

ORIGINAL RESEARCH

STRUCTURAL

# Sex-Specific Differences in Upstream Cardiac Damage in Patients With Aortic Stenosis Undergoing TAVR



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ABSTRACT

**BACKGROUND** Cardiac damage caused by aortic stenosis (AS) can be categorized into stages, which are associated with a progressively increasing risk of death after transcatheter aortic valve replacement (TAVR).

**OBJECTIVES** The authors investigated sex-related differences in cardiac damage among patients with symptomatic AS and the prognostic value of cardiac damage classification in women and men undergoing TAVR.

**METHODS** In a prospective registry, pre-TAVR echocardiograms were used to categorize patients into 5 stages of cardiac damage caused by AS. Differences in the extent of cardiac damage were compared according to sex, and its implications on clinical outcomes after TAVR were explored.

**RESULTS** Among 2,026 patients undergoing TAVR between August 2007 and June 2022 (995 [49.1%] women and 1,031 [50.9%] men), we observed sex-specific differences in the pattern of cardiac damage (women vs men; stage 0: 2.6% vs 3.1%, stage 1: 13.4% vs 10.1%, stage 2: 37.1% vs 39.5%, stage 3: 27.5% vs 15.6%, and stage 4: 19.4% vs 31.7%). There was a stepwise increase in 5-year all-cause mortality according to stage in women (HR<sub>adjusted</sub>: 1.43; 95% CI: 1.28-1.60, for linear trend) and men (HR<sub>adjusted</sub>: 1.26; 95% CI: 1.14-1.38, for linear trend). Female sex was associated with a lower 5-year mortality in early stages (stage 0, 1, or 2) but not in advanced stages (stage 3 or 4).

**CONCLUSIONS** The pattern of cardiac damage secondary to AS differed by sex. In early stages of cardiac damage, women had a lower 5-year mortality than men, whereas in more advanced stages, mortality was comparable between sexes. (SwissTAVI Registry; [NCT01368250](https://clinicaltrials.gov/ct2/show/study/NCT01368250)) (J Am Coll Cardiol Intv 2024;17:1252-1264) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

**A**ortic stenosis (AS) is the leading valvular heart disease lesion in high-income countries and has a comparable prevalence among elderly women and men.<sup>1,2</sup> In the absence of effective prevention, aortic valve replacement (AVR) is the only therapeutic intervention of AS.<sup>3</sup> Before the advent of

transcatheter aortic valve replacement (TAVR), a notable sex-related disparity existed in access to AVR, with fewer women than men undergoing surgical intervention.<sup>4-6</sup> This discrepancy has been attributed primarily to advanced age, increased frailty, and a higher risk of procedural complications in female

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patients.<sup>4-7</sup> Consequently, women experienced a higher likelihood of undertreatment, ultimately resulting in more advanced cardiac damage because of long-standing pressure overload caused by AS and adverse prognosis.<sup>6</sup> TAVR effectively mitigated historical sex-related disparities in access to treatment of AS.<sup>5,8-11</sup> A recent meta-analysis in patients undergoing TAVR reported lower long-term mortality in women compared to men, potentially attributable to a longer life expectancy and fewer comorbidities in women.<sup>12</sup> Notwithstanding, even within the TAVR population, women have been found to be older and undergo intervention at a later stage of disease.<sup>5,8-14</sup>

Recently, G n reux et al<sup>15</sup> introduced a staging classification to semiquantitatively assess the extent of extra-aortic valve cardiac damage.<sup>15</sup> This staging scheme has been associated with prognosis in patients undergoing TAVR,<sup>16-19</sup> and it may provide insights into the appropriate timing of TAVR. Given the sex-specific differences in myocardial remodeling to AS<sup>20,21</sup> and the influence of sex hormones on pulmonary vascular resistance,<sup>22</sup> the accumulation of cardiac damage and its prognostic value may differ between the sexes. In this study, we aimed to investigate sex-related differences in the extent of extra-aortic valve cardiac damage in patients undergoing TAVR and explore their association with prognosis.

## METHODS

**STUDY DESIGN AND POPULATION.** Consecutive patients with AS who underwent TAVR at Bern University Hospital were systematically enrolled in an institutional prospective registry. This registry is nested into the nationwide SwissTAVI registry (NCT01368250).<sup>23</sup> For the purpose of the present study, we excluded patients with incomplete or unavailable echocardiographic records to assess cardiac damage before TAVR. The registry was 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 assessed according to the established classification by G n reux et al.<sup>15</sup> Patients were categorized as follows: stage 0, no extra-aortic valve cardiac damage; stage 1, left ventricular (LV) damage (left ventricular ejection fraction [LVEF] <50%, LV mass index >95 g/m<sup>2</sup> in women, >115 g/m<sup>2</sup> in men, or LV diastolic dysfunction grade  $\geq$  II); stage 2, left atrial or mitral valve damage (left atrial volume index >34 mL/m<sup>2</sup>, mitral regurgitation  $\geq$  moderate, or presence of atrial fibrillation [AF]); stage 3, pulmonary vasculature or

tricuspid valve damage (systolic pulmonary artery pressure  $\geq$ 60 mm Hg or tricuspid regurgitation  $\geq$  moderate); and stage 4, right ventricular (RV) damage. Patients were hierarchically categorized into the most advanced stage if they met at least 1 of the criteria within that stage. As previously validated, we grouped these 5 stages into early (stage 0, 1, or 2) and advanced (stage 3 or 4) and compared baseline characteristics between sexes.<sup>24</sup>

Comprehensive transthoracic echocardiography was conducted by a board-certified cardiologist and echocardiography specialist before TAVR according to the current American Society of Echocardiography guidelines.<sup>25</sup> Acquired images were independently re-evaluated by experienced imaging specialists in the Bern imaging core laboratory. RV dysfunction was defined based on the recommendation by the American Society of Echocardiography.<sup>26</sup>

**DATA COLLECTION AND CLINICAL ENDPOINTS.** Baseline clinical, procedural, and follow-up data were prospectively recorded in a dedicated database maintained by the clinical trial unit of the University of Bern. Regular clinical follow-up was scheduled at 30 days, 1 year, 5 years, and 10 years after TAVR, and the data were collected through standardized interviews, documentation from referring physicians, and hospital discharge summaries, as previously described.<sup>27</sup> All adverse events were systematically documented and adjudicated by an independent clinical event committee in accordance with the Valve Academic Research Consortium definitions applicable at the time of the procedure.<sup>28-30</sup> The primary outcomes of interest in the present study were all-cause and cardiovascular mortality after TAVR.

