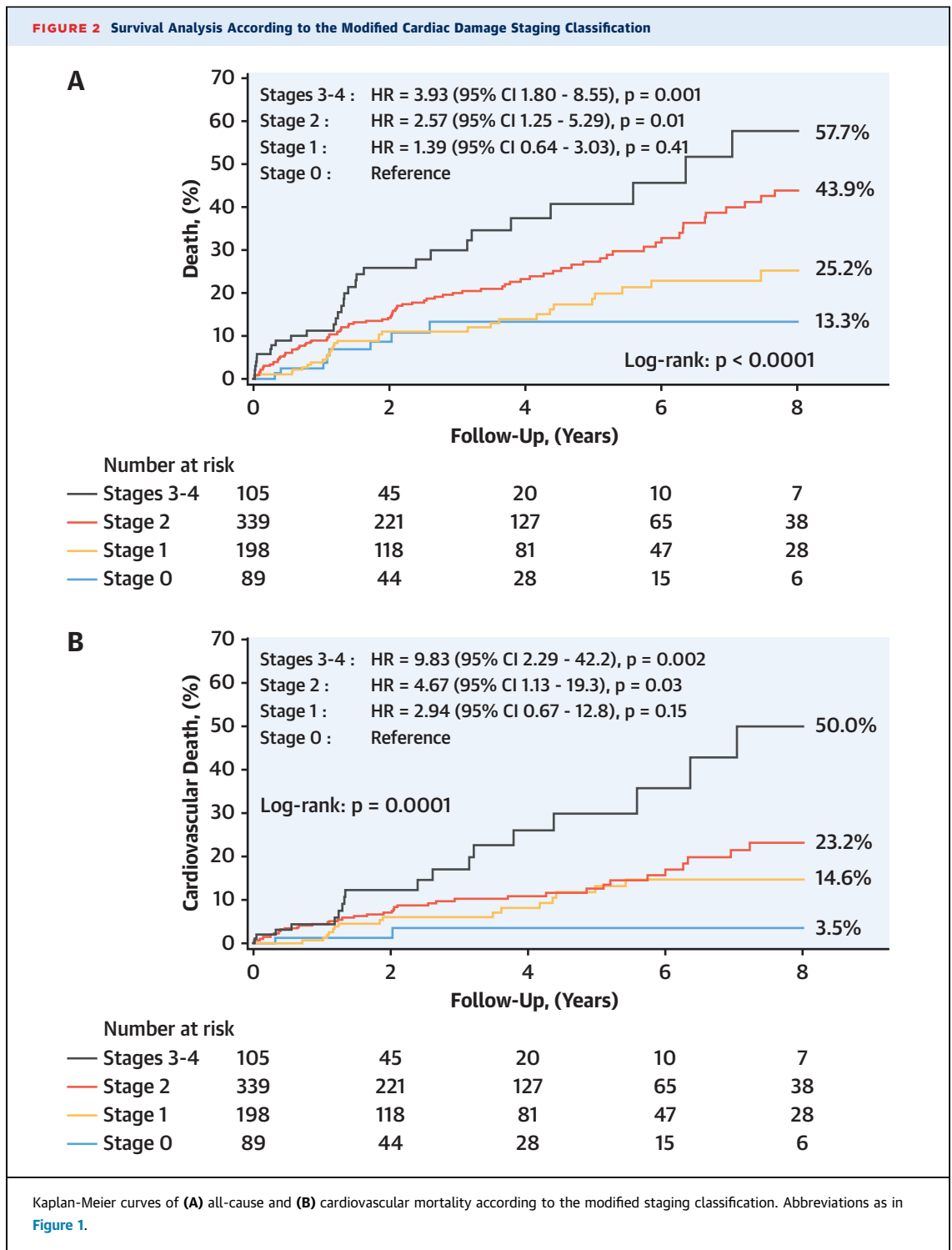


Number at risk						
—	Stages 3-4	63	21	9	5	3
—	Stage 2	366	236	134	69	41
—	Stage 1	193	112	78	45	28
—	Stage 0	109	59	35	18	7



Number at risk						
—	Stages 3-4	63	21	9	5	3
—	Stage 2	366	236	134	69	41
—	Stage 1	193	112	78	45	28
—	Stage 0	109	59	35	18	7

Kaplan-Meier curves of (A) all-cause and (B) cardiovascular mortality according to the original staging classification by Généreux et al. (8). The percentages are mortality rates after 8 years of follow-up. The numbers at the bottom of the graphs are numbers of patients at risk at each time interval. CI = confidence interval; HR = hazard ratio.



function according to each cardiac damage stage. Multivariable Cox proportional hazards model adjusted for age, sex, body mass index, hypertension, diabetes, coronary artery disease, renal disease, chronic obstructive pulmonary disease, V_{peak} , and

AVR (included as a time-dependent variable) was used to determine the independent association between the staging classification and mortality. The selection of the variables for the multivariable analysis was based on their clinical relevance (i.e., known

risk factors) and/or because of their significant association with mortality in univariable analysis. Subgroup analyses were performed to determine the association between staging classification and mortality in each subgroup of AS patients (i.e., moderate and severe). Continuous net reclassification index (NRI) was used to determine the incremental value of the staging classification in predicting 5-year risk of mortality. A p value <0.05 was considered statistically significant. Statistical analyses were performed with Stata software version 14.2 (StataCorp, College Station, Texas).

