Extent of Cardiac Damage and Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation

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Research Article
Abstract

Purpose

We sought to assess the prognostic role of the extent of cardiac damage among real-world patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

Methods

A staging classification was applied to 262 patients from the EffecTAVI Registry at baseline and re-assessed within 30-day after TAVI. All-cause mortality at 1-year was the primary endpoint of the study. Cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis and re-hospitalization for all caused were included as secondary endpoints.

Results

At baseline, 23 (8.7%) patients were in Stage 0/1 (no cardiac damage/left ventricular damage), 106 (40.4%) in Stage 2 (left atrial or mitral valve damage), 59 (22.5%) in Stage 3 (pulmonary vasculature or tricuspid valve damage) and 74 (28.3%) in Stage 4 (right ventricular damage). At 30-day after TAVI, a lower prevalence of advanced stages of cardiac damage than baseline, mainly driven by a significant improvement in left ventricular diastolic parameters and right ventricular function, was reported. At 1-year, a stepwise increase in mortality rates was observed according to staging at baseline: 4.3% in Stage 0/1, 6.6% in Stage 2, 18.6% in Stage 3 and 21.6% in Stage 4 (p= 0.08). No differences were found in secondary endpoints.

Conclusions

Although TAVI might be associated with an amelioration of the left ventricular diastolic and right ventricular function, patients with a greater extent of cardiac damage at baseline are at higher risk of mortality at 1-year after the procedure.

Introduction

Degenerative aortic stenosis (AS) is the most common heart valve disease among people ≥ 65 years in developed countries, with an increasing prevalence due to population ageing.(1, 2) AS commonly leads to left ventricular (LV) pressure overload resulting in concentric hypertrophy that prevents symptoms onset for a long time while yielding progressive left and right ventricular dysfunction and impaired survival. (3, 4)

Current guidelines recommend intervention in patients with AS according to the severity of the disease and the presence of the symptoms.(5, 6) However, benefits of valve replacement may be limited in patients with advanced functional and structural myocardial changes.
AS induces structural and functional cardiac changes, recently classified by Genereux et al. in a staging model that showed prognostic ability either among patients from the PARTNER 2 trial or in asymptomatic subjects with moderate to severe AS, thus challenging the current management of the disease.(7, 8)

The aim of our study was to assess the prognostic performance of this staging classification in a real-world cohort of patients undergoing transcatheter aortic valve implantation (TAVI) and to investigate the eventual impact of the procedure on the extent of extra-aortic valve cardiac damage.

Methods

Patient population and data collection

All consecutive patients with severe symptomatic AS undergoing TAVI between 2014 and 2019 at our institution were enrolled in the EffecTAVI registry. Severe AS was defined according to current guidelines as a mean aortic valve gradient $\geq$ 40 mmHg and/or aortic valve area < 1.0 cm$^2$ (or an indexed aortic valve area < 0.6 cm$^2$/m$^2$) and/or a peak aortic jet velocity $\geq$ 4 m/s.(9). TAVI suitability was established by the local multi-disciplinary Heart Team. Patients with a complete echocardiographic evaluation at baseline were considered eligible for the present analysis. Clinical, procedural and follow-up data were anonymously entered in a web-based database (https://www.redcap.unina.it/redcap/). The EffecTAVI registry has been approved by the local ethic committee and all study-related procedures were carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained for all patients for participation in this registry.

Cardiac damage staging classification

The following criteria for staging classification of cardiac damage were applied at baseline (within 1 month before TAVI) and after the procedure (within 30-day): 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/m$^2$ for women, > 115 g/m$^2$ for men),(10) severe LV diastolic dysfunction (E/e’ >14) (11) or LV systolic dysfunction (LV ejection fraction, LVEF < 50%); Stage 2, left atrial (LA) and/or mitral valve damage as defined by the presence of LA enlargement (LA volume > 34 ml/m$^2$) and/or moderate-severe mitral regurgitation and/or atrial fibrillation; Stage 3, pulmonary vasculature and/or tricuspid valve damage as defined by the presence of systolic pulmonary hypertension (systolic pulmonary arterial pressure, PAPS $\geq$ 60 mmHg) and/or moderate/severe tricuspid valve regurgitation (12, 13); Stage 4, right ventricular (RV) damage as defined by the presence of moderate-severe RV systolic dysfunction (tricuspid annular systolic excursion, TAPSE < 17 mm).(10, 11, 14, 15)

To improve the identification of subclinical LV dysfunction, we added the LV global longitudinal strain (GLS) to the Stage 1, using a cutoff value of <-20% to define impaired LV-GLS.(10) Patients were hierarchically classified in a given stage (worst stage) if at least 1 of the proposed criteria was met within that stage (Figure S1).
Clinical follow-up and endpoint assessment

After hospital discharge, follow-up was performed by clinical or phone visits at 30-day and 1-year after TAVI. All adverse events were systematically collected and classified according to the definitions of the Valve Academic Research Consortium-2. The primary endpoint of the study was all-cause mortality at 1-year after TAVI. Secondary endpoints included cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis and re-hospitalization for all causes.