**STATISTICAL ANALYSIS.** Categorical variables were expressed as frequencies and percentages, and group comparisons were assessed using the chi-square test or Fisher exact test as appropriate. Continuous variables were presented as mean  $\pm$  SD and analyzed among groups using the F test derived from an analysis of variance or Kruskal-Wallis test complemented by pairwise Wilcoxon tests with correction for multiple testing when necessary. Time-to-event curves were constructed using the Kaplan-Meier method. First, we used a univariate Kaplan-Meier analysis with a log-rank test to evaluate the associations between each independent candidate variable and the primary outcome. Second, we conducted a comparison of the residuals from the resulting survival curves and the Schoenfeld global test to assess the proportional hazards assumption for these variables. For comparisons

## ABBREVIATIONS AND ACRONYMS

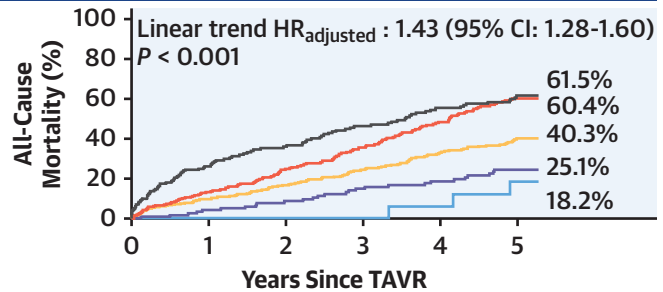
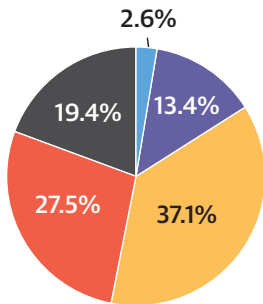
<b>AF</b>	= atrial fibrillation
<b>AS</b>	= aortic stenosis
<b>AVR</b>	= aortic valve replacement
<b>COPD</b>	= chronic obstructive pulmonary disease
<b>LV</b>	= left ventricular
<b>LVEF</b>	= left ventricular ejection fraction
<b>RV</b>	= right ventricular
<b>TAVR</b>	= transcatheter aortic valve replacement

**CENTRAL ILLUSTRATION** Prognostic Value of Cardiac Damage Staging Classification in Women and Men and the Association of Female Sex With All-Cause Mortality in Each Stage of Cardiac Damage

**Bern TAVI Registry: Sex-Specific Differences in Upstream Cardiac Damage in Patients With Aortic Stenosis Undergoing TAVR, N = 2,026**

**Clinical Outcome According to Cardiac Damage Staging Classification in Women (n = 995)**

Cardiac Damage Stage in Women

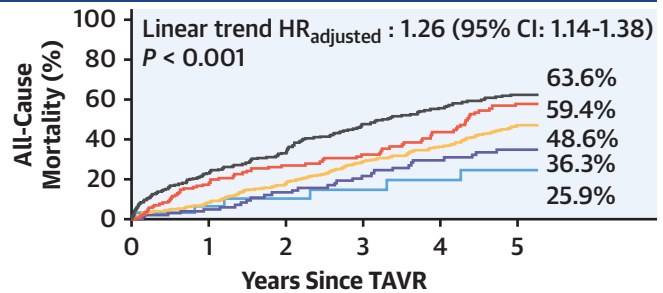
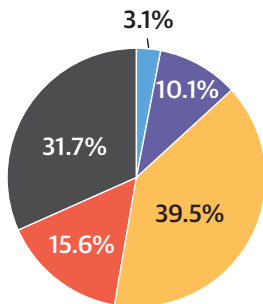


No. at Risk:

	0	1	2	3	4	5
Stage 0	26	24	20	19	16	12
Stage 1	133	115	102	94	85	65
Stage 2	369	296	235	207	171	122
Stage 3	274	203	160	133	96	62
Stage 4	193	126	93	76	59	44

**Clinical Outcome According to Cardiac Damage Staging Classification in Men (n = 1,031)**

Cardiac Damage Stage in Men



No. at Risk:

	0	1	2	3	4	5
Stage 0	32	26	21	19	16	13
Stage 1	104	87	70	61	52	38
Stage 2	407	327	247	206	166	109
Stage 3	161	107	79	71	54	32
Stage 4	327	208	149	114	83	54

■ Stage 0 ■ Stage 1 ■ Stage 2 ■ Stage 3 ■ Stage 4

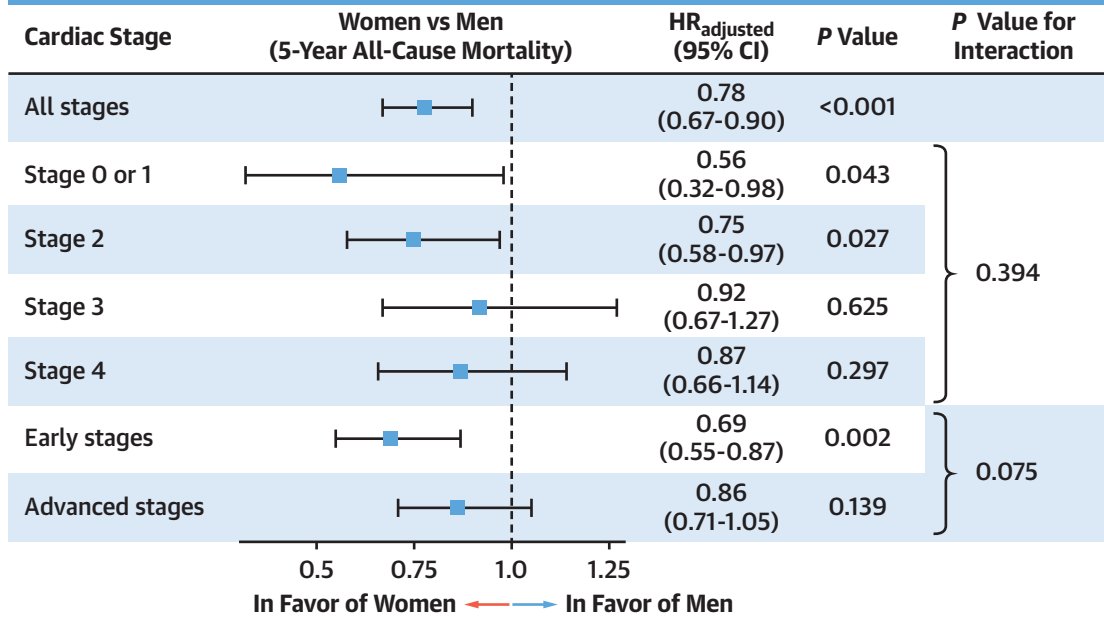
Nakase M, et al. J Am Coll Cardiol Intv. 2024;17(10):1252-1264.

TAVR = transcatheter aortic valve replacement.

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**CENTRAL ILLUSTRATION** Continued

**The Impact of Female Sex on All-Cause Mortality in Each Stage of Cardiac Damage**



- The distribution of cardiac damage stage differed by sex, with stage 3 being more prevalent in women and stage 4 being more prevalent in men
- The cardiac damage staging classification stratified long-term survival after TAVR, irrespective of sex
- Female sex was an independent predictor of lower mortality in early stages (stages 0, 1, or 2), but not in advanced stages of upstream cardiac damage (stages 3 or 4)

Nakase M, et al. J Am Coll Cardiol Interv. 2024;17(10):1252-1264.

involving more than 2 cardiac stages, HRs with 95% CIs and P values for linear trends were also reported. Multivariable models selected and introduced the following covariates: age, body mass index, Society of Thoracic Surgeons Predicted Risk of Mortality, NYHA functional class III or IV, hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD), coronary artery disease, peripheral artery disease, and the use of a contemporary device (SAPIEN 3/Ultra [Edwards], Evolut R/Pro/Pro+ [Medtronic], ACURATE Neo/Neo2 [Boston Scientific], and Navitor [Abbott]). Statistical analysis was performed using SPSS software version 23.0 (IBM Corp). All statistical tests were 2-sided, and significance was set at P values < 0.05.