RESULTS

STUDY GROUP. Clinical and echocardiographic characteristics of the study group are presented in [Online Table 1](#). A total of 61% of patients had severe AS (defined as aortic valve area <1 cm²) at the time of the baseline echocardiography. None of the patients had AS-related symptoms at baseline, 82% were in NYHA functional class I, and 18% were in NYHA functional class II ([Online Table 1](#)).

The prevalence of the original and modified cardiac damage stages and the distribution of their individual components are presented in [Table 1](#) and [Online Tables 2 and 3](#). According to the modified staging scheme, 89 (12.1%) patients were in Stage 0, 200 (27.2%) patients were in Stage 1, 341 (46.4%) patients were in Stage 2, 15 (2.0%) patients were in Stage 3, and 90 (12.2%) patients were in Stage 4 ([Table 1](#)). Moreover, 140 (19%) patients underwent exercise testing to confirm their asymptomatic status, and in this subset, the distribution of the modified cardiac staging was similar to that in the whole cohort: 14.3% in Stage 0, 35.7% in Stage 1, 40.7% in Stage 2, 0.7% in Stage 3, and 8.6% in Stage 4. The clinical and echocardiographic characteristics of the study group according to each stage of the original and modified staging schemes are presented in [Online Tables 4 to 7](#). According to the modified staging scheme, the proportion of patients with NYHA functional class II was similar among the 5 cardiac stages (13%, 19%, 20%, 13%, and 17% in Stages 0, 1, 2, 3, and 4, respectively; $p = 0.74$). As expected, patients in the most advanced stages of cardiac damage were older, presented with higher logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation), and had a higher prevalence of hypertension, previous coronary artery bypass grafting, renal disease, and chronic obstructive pulmonary disease (all, $p < 0.05$) ([Online Tables 4 and 5](#)).

STAGING CLASSIFICATION AND RISK OF MORTALITY. During a median follow-up of 2.6 years (IQR: 1.1 to 5.2 years) (mean 3.5 ± 3.2 years), there were 161 (22%)

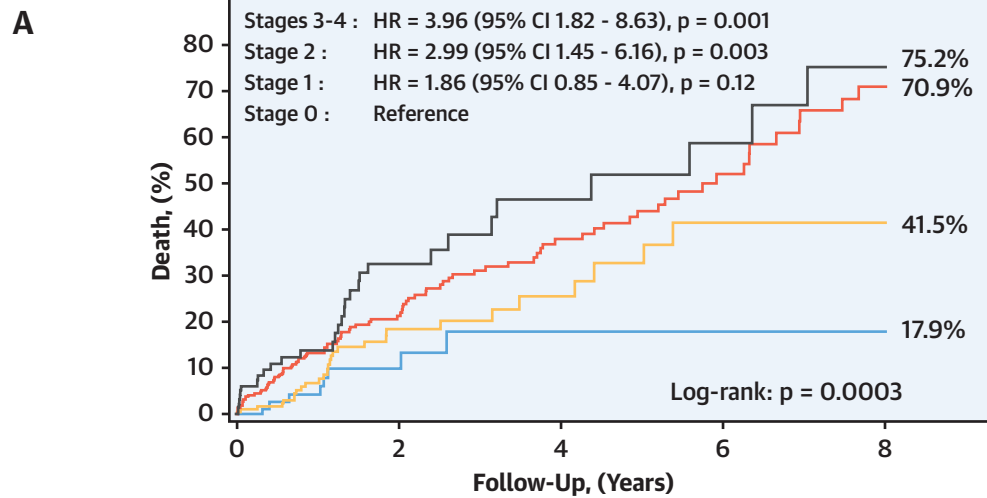
deaths, and 79 (49%) of them had a cardiovascular cause. A total of 352 (48%) patients were referred for AVR (including 32 transcatheter AVRs) at a median time of 1.8 years (IQR: 0.4 to 2.5 years) during follow-up. There were 129 (80%) deaths that occurred without AVR (1.3 years [IQR: 0.6 to 3.2 years]) and the remaining 32 (20%) after AVR (4.2 years [IQR: 1.8 to 6.9 years]). According to the modified staging scheme, the proportion of patients who underwent AVR were: 36.0% in Stage 0 (0.8 years [IQR: 0.5 to 1.7 years]), 59.5% in Stage 1 (0.8 years [IQR: 0.4 to 1.8 years]), 48.7% in Stage 2 (0.7 years [IQR: 0.2 to 1.6 years]), 6.7% in Stage 3 (0.8 years [IQR: 0.8 to 0.8 years]), and 37.8% in Stage 4 (0.3 years [IQR: 0.1 to 1.1 years]) ($p < 0.0001$). Similar results were also observed according to the original staging scheme ([Online Appendix](#)).