Statistical analysis

Continuous data are reported as mean ± standard deviation SD and compared using Student’s t-test or Wilcoxon-Mann-Whitney test as appropriate. Categorical data are reported as frequencies and percentages and compared using chi-square test or Fisher exact test as appropriate. Kaplan-Meier curves were used to compare survival according to each stage of cardiac damage. Each variable and outcome were analyzed with the p-value test and a value < 0.05 was considered statistically significant. Statistical analyses were performed with Stata software version 14.2 (StataCorp, College Station, Texas).

Results

Baseline characteristics

From the EffecTAVI registry, we included 262 patients who received a detailed echocardiographic assessment before and after TAVI, between 2014 and 2019. Patients were classified according to the presence and extent of extra-aortic valvular cardiac damage. At baseline, 4 (1.4%) patients were in Stage 0 (no cardiac damage), 19 (7.2%) patients were in Stage 1 (LV damage), 106 (40.4%) patients were in Stage 2 (LA or mitral valve damage), 59 (22.7%) patients were in Stage 3 (pulmonary vasculature or tricuspid valve damage) and 74 (28.3%) patients were in Stage 4 (RV damage). We merged in a single Stage (Stage 0/1) patients in Stage 0 and 1, given the small number of patients in these groups. The prevalence of cardiac damage stages and the distribution of their individual components are presented in Fig. 1 and Table S1. Baseline characteristics of the study population according to stage of myocardial damage are shown in Table 1. Patients in more advanced stages of cardiac damage were older and had higher STS score compared with those in lower levels. They also presented with a worse NYHA functional class status and had lower LVEF. Procedural characteristics are summarized in Table S2. Transfemoral approach was used in the vast majority of cases (97.3%), and self-expanding prosthesis were implanted in the 73.3% of patients. Procedural success according to VARC2 criteria was 98.5% and 6.8% of patients experienced periprocedural complications.
### Table 1
Baseline characteristics of patient population according to the stage of cardiac damage