**RESULTS**

**STUDY POPULATION AND BASELINE CHARACTERISTICS.**

Among 3,586 consecutive patients undergoing TAVR

between August 2007 and June 2022, 2,026 patients were included in the present analysis. Of these, 995 patients (49.1%) were women (mean age: 83.1 ± 5.7 years), and 1,031 (50.9%) were men (mean age: 81.2 ± 6.8 years). The prevalence of stages of cardiac damage in women and men is summarized in the Central Illustration and Table 1. In women, 26 (2.6%) patients had stage 0, 133 (13.4%) had stage 1, 369 (37.1%) had stage 2, 274 (27.5%) had stage 3, and 193 (19.4%) had stage 4. In men, 32 (3.1%) patients were categorized as stage 0, 104 (10.1%) as stage 1, 407 (39.5%) as stage 2, 161 (15.6%) as stage 3, and 327 (31.7%) as stage 4. There was no significant difference in the distribution of early (52.7% vs 53.1%) and advanced stages of cardiac damage (47.3% vs 46.9%) according to sex (P = 0.858). Baseline characteristics according to the cardiac damage stage in women and men are shown in Tables 2 and 3. In both sexes, a gradual increase in the cardiac damage stage was associated with an increased

**TABLE 1** The Differences in Components of Cardiac Damage Between Sexes

	Women (n = 995)	Men (n = 1,031)	P Value
Stage 0	26 (2.6)	32 (3.1)	0.508
Stage 1	133 (13.4)	104 (10.1)	0.022
LVEF <50%	227/992 (22.9)	374/1,029 (36.5)	<0.001
LV hypertrophy	571/689 (82.9)	490/699 (70.1)	<0.001
E/e' ≥14	393/525 (74.9)	321/523 (61.4)	<0.001
Stage 2	369 (37.1)	407 (39.5)	0.268
Left atrial dilatation	620/888 (69.8)	705/947 (74.4)	0.027
Presence of atrial fibrillation	352/995 (35.4)	417/1,031 (40.4)	0.019
Moderate/severe mitral regurgitation	289/988 (29.3)	233/1,021 (22.8)	0.001
Stage 3	274 (27.5)	161 (15.6)	<0.001
PASP ≥60 mm Hg	232/959 (24.2)	174/971 (17.9)	<0.001
Moderate/severe tricuspid regurgitation	227/992 (22.9)	179/1,024 (17.5)	0.002
Stage 4	193 (19.4)	327 (31.7)	<0.001
RV dysfunction	193/995 (19.4)	327/1,031 (31.7)	<0.001

Values are n (%) or n/N (%).  
LV = left ventricular; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; RV = right ventricular.

surgical risk, advanced heart failure symptoms (NYHA functional class III or IV), a higher prevalence of concomitant disease including hypertension, chronic kidney disease, AF, previous history of myocardial infarction, cardiac surgery, permanent pacemaker implantation, and higher prescription of beta-blockers. In women, the aortic valve area decreased with worsening stage of cardiac damage but not in men. All components of cardiac damage assessed by echocardiography worsened as the cardiac stage progressed.

**Table 4** shows the differences in baseline characteristics between women and men in early (stage 0, 1, or 2) and advanced stages (stage 3 or 4) of cardiac damage. In both early and advanced stages, women were more likely to be older, have a higher surgical risk, have greater LVEF, and have chronic kidney disease compared with men. Men had a higher prevalence of COPD, coronary artery disease, peripheral artery disease, and a previous history of myocardial infarction and cardiac surgery than women in both early and advanced stages. There was no significant difference in the prescription rate of cardioprotective medication. Comparisons between women and men for each stage of cardiac damage are shown in **Supplemental Table 1**. The observed trends remained consistent across all stages of cardiac damage.

**CLINICAL OUTCOMES.** The median follow-up time after TAVR was 1,112 days (Q1-Q3: 367-1,825 days) in women and 947 days (Q1-Q3: 364-1,824 days) in men. Clinical outcomes at 1 and 5 years according to cardiac damage stage are summarized in **Table 5** and depicted

in the **Central Illustration** and **Figure 1**. There was a stepwise increase in 5-year all-cause and cardiovascular mortality according to the cardiac damage stage in both women (HR<sub>adjusted</sub>: 1.43; 95% CI: 1.28-1.60;  $P < 0.001$  and HR<sub>adjusted</sub>: 1.49; 95% CI: 1.31-1.70;  $P < 0.001$ , for linear trend) and men (HR<sub>adjusted</sub>: 1.26; 95% CI: 1.14-1.38;  $P < 0.001$  and HR<sub>adjusted</sub>: 1.36; 95% CI: 1.21-1.53;  $P < 0.001$ , for linear trend). The **Central Illustration** shows the association of female sex with 5-year all-cause mortality. In the overall population, women had a lower mortality than men (HR<sub>adjusted</sub>: 0.78; 95% CI: 0.67-0.90;  $P < 0.001$ ). This trend was consistent across early stages of cardiac damage including stage 0 or 1 (HR<sub>adjusted</sub>: 0.56; 95% CI: 0.32-0.98;  $P = 0.043$ ) and stage 2 (HR<sub>adjusted</sub>: 0.75; 95% CI: 0.58-0.97;  $P = 0.027$ ), but there was similar mortality between sexes in advanced stages of cardiac damage including stages 3 (HR<sub>adjusted</sub>: 0.92; 95% CI: 0.67-1.27;  $P = 0.625$ ) and 4 (HR<sub>adjusted</sub>: 0.87; 95% CI: 0.66-1.14;  $P = 0.297$ ) ( $P$  for interaction = 0.394 among all stages and  $P$  for interaction = 0.075 between early and advanced stages). A similar trend was observed for cardiovascular mortality (**Figure 2**).

**SENSITIVITY ANALYSIS.** Given the long enrollment period of this study, we performed a sensitivity analysis including 1,290 patients treated with contemporary devices. As shown in **Supplemental Figures 1** and **2**, the distribution of cardiac damage was similar to that in the main analysis, and the cardiac staging classification stratified long-term mortality in both women and men. Women tended to have lower mortality in early stages of cardiac damage, but this advantage was not statistically significant (**Supplemental Figure 3**).

Considering the difference in patient characteristics between AS subtypes according to the flow-gradient pattern,<sup>24,31</sup> we investigated the interaction of sex and cardiac damage in 3 major subtypes, including high-gradient AS, classical low-flow low-gradient AS, and low-flow low-gradient AS with preserved LVEF. As shown in **Supplemental Figure 4**, women with early stages of cardiac damage had a lower 5-year mortality than men only in the high-gradient AS subtype.