Given that there was a small number of patients in Stage 3 and that patients in Stages 3 and 4 had similar mortality rates, these 2 stages were merged together in a single group (i.e., Stages 3 to 4) for subsequent analyses. [Figures 1 and 2](#) show the overall survival for all-cause and cardiovascular mortality according to the original and modified staging scheme, respectively. With both staging schemes, there was a significant increase in the risk of all-cause and cardiovascular mortality for each increase in the cardiac damage stage (all, $p \leq 0.002$) ([Figures 1A, 1B, 2A, and 2B](#)). However, the modified staging scheme showed better discrimination in the mortality curves between Stage 2 and the merged Stages 3 to 4. The analyses censored at the time of AVR showed an even more pronounced increase in all-cause ([Figure 3A](#)) and cardiovascular ([Figure 3B](#)) mortality with more advanced stages (all-cause 8-year mortality $\geq 40\%$ for patients in modified stage ≥ 2).

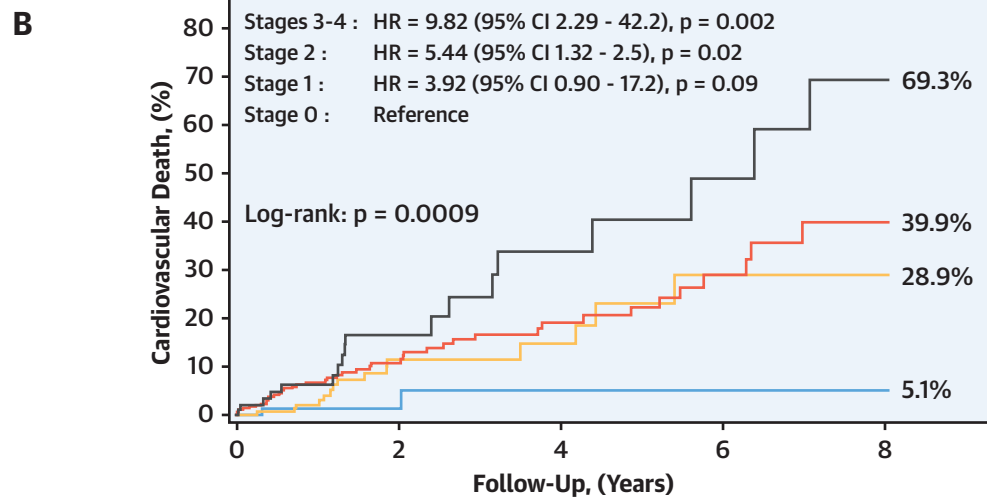
After multivariable adjustment for several risk factors and AVR, the modified staging classification remained significantly associated with increased risk of all-cause (hazard ratio [HR]: 1.31; 95% confidence interval [CI]: 1.06 to 1.61; $p = 0.01$) and cardiovascular mortality (HR: 1.52; 95% CI: 1.12 to 2.07; $p = 0.008$) ([Table 2](#)). The [Central Illustration](#) shows the adjusted all-cause and cardiovascular mortality Cox curves according to the modified damage staging scheme. Early during the follow-up period (i.e., ≤ 1 year), there was a marked increase in mortality rate in Stage ≥ 2 .

INCREMENTAL PROGNOSTIC VALUE OF STAGING CLASSIFICATION. The modified cardiac damage staging provided significant incremental value to predict 5-year mortality over the original staging scheme (NRI = 0.25; $p = 0.02$), parameter of AS severity (NRI = 0.33; $p = 0.003$) alone, or the

FIGURE 3 Survival Analysis Censored at the Time of Aortic Valve Replacement According to the Modified Cardiac Damage Staging Classification



Number at risk						
—	Stages 3-4	104	31	11	5	3
—	Stage 2	339	122	57	24	9
—	Stage 1	197	57	23	9	6
—	Stage 0	89	27	13	8	3



Number at risk						
—	Stages 3-4	104	31	11	5	3
—	Stage 2	339	122	57	24	9
—	Stage 1	197	57	23	9	6
—	Stage 0	89	27	13	8	3

Kaplan-Meier curves censored at time of aortic valve replacement: (A) all-cause and (B) cardiovascular mortality according to the modified staging classification. Abbreviations as in Figure 1.

TABLE 2 Association of Modified Staging Classification With Increased Risk of Mortality