## DISCUSSION

The main findings of this study are as follows:

1. The distribution of cardiac damage stage differed by sex, with stage 3 more prevalent in women and stage 4 more prevalent in men, but there was no significant difference in early vs advanced stages according to sex.

**TABLE 2 Baseline Clinical and Echocardiographic Characteristics in Women**

	Total Population (N = 995)	Stage 0 (n = 26)	Stage 1 (n = 133)	Stage 2 (n = 369)	Stage 3 (n = 274)	Stage 4 (n = 193)	P Value
Age, y	83.1 ± 5.7	82.3 ± 5.2	81.5 ± 6.3	83.2 ± 5.3	84.1 ± 5.6	82.6 ± 6.0	<0.001
Body mass index, kg/cm <sup>2</sup>	26.1 ± 6.1	27.5 ± 7.7	26.0 ± 5.7	26.7 ± 5.9	26.2 ± 6.1	24.9 ± 6.1	0.02
STS-PROM, %	6.1 ± 4.2	4.4 ± 2.4	4.6 ± 2.9	5.5 ± 4.0	6.7 ± 4.3	7.7 ± 4.9	<0.001
NYHA functional class III or IV	698 (70.2)	15 (57.7)	83 (62.4)	245 (66.6)	205 (74.8)	150 (77.7)	0.003
Concomitant diseases							
Hypertension	857 (86.1)	19 (73.1)	108 (81.2)	325 (88.1)	242 (88.3)	163 (84.5)	0.058
Diabetes mellitus	243 (24.4)	5 (19.2)	32 (24.1)	74 (20.1)	78 (28.5)	54 (28.0)	0.093
CKD, eGFR <60 mL/min/1.73 m <sup>2</sup>	769 (77.4)	15 (57.7)	94 (70.7)	274 (74.3)	227 (82.8)	159 (82.8)	<0.001
COPD	85 (8.6)	1 (3.8)	11 (8.3)	26 (7.1)	32 (11.7)	15 (7.8)	0.245
Coronary artery disease	496 (49.8)	6 (23.1)	65 (48.9)	171 (46.3)	134 (48.9)	120 (62.2)	<0.001
Atrial fibrillation	352 (35.4)	0 (0)	0 (0)	129 (35.0)	115 (42.0)	108 (56.0)	<0.001
Previous history							
Previous myocardial infarction	98 (9.8)	0 (0)	12 (9.0)	28 (7.6)	25 (9.1)	33 (17.1)	0.002
Previous cardiac surgery	76 (7.6)	0 (0)	4 (3.0)	16 (4.3)	17 (6.2)	39 (20.2)	<0.001
Previous stroke	115 (11.6)	1 (3.8)	12 (9.0)	45 (12.2)	31 (11.3)	26 (13.5)	0.524
Previous permanent pacemaker implantation	78 (7.8)	1 (3.8)	6 (4.5)	26 (7.0)	24 (8.8)	21 (10.9)	0.221
Peripheral artery disease	111 (11.2)	1 (3.8)	12 (9.0)	40 (10.8)	31 (11.3)	27 (14.0)	0.46
Echocardiographic parameter							
Aortic valve area, cm <sup>2</sup>	0.71 ± 0.24	0.81 ± 0.23	0.76 ± 0.32	0.72 ± 0.21	0.71 ± 0.26	0.63 ± 0.22	<0.001
Aortic valve area index, cm <sup>2</sup> /m <sup>2</sup>	0.42 ± 0.15	0.45 ± 0.12	0.46 ± 0.22	0.42 ± 0.12	0.42 ± 0.15	0.38 ± 0.13	0.014
Aortic valve mean gradient, mm Hg	41.1 ± 17.7	31.9 ± 11.3	41.7 ± 15.1	44.0 ± 17.5	42.2 ± 18.7	35.7 ± 17.1	<0.001
LVEF, %	56.2 ± 13.5	65.4 ± 5.1	59.7 ± 10.9	59.3 ± 11.6	56.1 ± 12.2	46.9 ± 16.1	<0.001
LVEF <50%	227 (22.9)	0 (0)	19 (14.4)	53 (14.4)	60 (22.0)	95 (50.5)	<0.001
LVEF <40%	122 (12.3)	0 (0)	9 (6.8)	26 (7.1)	29 (10.6)	58 (30.1)	<0.001
E/e'	21.6 ± 11.4	10.2 ± 3.0	18.7 ± 7.7	21.1 ± 11.0	25.1 ± 11.2	23.8 ± 14.7	<0.001
Left ventricular mass index, g/m <sup>2</sup>	131.1 ± 46.1	78.1 ± 17.8	125.9 ± 45.1	131.0 ± 46.8	137.1 ± 46.6	134 ± 42.8	<0.001
Left atrial volume index, mL/m <sup>2</sup>	44.2 ± 17.2	27.6 ± 4.6	26.5 ± 5.6	45.6 ± 14.4	48.8 ± 17.8	51.3 ± 17.8	<0.001
Moderate or severe mitral regurgitation	289 (29.3)	0 (0)	0 (0)	77 (21.0)	115 (42.4)	97 (50.5)	<0.001
Moderate or severe tricuspid regurgitation	227 (22.9)	0 (0)	0 (0)	0 (0)	156 (57.4)	71 (37.0)	<0.001
Pulmonary artery systolic pressure, mm Hg	46.0 ± 19.8	28.4 ± 15.9	32.2 ± 15.5	37.2 ± 14.6	61.1 ± 16.9	55.5 ± 16.8	<0.001
Tricuspid annular plane systolic excursion, cm	0.71 ± 0.24	0.81 ± 0.23	0.76 ± 0.32	0.72 ± 0.21	0.71 ± 0.26	0.63 ± 0.22	<0.001
S', cm/s	41.1 ± 17.7	31.9 ± 11.3	41.7 ± 15.1	44.0 ± 17.5	42.2 ± 18.7	35.7 ± 17.1	<0.001
Fractional area change, %	56.2 ± 13.5	65.4 ± 5.1	59.7 ± 10.9	59.3 ± 11.6	56.1 ± 12.2	46.9 ± 16.1	<0.001
Medication							
Beta-blocker	537 (54.0)	8 (30.8)	53 (39.8)	192 (52.0)	155 (56.6)	129 (66.8)	<0.001
RAS inhibitor	559 (56.2)	15 (60.0)	76 (57.1)	220 (59.6)	141 (51.5)	107 (55.4)	0.343

Values are mean ± SD or n (%). RAS inhibitors include angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor/neprilysin inhibitor.  
CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; RAS = renin-angiotensin-system; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; other abbreviation as in Table 1.

- Women were older and had a higher surgical risk across all stages, whereas comorbidities that may contribute to worsening cardiac damage, including COPD, ischemic heart disease, or a history of cardiac surgery, were more common in men across all stages.
- The cardiac damage staging classification was useful to stratify long-term survival after TAVR irrespective of sex.
- Female sex was associated with lower mortality in early stages (stages 0, 1, or 2) but not in advanced stages of upstream cardiac damage (stages 3 or 4).