	All-Cause Mortality (161 Deaths)				Cardiovascular Mortality (79 Cardiovascular Deaths)			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Stage of cardiac damage (per 1-stage increase)	1.65 (1.34-2.02)	<0.0001	1.31 (1.06-1.61)	0.01	1.92 (1.42-2.59)	<0.0001	1.52 (1.12-2.07)	0.008
Age (per 5 yr increase)	1.52 (1.38-1.66)	<0.0001	1.41 (1.28-1.55)	<0.0001	1.62 (1.41-1.87)	<0.0001	1.53 (1.32-1.78)	<0.0001
Sex	0.79 (0.58-1.08)	0.14	0.94 (0.68-1.32)	0.73	0.65 (0.42-1.01)	0.05	0.81 (0.52-1.29)	0.38
Body mass index (per 5 kg/m ² increase)	0.72 (0.60-0.87)	0.001	0.80 (0.65-0.98)	0.04	0.77 (0.59-1.01)	0.06	—	—
Hypertension	1.67 (1.16-2.42)	0.006	0.96 (0.65-1.42)	0.85	1.83 (1.07-3.14)	0.03	0.94 (0.54-1.62)	0.82
Diabetes mellitus	1.18 (0.83-1.68)	0.35	1.06 (0.73-1.55)	0.75	1.51 (0.94-2.42)	0.09	—	—
Coronary artery disease	0.98 (0.66-1.45)	0.91	1.00 (0.66-1.51)	0.99	1.69 (1.04-2.75)	0.03	1.73 (1.04-2.86)	0.03
Renal disease	2.13 (1.54-2.95)	<0.0001	1.26 (0.89-1.78)	0.19	1.60 (0.98-2.60)	0.06	—	—
COPD	1.80 (1.21-2.70)	0.004	1.63 (1.07-2.47)	0.02	1.18 (0.56-2.48)	0.66	—	—
Peak aortic jet velocity (per 1.0 m/s increase)	0.79 (0.65-0.96)	0.02	1.06 (0.87-1.28)	0.57	0.81 (0.62-1.06)	0.13	—	—
AVR treatment (as time-dependent variable)	0.32 (0.21-0.48)	<0.0001	0.48 (0.31-0.75)	0.001	0.42 (0.24-0.72)	0.002	0.63 (0.36-1.11)	0.11

Bold indicates statistical significance.

AVR = aortic valve replacement; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

combination of several clinical and AS severity variables (NRI = 0.35; p = 0.002) (Table 3). The addition of the modified staging classification into the multivariable model including clinical variables as well as the original staging scheme resulted in further improvement of 5-year survival risk prediction (NRI = 0.34; p = 0.003) (Table 3).

IMPACT OF STAGING CLASSIFICATION ACCORDING TO AS SEVERITY. In the subset of 450 (61%) patients with hemodynamically severe AS (defined as aortic valve area <1 cm²), 44 (9.8%) patients were in Stage 0, 121 (26.9%) in Stage 1, 209 (46.4%) patients in Stage 2, 9 (2.0%) patients in Stage 3, and 67 (14.9%) patients in Stage 4 according to the modified staging scheme. More advanced stage (i.e., Stage ≥2) was also associated with increased risk of all-cause and cardiovascular mortality (Figures 4A and 4B). In multivariable analysis, the cardiac damage staging was significantly associated with all-cause mortality (HR: 1.43; 95% CI: 1.06 to 1.94; p = 0.02) and cardiovascular mortality (HR: 1.64; 95% CI: 1.08 to 2.49; p = 0.02) (Table 4).

In the subset of patients with moderate AS (n = 285; 39%), 45 (15.8%) patients were in Stage 0, 79 (27.7%) in Stage 1, 132 (46.3%) patients in Stage 2, 6 (2.1%) patients in Stage 3, and 23 (8.1%) patients in Stage 4 according to the modified staging scheme. In this subset, the association between cardiac damage staging and increased risk of all-cause or cardiovascular death was not significant (all, p ≥ 0.12) (Online Figures 2A and 2B).

INTERACTION BETWEEN STAGING CLASSIFICATION AND SUBGROUPS OF AS PATIENTS. The interaction between staging classification and several subgroups of AS patients with regard to association with mortality is presented in Online Figure 3. There was no