Previous studies have shown that women compared to men exhibit a more gradual progression of AS,<sup>32</sup> present with symptoms of AS at an older age, and have more advanced frailty.<sup>7</sup> During the era when surgical AVR was the predominant treatment modality, women experienced higher rates of adverse events and in-hospital mortality, resulting in an increased rate of undertreatment.<sup>4,5,7</sup> In the TAVR population, female patients also tend to be older and have a higher prevalence of heart failure symptoms.<sup>5,8-14</sup> However, these differences did not translate into significant differences in clinical outcomes after TAVR between women and men.<sup>9,10</sup>

**TABLE 3** Baseline Clinical and Echocardiographic Characteristics in Men

	Total Population (N = 1,031)	Stage 0 (n = 32)	Stage 1 (n = 104)	Stage 2 (n = 407)	Stage 3 (n = 161)	Stage 4 (n = 327)	P Value
Age, y	81.2 ± 6.8	78.7 ± 7.7	79.6 ± 6.1	81.5 ± 6.3	82.7 ± 6.0	80.8 ± 7.7	<0.001
Body mass index, kg/cm <sup>2</sup>	26.4 ± 4.8	26.1 ± 5.7	27.1 ± 4.6	26.7 ± 4.8	26.5 ± 4.4	25.8 ± 4.7	0.06
STS-PROM, %	5.0 ± 3.7	3.7 ± 2.3	3.3 ± 2.2	4.5 ± 3.2	5.4 ± 4.0	6.1 ± 4.3	<0.001
NYHA functional class III or IV	674 (65.4)	15 (46.9)	54 (51.9)	250 (61.4)	108 (67.1)	247 (75.8)	<0.001
Concomitant diseases							
Hypertension	883 (85.6)	26 (81.3)	86 (82.7)	353 (86.7)	140 (87.0)	278 (85.0)	0.743
Diabetes mellitus	293 (28.4)	11 (34.4)	23 (22.1)	104 (25.6)	42 (26.1)	113 (34.6)	0.03
CKD, eGFR <60 mL/min/1.73 m <sup>2</sup>	651 (63.2)	16 (50.0)	49 (47.1)	247 (60.7)	110 (68.3)	229 (70.2)	<0.001
COPD	159 (15.4)	6 (18.8)	17 (16.3)	58 (14.3)	24 (14.9)	54 (16.6)	0.89
Coronary artery disease	714 (69.3)	22 (68.8)	69 (66.3)	267 (65.6)	111 (68.9)	245 (74.9)	0.095
Atrial fibrillation	417 (40.4)	0 (0)	0 (0)	165 (40.5)	78 (48.4)	174 (53.2)	<0.001
Previous history							
Previous myocardial infarction	211 (20.5)	2 (6.3)	15 (14.4)	73 (17.9)	36 (22.4)	85 (26.0)	0.006
Previous cardiac surgery	241 (23.4)	7 (21.9)	14 (13.5)	70 (17.2)	27 (16.8)	123 (37.6)	<0.001
Previous stroke	147 (14.3)	2 (6.3)	8 (7.7)	68 (16.7)	23 (14.3)	46 (14.1)	0.118
Previous permanent pacemaker implantation	114 (11.1)	0 (0)	2 (1.9)	36 (8.8)	19 (11.8)	57 (17.4)	<0.001
Peripheral artery disease	167 (16.2)	3 (9.4)	18 (17.3)	57 (14.0)	27 (16.8)	62 (19.0)	0.341
Echocardiographic parameter							
Aortic valve area, cm <sup>2</sup>	0.82 ± 0.30	0.82 ± 0.17	0.81 ± 0.24	0.85 ± 0.35	0.79 ± 0.27	0.82 ± 0.28	0.501
Aortic valve area index, cm <sup>2</sup> /m <sup>2</sup>	0.44 ± 0.17	0.45 ± 0.10	0.41 ± 0.11	0.45 ± 0.21	0.42 ± 0.14	0.43 ± 0.15	0.400
Aortic valve mean gradient, mm Hg	36.7 ± 16.1	36.1 ± 15.1	41.9 ± 14.4	39.8 ± 15.8	38.7 ± 16.6	31.1 ± 15.3	<0.001
LVEF, %	50.6 ± 14.7	61.3 ± 4.3	57.7 ± 11.4	53.8 ± 13.1	49.9 ± 14.4	43.9 ± 15.4	<0.001
LVEF <50%	376 (36.5)	0 (0)	20 (19.2)	116 (28.6)	62 (38.5)	178 (54.6)	<0.001
LVEF <40%	234 (22.7)	0 (0)	8 (7.7)	66 (16.3)	36 (22.4)	124 (38.0)	<0.001
E/e'	17.9 ± 8.6	11.2 ± 1.8	16.3 ± 6.4	17.5 ± 8.4	21.5 ± 9.8	19.5 ± 9.6	<0.001
Left ventricular mass index, g/m <sup>2</sup>	142.7 ± 47.2	88.9 ± 16.4	138.3 ± 35.4	142.5 ± 45.7	143.7 ± 48.4	150.3 ± 50.3	<0.001
Left atrial volume index, mL/m <sup>2</sup>	45.0 ± 21.2	25.6 ± 5.9	26.2 ± 5.7	45.9 ± 12.4	48.4 ± 26.7	50.8 ± 26.1	<0.001
Moderate or severe mitral regurgitation	233 (22.8)	0 (0)	0 (0)	63 (15.6)	60 (37.7)	110 (34.3)	<0.001
Moderate or severe tricuspid regurgitation	179 (17.5)	0 (0)	0 (0)	0 (0)	82 (51.6)	97 (30.1)	<0.001
Pulmonary artery systolic pressure, mm Hg	43.0 ± 19.8	34.1 ± 13.9	30.6 ± 16.2	35.3 ± 16.0	61.4 ± 19.7	49.9 ± 17.1	<0.001
Tricuspid annular plane systolic excursion, cm	19.2 ± 5.8	21.4 ± 3.8	23.5 ± 4.6	22.2 ± 4.4	21.1 ± 4.2	13.0 ± 2.7	<0.001
S', cm/s	11.5 ± 3.2	13.1 ± 2.5	13.6 ± 2.9	12.8 ± 2.5	12.4 ± 2.2	8.6 ± 2.3	<0.001
Fractional area change, %	39.5 ± 10.4	47.5 ± 5.5	43.8 ± 10.2	44.2 ± 7.7	42.5 ± 9.1	31.2 ± 8.8	<0.001
Medication							
Beta-blocker	552 (53.6)	14 (43.8)	50 (48.1)	205 (50.4)	88 (54.7)	195 (60.0)	0.047
RAS inhibitor	585 (56.9)	19 (59.4)	56 (53.8)	233 (57.4)	74 (46.3)	203 (62.3)	0.019

Values are mean ± SD or n (%).

Abbreviations as in Table 2.