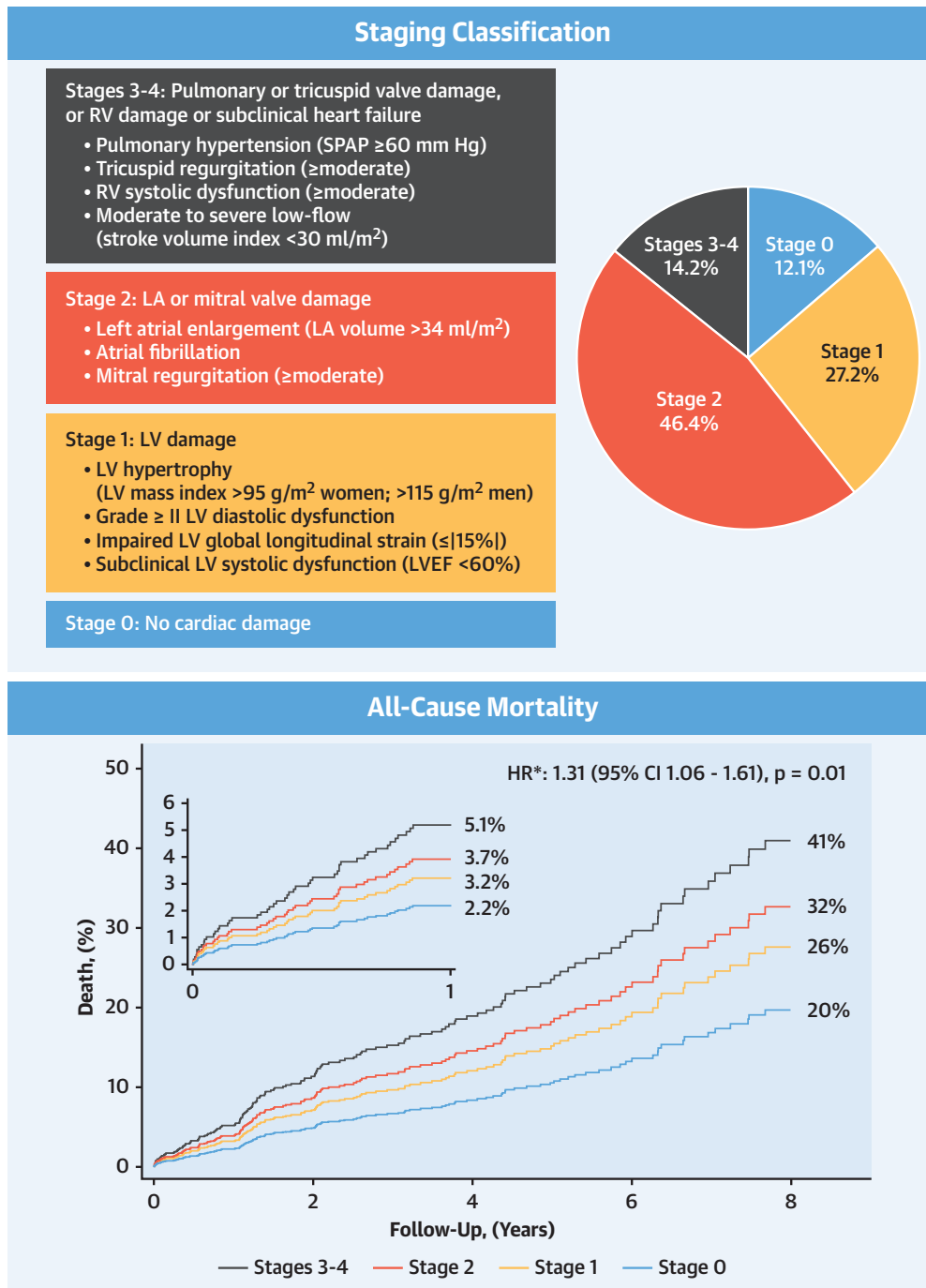
significant interaction between subgroups and staging classification, except for renal disease (p = 0.04) (Online Figure 3).

DISCUSSION

This study is, to the best of our knowledge, the first to test and validate the prognostic value of a new staging classification that was based on extent of cardiac damage in a large international multicenter cohort of patients with asymptomatic moderate to severe AS. We showed that there was a stepwise increase in all-cause and cardiovascular mortality for each increment in the stage of cardiac damage in the whole cohort. Moreover, the staging classification provided significant incremental prognostic value beyond the traditional risk factors and clinical risk score to predict long-term survival. These findings suggest that this new staging system could be an additive clinical tool to enhance risk stratification and therapeutic decision making in asymptomatic severe AS.

CLINICAL RELEVANCE AND UTILITY OF THE CARDIAC DAMAGE STAGING SYSTEM IN ASYMPTOMATIC AS. In the present study that included patients with asymptomatic moderate to severe AS, we observed a high rate of events: ~65% of patients underwent AVR or died within a mean time of 3.5-year follow-up after initial diagnosis. Notwithstanding these findings, the decision-making process regarding the timing of intervention in patients with asymptomatic severe AS remains uncertain and controversial (2-5).

Recent nonrandomized studies suggest that an early intervention strategy may improve survival of patients with asymptomatic severe AS (22,23). Several randomized trials, including the EARLY-TAVR

CENTRAL ILLUSTRATION Association Between Cardiac Damage Staging Classification and Risk of Mortality

Tastet, L. et al. *J Am Coll Cardiol.* 2019;74(4):550-63.

The figure shows the modified cardiac damage staging classification and the prevalence of cardiac damage stages in (top) the study group and (bottom) the association with increased risk of all-cause mortality for each increment in stage of cardiac damage. The upper left insert (bottom) shows the adjusted Cox curves between baseline and 1-year follow-up. *HR is the hazard ratio for all-cause mortality, per 1 stage increase, obtained by Cox multivariable analysis adjusted for age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, renal disease, chronic obstructive pulmonary disease, peak aortic jet velocity, aortic valve replacement treatment, and stage of damage as continuous variable expressed by 1-step increase. CI = confidence interval; HR = hazard ratio; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular; SPAP = systolic pulmonary arterial pressure.

(Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis) and EVoLVeD (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS) trials, are currently assessing the timing of intervention in asymptomatic severe AS. However, even if these trials are positive, it is likely that not all patients will benefit from an early intervention. There is thus an urgent need to develop an individualized strategy that would allow the cardiologist to select the best timing of AVR for the given patient. The staging scheme that we proposed in this study has the potential to identify the patients who may benefit from early elective intervention versus those who can be managed conservatively.

One potential criticism of this staging scheme is that it is not specific to AS. However, even if the cardiac damage is not related (or related only in part) to AS but rather to concomitant disease (e.g., ischemic heart disease), the patient is, nevertheless, more vulnerable to the LV afterload excess imposed by AS and thus at higher risk for cardiovascular events. Such patient might still potentially benefit from early elective AVR in addition to treating the concomitant disease if feasible and indicated.

PARAMETERS AND CRITERIA INCLUDED IN THE CARDIAC DAMAGE CLASSIFICATION. The cardiac damage staging scheme proposed by Généreux et al. (8) was a powerful and independent predictor of mortality following AVR, with ~45% increased risk of mortality at 1 year for each stage increment in symptomatic patients with severe AS who were undergoing AVR. In the present study, we applied this staging scheme (original staging scheme) to the asymptomatic AS group, and we proposed the several modifications in the parameters and criteria included in the stages definition to adapt and optimize the staging for this specific group (modified staging scheme).

First, the LVEF underestimates the extent of LV systolic dysfunction in AS, and about one-third of patients with asymptomatic AS and preserved LVEF have some degree of subclinical LV systolic dysfunction as documented by impaired LV GLS (18,24). To improve the identification of subclinical LV dysfunction, we raised the cutoff value of the LVEF from 50% to 60% (12-15,25), and we included the LV GLS in Stage 1 using a cutoff value of <15% to define impaired LV GLS (18). Recent studies, indeed, suggest that patients with asymptomatic moderate to severe AS and LVEF <60% display an increased risk of adverse events compared with patients with

TABLE 3 Incremental Prognostic Value of the Modified Staging Classification

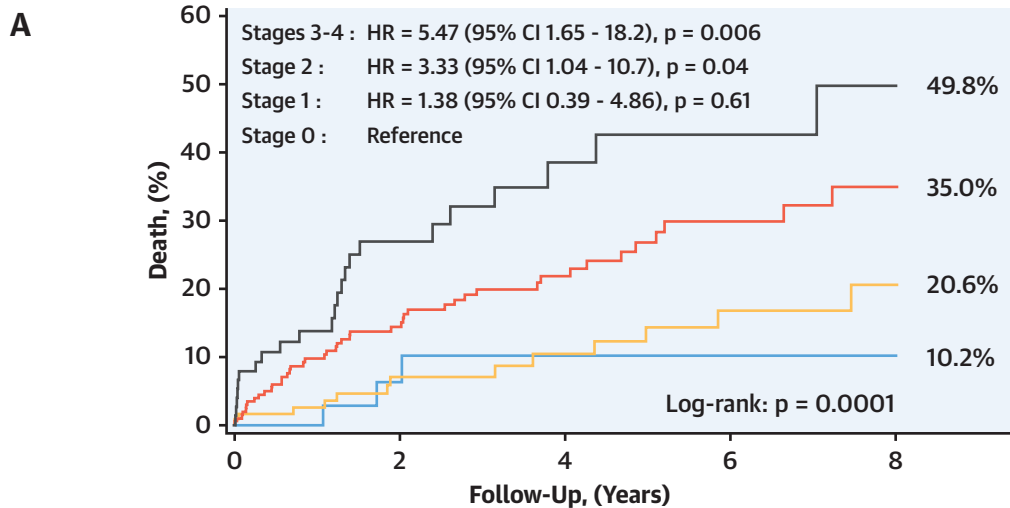
	NRI	p Value
Multivariable model including:		
Original staging classification*	Referent	
Modified staging classification	0.25	0.02
Multivariable model including:		
Age	Referent	
Modified staging classification	0.30	0.006
Multivariable model including:		
V _{peak}	Referent	
Modified staging classification	0.33	0.003
Multivariable model including:		
Original staging classification*, age, sex, logistic EuroSCORE, and V _{peak}	Referent	
Modified staging classification	0.35	0.002
Multivariable model including:		
Original staging classification*, age, sex, BMI, logistic EuroSCORE, hypertension, diabetes mellitus, and V _{peak}	Referent	
Modified staging classification	0.34	0.003

*Cardiac damage staging classification as proposed by Généreux et al. (8).
 BMI = body mass index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NRI = net reclassification index; V_{peak} = peak aortic jet velocity.

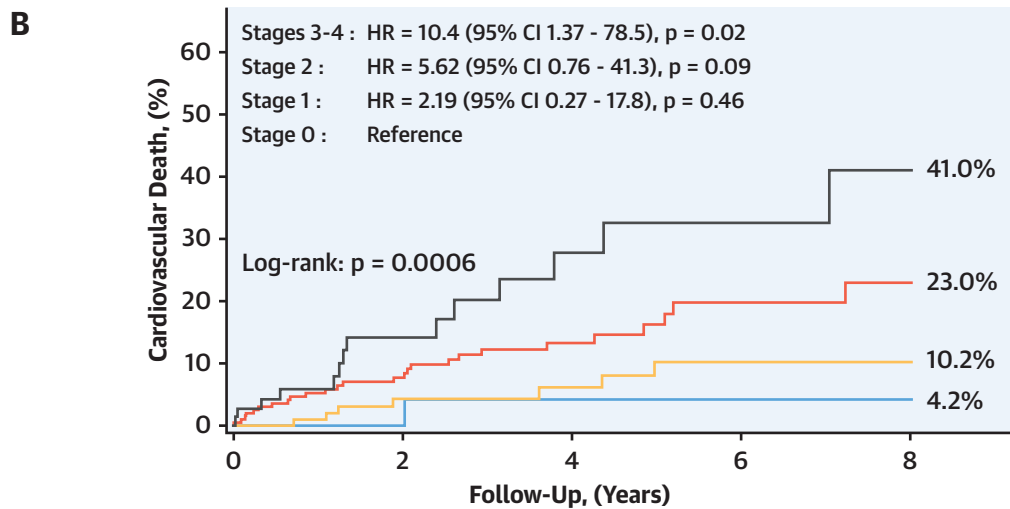
LVEF ≥60% (12-15,25). We also replaced the elevated LV filling pressures criteria (E/e' >14) in the Stage 1 of the original staging scheme with grade ≥II LV diastolic dysfunction as assessed using the multiparameter approach recommended by the American Society of Echocardiography guidelines (11). Finally, we added SV index <30 ml/m², a marker of the earlier phase of heart failure, in the Stage 4 of the classification. SV index is, indeed, a good marker of the overall performance of the cardiac pump, and several types of damage or dysfunction of the cardiac chambers may lead to a reduction in pump performance and thus to a low-flow state, including LV systolic and diastolic dysfunction, mitral regurgitation, atrial fibrillation, pulmonary hypertension, tricuspid regurgitation, and RV dysfunction. Furthermore, we used the SV index cutoff value (<30 ml/m²) for a moderate to severe low-flow state rather than the larger value (<35 ml/m²) for an overall low-flow state proposed in the guidelines (2,3).