Prolonged pressure overload resulting from AS causes upstream myocardial damage that impacts prognosis.<sup>33</sup> The cardiac damage staging classification introduced by Généreux et al has proven to have important prognostic implications after AVR.<sup>15</sup> In the present study, there was a similar distribution of early stages (52.7% vs 53.1%) and advanced stages (47.3% vs 46.9%) of cardiac damage between sexes. These results suggest that women undergoing TAVR do not necessarily present with more advanced cardiac damage than men despite being older and frailer. However, these results must be interpreted in light of

the fact that cardiac damage exclusively caused by AS is difficult to compare because of sex-related differences in comorbidities, which may influence cardiac damage. Men had a higher prevalence of COPD, coronary artery disease, and previous cardiac surgery across all stages of cardiac damage. These comorbidities have the potential to independently induce myocardial damage irrespective of the cumulative cardiac damage associated with AS.<sup>34</sup> In contrast, women had fewer comorbidities, suggesting that the accumulation of cardiac damage may be primarily attributable to the persistent pressure overload caused

**TABLE 4** Baseline Characteristics in Early Stage and Advanced Stage of Cardiac Damage According to Sex

	Total Population			Early Stages			Advanced Stages		
	Women (N = 995)	Men (N = 1,031)	P Value	Women (n = 528)	Men (n = 543)	P Value	Women (n = 467)	Men (n = 488)	P Value
Age, y	83.1 ± 5.7	81.2 ± 6.8	<0.001	82.7 ± 5.6	80.9 ± 6.4	<0.001	83.5 ± 5.8	81.4 ± 7.2	<0.001
Body mass index, kg/cm <sup>2</sup>	26.1 ± 6.1	26.4 ± 4.8	0.254	26.5 ± 6.0	26.8 ± 4.8	0.523	25.7 ± 6.1	26.0 ± 4.6	0.315
STS-PROM, %	6.1 ± 4.2	5.0 ± 3.7	<0.001	5.2 ± 3.7	4.3 ± 3.0	<0.001	7.1 ± 4.5	5.9 ± 4.2	<0.001
NYHA functional class III or IV	698 (70.2)	674 (65.4)	0.021	343 (65.1)	319 (58.7)	0.033	355 (76.0)	355 (72.9)	0.269
Concomitant diseases									
Hypertension	857 (86.1)	883 (85.6)	0.754	452 (85.6)	465 (85.6)	0.989	405 (86.7)	418 (85.7)	0.633
Diabetes mellitus	243 (24.4)	293 (28.4)	0.041	111 (21.0)	138 (25.4)	0.089	132 (28.3)	155 (31.8)	0.239
CKD, eGFR <60 mL/min/1.73 m <sup>2</sup>	769 (77.4)	651 (63.2)	<0.001	383 (72.5)	312 (57.5)	<0.001	386 (82.8)	339 (69.6)	<0.001
COPD	85 (8.6)	159 (15.4)	<0.001	38 (7.2)	81 (14.9)	<0.001	47 (10.1)	78 (16.0)	0.007
Coronary artery disease	496 (49.8)	714 (69.3)	<0.001	242 (45.8)	358 (65.9)	<0.001	254 (54.4)	356 (73.0)	<0.001
Atrial fibrillation	352 (35.4)	417 (40.4)	0.019	129 (24.4)	165 (30.4)	0.029	223 (47.8)	252 (51.6)	0.23
Previous history									
Previous myocardial infarction	98 (9.8)	211 (20.5)	<0.001	40 (7.6)	90 (16.6)	<0.001	58 (12.4)	121 (24.8)	<0.001
Previous cardiac surgery	76 (7.6)	241 (23.4)	<0.001	20 (3.8)	91 (16.8)	<0.001	56 (12.0)	150 (30.7)	<0.001
Previous stroke	115 (11.6)	147 (14.3)	0.07	58 (11.0)	78 (14.4)	0.097	57 (12.2)	69 (14.1)	0.377
Previous permanent pacemaker implantation	78 (7.8)	114 (11.1)	0.013	33 (6.3)	38 (7.0)	0.623	45 (9.6)	76 (15.6)	0.006
Peripheral artery disease	111 (11.2)	167 (16.2)	<0.001	53 (10.0)	78 (14.4)	0.031	58 (12.4)	89 (18.2)	0.013
Echocardiographic parameter									
Aortic valve area, cm <sup>2</sup>	0.71 ± 0.24	0.82 ± 0.30	<0.001	0.74 ± 0.24	0.84 ± 0.32	<0.001	0.68 ± 0.24	0.81 ± 0.28	<0.001
Aortic valve area index, cm <sup>2</sup> /m <sup>2</sup>	0.42 ± 0.15	0.44 ± 0.17	0.051	0.43 ± 0.15	0.44 ± 0.19	0.412	0.41 ± 0.14	0.43 ± 0.15	0.052
Aortic valve mean gradient, mm Hg	41.1 ± 17.7	36.7 ± 16.1	<0.001	43.0 ± 17.0	39.9 ± 15.6	0.011	39.3 ± 18.3	33.6 ± 16.1	<0.001
LVEF, %	56.2 ± 13.5	50.6 ± 14.7	<0.001	59.7 ± 11.3	55.0 ± 12.7	<0.001	52.3 ± 14.7	45.9 ± 15.3	<0.001
LVEF <50%	227 (22.9)	376 (36.5)	<0.001	72 (13.7)	136 (25.1)	<0.001	155 (33.3)	240 (49.3)	<0.001
LVEF <40%	122 (12.3)	234 (22.7)	<0.001	35 (6.7)	74 (13.7)	<0.001	87 (18.7)	160 (32.9)	<0.001
E/e'	21.6 ± 11.4	17.9 ± 8.6	<0.001	19.7 ± 10.1	16.7 ± 7.8	<0.001	24.6 ± 12.5	20.2 ± 9.7	<0.001
Left ventricular mass index, g/m <sup>2</sup>	131.1 ± 46.1	142.7 ± 47.2	<0.001	126.9 ± 46.7	137.8 ± 44.4	<0.001	136.0 ± 45.1	148.1 ± 49.7	<0.001
Left atrial volume index, mL/m <sup>2</sup>	44.2 ± 17.2	45.0 ± 21.2	0.383	44.2 ± 17.2	45.0 ± 21.2	0.209	49.9 ± 17.8	50.1 ± 26.3	0.003
Moderate or severe mitral regurgitation	289 (29.3)	233 (22.8)	0.001	77 (14.7)	63 (11.6)	0.144	212 (45.8)	170 (35.4)	0.001
Moderate or severe tricuspid regurgitation	227 (22.9)	179 (17.5)	0.002	0 (0)	0 (0)	—	227 (48.9)	179 (37.2)	<0.001
Pulmonary artery systolic pressure, mm Hg	46.0 ± 19.8	43.0 ± 19.8	<0.001	35.5 ± 15.1	34.3 ± 16.0	0.241	58.8 ± 17.1	53.9 ± 18.9	<0.001
Tricuspid annular plane systolic excursion, cm	20.0 ± 5.6	19.2 ± 5.8	0.011	22.4 ± 4.2	22.4 ± 4.6	0.94	17.6 ± 5.7	15.8 ± 5.1	<0.001
S', cm/s	12.1 ± 3.1	11.5 ± 3.2	<0.001	13.2 ± 2.8	13.0 ± 2.6	0.295	11.0 ± 3.1	9.9 ± 2.9	<0.001
Fractional area change, %	42.5 ± 10.1	39.5 ± 10.4	<0.001	46.4 ± 8.5	44.3 ± 8.1	0.009	38.6 ± 10.2	35.0 ± 10.4	<0.001
Medication									
Beta-blocker	537 (54.0)	552 (53.6)	0.883	253 (47.9)	269 (49.5)	0.595	284 (60.8)	283 (58.2)	0.417
RAS inhibitor	559 (56.2)	585 (56.9)	0.762	311 (59.0)	308 (56.8)	0.469	248 (53.1)	277 (57.0)	0.227

Values are mean ± SD or n (%).  
Abbreviations as in Table 2.

by AS. These findings underscore that the progression of cardiac damage is driven by AS itself as well as comorbidities, highlighting the importance of tailored treatment strategies to address underlying disease in patients with severe AS undergoing AVR. Importantly, despite these differences, cardiac damage staging classification proved effective in the stratification of 5-year outcomes in both women and men.