Several studies reported that a low-flow state as documented by reduced SV index is associated with an increased risk of cardiac events both before and after AVR (12,19,20,26). Adding the SV index criteria in the Stage 4 definition of the modified staging scheme obviously improved the discrimination between Stage 2 and Stages 3 to 4 with respect to prediction of outcomes. In the asymptomatic AS patients included in the present study, only 12% of patients were in Stage 0, and still 14% were in Stages 3 to 4.

FIGURE 4 Survival According to the Modified Cardiac Damage Staging Classification in the Subgroup of Patients with Severe Aortic Valve Stenosis



Number at risk						
—	Stages 3-4	76	35	15	8	7
—	Stage 2	208	134	74	33	21
—	Stage 1	121	74	50	32	19
—	Stage 0	44	24	15	8	4



Number at risk						
—	Stages 3-4	76	35	15	8	7
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—	Stage 1	121	74	50	32	19
—	Stage 0	44	24	15	8	4

Kaplan-Meier curves of (A) all-cause and (B) cardiovascular mortality according to the modified staging classification. Abbreviations as in Figure 1.

TABLE 4 Association of Modified Staging Classification With Increased Risk of Mortality in the Stratum of Patients With Severe AS

	All-Cause Mortality (89 Deaths)				Cardiovascular Mortality (51 Cardiovascular Deaths)			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Stage of cardiac damage (per 1-stage increase)	1.89 (1.43-2.49)	<0.0001	1.43 (1.06-1.94)	0.02	2.14 (1.47-3.10)	<0.0001	1.64 (1.08-2.49)	0.02
Age (per 5 yr increase)	1.61 (1.42-1.83)	<0.0001	1.46 (1.28-1.67)	<0.0001	1.73 (1.46-2.06)	<0.0001	1.61 (1.34-1.92)	<0.0001
Sex	0.87 (0.57-1.32)	0.52	1.09 (0.70-1.70)	0.71	0.78 (0.45-1.36)	0.39	0.99 (0.57-1.74)	0.99
Body mass index (per 5 kg/m ² increase)	0.63 (0.49-0.82)	0.001	0.72 (0.54-0.95)	0.02	0.75 (0.53-1.04)	0.09	--	--
Hypertension	1.74 (1.07-2.83)	0.02	1.06 (0.64-1.77)	0.81	2.12 (1.09-4.15)	0.03	1.09 (0.56-2.15)	0.79
Diabetes mellitus	0.95 (0.58-1.56)	0.84	--	--	1.23 (0.66-2.28)	0.51	--	--
Coronary artery disease	1.17 (0.72-1.89)	0.53	--	--	1.78 (0.99-3.19)	0.05	--	--
Renal disease	1.78 (1.10-2.88)	0.02	0.96 (0.57-1.61)	0.88	1.45 (0.74-2.83)	0.28	--	--
COPD	2.33 (1.41-3.84)	0.001	2.03 (1.21-3.42)	0.007	2.00 (1.00-4.00)	0.05	--	--
Peak aortic jet velocity (per 1.0 m/s increase)	0.91 (0.69-1.20)	0.50	--	--	0.79 (0.54-1.15)	0.22	--	--
AVR treatment (as time-dependent variable)	0.36 (0.22-0.61)	<0.0001	0.61 (0.35-1.04)	0.07	0.35 (0.18-0.67)	0.002	0.62 (0.31-1.24)	0.18

Bold indicates statistical significance.
 AS = aortic stenosis; other abbreviations as in Table 2.

Overall, 61% of the patients in this cohort (50% in the subset with exercise testing) were in Stage ≥2 and yet did not report any symptoms.