Among advanced stages of cardiac damage, stage 3 was more prevalent in women, whereas stage 4 was more frequently observed in men. This trend is

consistent with previous studies that validated the cardiac damage classification.<sup>17-19</sup> Sex-specific differences in myocardial and pulmonary vascular response to AS may result in differences in upstream cardiac damage.<sup>20,21</sup> Female sex is associated with a higher risk of pulmonary vascular disease, possibly influenced by the multifactorial effects of estrogen on pulmonary vascular remodeling.<sup>22</sup> In this context, women with AS may be more susceptible to pulmonary hypertension than men with AS. A meta-analysis showed that pulmonary hypertension was more



**TABLE 5 Clinical Outcomes According to Cardiac Damage Stage and Sex**

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Linear Trend HR <sub>adjusted</sub> (95% CI)	P Value
<b>Women</b>							
At 1 y							
All-cause mortality	0 (0)	5 (4.2)	34 (10.3)	34 (14.3)	49 (28.0)	1.63 (1.33-1.99)	<0.001
Cardiovascular mortality	0 (0)	1 (0.8)	21 (6.4)	24 (10.1)	35 (20.0)	1.90 (1.47-2.45)	<0.001
At 5 y							
All-cause mortality	3 (18.2)	27 (25.1)	116 (40.3)	128 (60.4)	99 (61.5)	1.43 (1.28-1.60)	<0.001
Cardiovascular mortality	3 (18.2)	17 (16.8)	78 (30.5)	93 (49.2)	73 (49.8)	1.49 (1.31-1.70)	<0.001
<b>Men</b>							
At 1 y							
All-cause mortality	2 (7.1)	5 (5.4)	33 (9.3)	28 (21.1)	73 (26.3%)	1.51 (1.27-1.80)	<0.001
Cardiovascular mortality	0 (0)	1 (1.0)	19 (5.4)	15 (11.3)	55 (19.8%)	1.90 (1.50-2.41)	<0.001
At 5 y							
All-cause mortality	6 (25.9)	29 (36.3)	145 (48.6)	69 (59.4)	158 (63.6)	1.26 (1.14-1.38)	<0.001
Cardiovascular mortality	2 (10.7)	18 (24.4)	90 (34.2)	44 (49.5)	115 (52.5)	1.36 (1.21-1.53)	<0.001

Values are n (%).

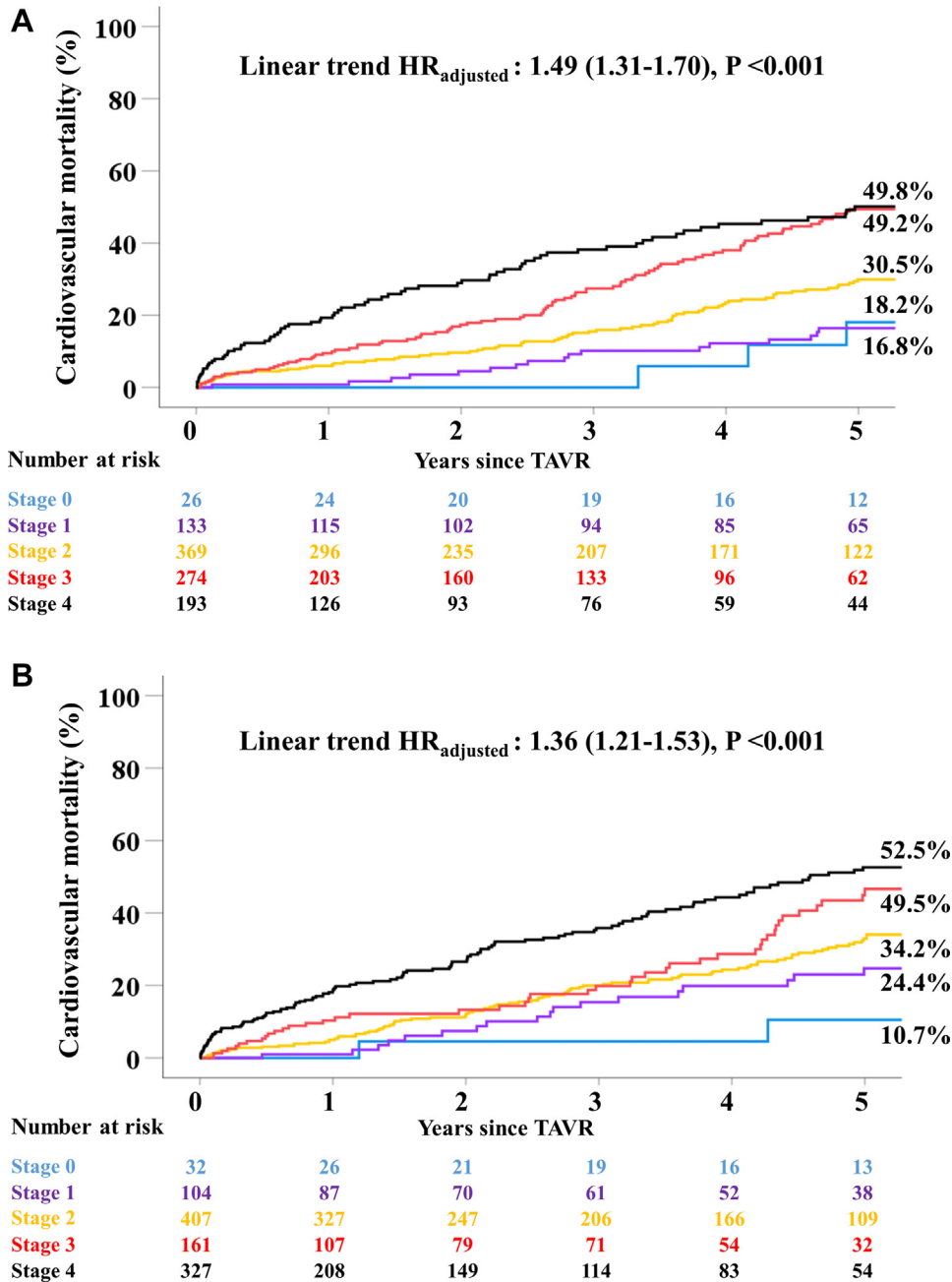
common in female than in male patients undergoing TAVR.<sup>35</sup> Similarly, a study of pulmonary hypertension in patients with mitral stenosis showed that women had more adverse and less reversible pulmonary vascular remodeling than men.<sup>36</sup> Indeed, female patients in stage 3 had a higher mortality, comparable to those in stage 4 in the present study.

In contrast, RV dysfunction is more common in men than in women in the AS population.<sup>17-19,37</sup> Estrogen has been reported to exert direct RV-protective effects, modifying disease progression independent of its effects in the pulmonary vasculature.<sup>22</sup> Indeed, a multicenter study based on cardiac magnetic resonance analysis demonstrated that men had greater RV mass, larger RV volume, and lower RV ejection fraction than women in patients with subclinical atherosclerosis.<sup>38</sup> Although there are few data on sex-related differences in RV remodeling associated with AS, previous studies have shown that male sex was associated with lower RV ejection fraction in patients with pulmonary artery hypertension,<sup>39,40</sup> indicating that men with AS-related pulmonary hypertension may tend to suffer from RV damage. In addition, a higher prevalence of comorbidities such as coronary artery disease, AF, and a pacemaker implantation, which adversely affect RV function, may also contribute to a higher incidence of RV dysfunction in men than in women.<sup>41</sup>

Previous reports indicated that women exhibit more favorable long-term prognosis compared to men, primarily because of longer life expectancy and

fewer comorbidities.<sup>11,12</sup> In our study, a favorable association of female sex with 5-year survival was observed in early stages (stages 0, 1, and 2) but not in the advanced stages (stages 3 and 4) of upstream cardiac damage. As mentioned previously, women are more susceptible to malignant pulmonary artery remodeling, which tends to be less reversible.<sup>36</sup> In addition, previous studies have reported that women with elevated pulmonary artery pressure exhibit equivalent or worse clinical outcomes compared with men.<sup>42,43</sup> Therefore, once female patients develop stage 3 or worse cardiac damage in the context of AS, they may have a similar long-term mortality rate after TAVR compared to men despite the benefits of longer life expectancy and fewer comorbidities. Interestingly, no survival advantage was observed in women with early stages of cardiac damage and low-gradient AS. Low-gradient AS is recognized as a more advanced type of AS with a higher prevalence of comorbidities<sup>24,31</sup> and may not benefit from the survival advantage of female sex even in early stages. However, these results must be interpreted in light of the fact that the number of patients with low-gradient AS is relatively small. In summary, sex-specific differences in cardiac damage may result from the differential effect of hormones on the myocardial and pulmonary artery, differences in the myocardial response to pressure overload caused by AS, and differences in the prevalence of comorbidities. Despite these differences, the cardiac damage staging classification stratified long-term outcomes regardless of sex, and timely

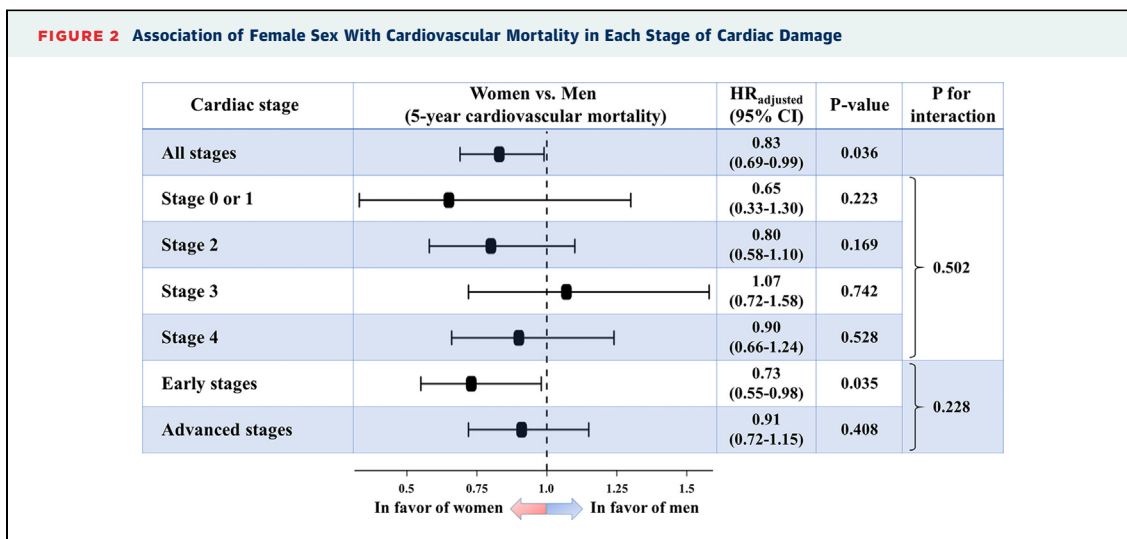
**FIGURE 1** 5-Year Cardiovascular Mortality According to Cardiac Damage Stage in Women and Men



(A) Women and (B) men. TAVR = transcatheter aortic valve replacement.

intervention at an early stage of cardiac damage is warranted in both women and men. Furthermore, female patients may benefit more from intervention at early stages (stage 0, 1, or 2), warranting a sex-tailored approach to TAVR.

**STUDY LIMITATIONS.** The present analysis was a retrospective, observational, single-center study with inherent limitations. First, more than 40% of the patients were excluded because of inadequate echocardiography for the assessment of upstream cardiac



damage, potentially introducing a degree of selection bias. Second, the grouping of cardiac stages into early and advanced stages was somewhat arbitrary. However, we have shown in a previous study that this classification is useful for stratifying long-term mortality after TAVR.<sup>24</sup> Third, the study cohort was predominantly composed of octogenarians, and the findings may not be readily applicable to younger patients with fewer comorbidities and a longer life expectancy. Finally, we did not evaluate follow-up echocardiography after TAVR. Further research is warranted to investigate sex-specific differences in reverse remodeling and changes in upstream cardiac damage during follow-up.

## CONCLUSIONS

Although the distribution of the stage of cardiac damage varied between sexes, the staging classification stratified mortality after TAVR for both women and men. Furthermore, female sex was associated with improved 5-year survival in early stages (stage 0, 1, or 2) but not in advanced stages of upstream cardiac damage (stage 3 or 4). It is essential to identify patients with AS in early stages of secondary cardiac damage and perform TAVR before progression to more advanced stages regardless of sex.

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## PERSPECTIVES

**WHAT IS KNOWN?** The extent of upstream cardiac damage stratifies prognosis in patients with severe AS undergoing TAVR.

**WHAT IS NEW?** Patterns of upstream cardiac damage differed between sexes, but the staging classification proved effective in the stratification of 5-year outcomes in both women and men. Women had favorable prognosis

compared to men in early stages of cardiac damage, but women in more advanced stages had comparable mortality to men.

**WHAT IS NEXT?** Further studies are warranted to investigate sex-specific differences in reverse cardiac remodeling and changes of cardiac damage after TAVR.

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**KEY WORDS** aortic stenosis, cardiac damage staging classification, sex difference, transcatheter aortic valve replacement

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**APPENDIX** For supplemental tables and figures, please see the online version of this paper.