These findings are consistent with those of other previous studies in AS or other valvular heart disease reporting that a substantial proportion of patients with echocardiographic evidence of heart failure are asymptomatic (23,27,28). They also provide support to the guidelines (2), which state that irreversible consequences of severe AS may primarily affect the status of the ventricles and pulmonary circulation and may occur despite the absence of symptoms. The results of this study further confirm the lack of sensitivity of symptoms to identify the presence and extent of cardiac damage and thus to determine the optimal timing for AVR in patients with AS. These findings therefore emphasize the importance of using a cardiac damage staging approach that is based on Doppler echocardiographic parameters to guide therapeutic management in patients with asymptomatic severe AS.

CLINICAL IMPLICATIONS. Although there was a gradual increase in the risk of long-term mortality with each increment in the staging, the risk of death in the short-term (i.e., within the first year following the index echocardiogram) was increased only when cardiac damage stage was ≥2. Hence, this threshold could be used to consider early elective intervention in patients with asymptomatic severe AS. Patients in Stage 1 may have a higher risk of adverse outcome, but in the longer term, and could thus undergo careful clinical and echocardiographic surveillance, and intervention may be considered when the patients develop symptoms, LV ejection

fraction becomes <50%, and/or cardiac damage stage becomes ≥2.

The outcome of patients with moderate AS is definitely not benign (24,29,30), and there is thus a need to enhance risk stratification in this subset as well. Patients with moderate AS and Stage ≥2 should likely receive closer follow-up than what is generally recommended in the guidelines (i.e., echocardiography every 2 years) (2).

STUDY LIMITATIONS. Although the clinical data were prospectively collected, the present analysis is retrospective and is thus subject to inherent limitations related to that design. The present study includes a “real-life” group of patients whose absence of AS-related symptoms was carefully assessed and monitored by experienced teams of physicians and nurses. The asymptomatic status was confirmed using exercise testing only if the history or symptoms were equivocal, as recommended in the guidelines. It is thus possible that, among the patients who did not undergo exercise testing, some may not have been “truly” asymptomatic. However, the patients with AS include a large proportion of older patients with several comorbidities, and in such patients, exercise testing may not be feasible and may lack specificity (4,24). The distribution of the cardiac damage stages was, nonetheless, similar in the subset of patients with exercise testing compared with the whole cohort. Furthermore, we elected to include patients with mild symptoms (i.e., NYHA functional class II) that were considered not related to AS by the treating cardiologist, because the determination of the optimal timing of AVR is also challenging in this subset of patients.

Doppler echocardiography may underestimate SV index and thus overestimate the prevalence of Stage 4 with the modified staging scheme. However, in the present study, all patients with the SV index <30 ml/m² criterion also had other criteria for Stages 1, 2, 3, and/or 4. Furthermore, in the Stage 3 to 4 group, the mortality rate was as high in patients with an SV index <30 as in those with an SV index ≥ 30 ml/m².

The LV GLS was available in only one-third of the patients included in this study. This may be explained by the fact that, in contrast to all other parameters included in the staging scheme, LV GLS is not yet included in the guidelines and/or is not measured in routine practice. Although LV GLS was not available in the majority of the patients in this study, using a higher cutoff value for the LVEF (60% vs. 50%) criterion considerably improves the sensitivity of LVEF to identify subclinical LV dysfunction and thus Stage 1.

To facilitate the implementation and generalization of the cardiac damage staging scheme in the clinical setting, we mainly included parameters that are measured in the context of the routine echocardiogram in AS patients. However, each of these parameters is subject to measurement errors and variability. One of the strengths of the proposed grading scheme in this context is that the definition of each stage does not rely on a single parameter but is rather based on a multiparameter approach. Further studies are needed to determine whether the addition of other imaging parameters (e.g., midwall fibrosis by cardiac magnetic resonance) or blood biomarkers (e.g., brain natriuretic peptide or troponin) could further improve the prognostic value of the proposed staging scheme in asymptomatic patients with AS.

CONCLUSIONS

This multicenter study shows that the cardiac damage staging classification provides incremental prognostic

value over traditional clinical risk factors and parameters of AS severity to predict survival in asymptomatic patients with moderate to severe AS. This staging system may be helpful to identify patients with severe AS at higher risk who could benefit from early elective intervention. The findings of this study suggest that a Stage ≥ 2 , which was identified in 61% of the present series, could be considered as a trigger for early elective AVR in asymptomatic patients with severe AS. In the subset of patients with moderate AS harboring a Stage ≥ 2 , more frequent (i.e., every year) and comprehensive active clinical and echocardiographic surveillance should be considered.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: In patients with asymptomatic severe AS, the risk of mortality increases in proportion to the extent of cardiac damage as assessed by echocardiography. With Stage 1 defined by LV hypertrophy, elevated filling pressure, and/or systolic dysfunction, Stage 2 by left atrial enlargement, atrial fibrillation, and/or mitral regurgitation, Stage 3 by systolic pulmonary hypertension and/or tricuspid regurgitation, and Stage 4 by right ventricular dysfunction, patients at Stage ≥ 2 exhibit reduced survival.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether incorporation of other risk markers or imaging findings can enhance the predictive value of this staging scheme.

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KEY WORDS aortic valve replacement, aortic valve stenosis, asymptomatic, disease staging, echocardiography

APPENDIX For supplemental methods and results sections, as well as tables, figures, and references, please see the online version of this paper.