<table>
<thead>
<tr>
<th></th>
<th>Stage 0/1 (n = 23)</th>
<th>Stage 2 (n = 106)</th>
<th>Stage 3 (n = 59)</th>
<th>Stage 4 (n = 74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>77.3 ± 6.8</td>
<td>79.2 ± 6.7</td>
<td>81.1 ± 5.2</td>
<td>80.4 ± 5.7</td>
<td>0.039</td>
</tr>
<tr>
<td>Female sex</td>
<td>14 (60.9%)</td>
<td>67 (63.2%)</td>
<td>41 (69.5%)</td>
<td>40 (54.1%)</td>
<td>0.326</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 ± 4.3</td>
<td>27.1 ± 5.9</td>
<td>27.3 ± 5.7</td>
<td>28.1 ± 6</td>
<td>0.551</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (82.6%)</td>
<td>94 (88.7%)</td>
<td>51 (86.4%)</td>
<td>65 (87.8%)</td>
<td>0.873</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (21.7%)</td>
<td>41 (38.7%)</td>
<td>16 (27.1%)</td>
<td>25 (33.8%)</td>
<td>0.285</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>12 (52.2%)</td>
<td>69 (65.1%)</td>
<td>34 (57.6%)</td>
<td>44 (59.5%)</td>
<td>0.606</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7 (30.4%)</td>
<td>49 (46.2%)</td>
<td>25 (42.4%)</td>
<td>36 (48.6%)</td>
<td>0.459</td>
</tr>
<tr>
<td>Previous myocardial</td>
<td>1 (4.3%)</td>
<td>18 (17%)</td>
<td>12 (20.3%)</td>
<td>16 (21.6%)</td>
<td>0.276</td>
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<tr>
<td>infarction</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Previous cerebrovascular</td>
<td>2 (8.7%)</td>
<td>11 (10.4%)</td>
<td>3 (5.1%)</td>
<td>12 (16.2%)</td>
<td>0.22</td>
</tr>
<tr>
<td>accident</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>11 (47.8%)</td>
<td>57 (53.8%)</td>
<td>23 (39%)</td>
<td>45 (60.8%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5 (21.7%)</td>
<td>34 (32.1%)</td>
<td>15 (25.4%)</td>
<td>21 (28.4%)</td>
<td>0.694</td>
</tr>
<tr>
<td>COPD</td>
<td>7 (30.4%)</td>
<td>26 (24.5%)</td>
<td>11 (18.6%)</td>
<td>27 (36.5%)</td>
<td>0.116</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11 (47.8%)</td>
<td>84 (79.2%)</td>
<td>43 (72.9%)</td>
<td>64 (86.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Angina</td>
<td>5 (21.7%)</td>
<td>27 (25.5%)</td>
<td>16 (27.1%)</td>
<td>20 (27%)</td>
<td>0.958</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (21.7%)</td>
<td>15 (14.2%)</td>
<td>6 (10.2%)</td>
<td>7 (9.5%)</td>
<td>0.398</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60.5 ± 8.9</td>
<td>55.9 ± 9.6</td>
<td>54.5 ± 11.7</td>
<td>49.3 ± 13.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>STS-PROM score (%)</td>
<td>3.5 ± 1.4</td>
<td>4.7 ± 3.1</td>
<td>5.2 ± 3.2</td>
<td>6.6 ± 4.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Frailty scale</td>
<td>11 (47.8%)</td>
<td>41 (38.6%)</td>
<td>22 (37.3%)</td>
<td>21 (28.4%)</td>
<td>0.371</td>
</tr>
<tr>
<td>0–1, n (%)</td>
<td>12 (52.2%)</td>
<td>60 (56.6%)</td>
<td>36 (61%)</td>
<td>52 (70.3%)</td>
<td>0.371</td>
</tr>
<tr>
<td>2–3, n (%)</td>
<td>0 (0%)</td>
<td>5 (4.7%)</td>
<td>1 (1.7%)</td>
<td>1 (1.4%)</td>
<td>0.384</td>
</tr>
<tr>
<td>4–5, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>18 (78.3%)</td>
<td>48 (45.3%)</td>
<td>25 (42.4%)</td>
<td>20 (27%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>I o II, n (%)</td>
<td>5 (21.7%)</td>
<td>58 (54.7%)</td>
<td>34 (57.6%)</td>
<td>54 (73%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>III o IV, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Echocardiographic assessment at follow-up**
Echocardiographic evaluation in overall population is reported in Table S3. A complete echocardiographic assessment at baseline, discharge and at 30-day after the procedure was available for 130 patients. Re-assessment of the staging classification yielded more patients in Stage 0/1 and 2 compared with baseline (Table 2 and Fig. 2). LVEF showed a marginally, non-significant improvement (55.3 ± 8.1% vs. 55.4 ± 7.3% vs. 58.4 ± 6.6% at baseline, discharge and 30-day after TAVI; p = 0.059). Similarly, GLS significantly improved from baseline to follow-up (16.84 ± 1.8% vs. 19.6% ± 2.3 vs. 19.2 ± 3.5% at baseline, discharge and 30-day after TAVI; p = 0.044). E/e’ ratio, a marker of diastolic dysfunction, showed a peculiar trend: from a mean value of 17.04 ± 4.4 at the baseline increased to 20.2 ± 5.7 at discharge and then decreased at 30-day after TAVI with a mean value of 12.19 ± 7.2 (p = 0.192). LA volume was significantly reduced (53.8 ± 5.1 mL/m² vs. 52.6 ± 13.9 mL/m² vs. 47.54 ± 11 mL/m² at baseline, discharge and 30-day after TAVI; p < 0.001) as well as systolic pulmonary artery pressure (43.7 ± 8.2 mmHg vs. 41.7 ± 7.4 vs. 37.7 ± 11.1 mmHg, at baseline, discharge and 30-day after TAVI; p < 0.001). Finally, improvement of RV function was demonstrated by an increase of TAPSE (20.46 ± 4.3 mm vs. 20.38 ± 3.7 mm vs. 22.1 ± 5.1, at baseline, discharge and 30-day after TAVI; p = 0.085).

Table 2
Re-assessment of cardiac damage at discharge and 30-day after TAVI

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Discharge</th>
<th>30-day</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0/1</td>
<td>12</td>
<td>18</td>
<td>46</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stage 2</td>
<td>47</td>
<td>75</td>
<td>79</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stage 3</td>
<td>32</td>
<td>27</td>
<td>4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stage 4</td>
<td>39</td>
<td>10</td>
<td>1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55.3 ± 8.1</td>
<td>55.4 ± 7.3</td>
<td>58.4 ± 6.6</td>
<td>0.059</td>
</tr>
<tr>
<td>GLS, %</td>
<td>-16.84 ± 1.8</td>
<td>-19.6 ± 2.3</td>
<td>-19.2 ± 3.5</td>
<td>0.044</td>
</tr>
<tr>
<td>E/e' ratio</td>
<td>17.04 ± 4.4</td>
<td>20.2 ± 5.7</td>
<td>12.09 ± 7.2</td>
<td>0.192</td>
</tr>
<tr>
<td>LAVI, mL/m²</td>
<td>53.83 ± 5.1</td>
<td>52.6 ± 13.9</td>
<td>47.54 ± 11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PAPS, mmHg</td>
<td>43.7 ± 8.2</td>
<td>41.7 ± 7.4</td>
<td>37.7 ± 11.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>20.46 ± 4.3</td>
<td>20.38 ± 3.7</td>
<td>22.04 ± 5.1</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Clinical outcomes

Clinical outcomes at 1-year after TAVI stratified by stage of cardiac damage are presented in Table 3. All-cause mortality progressively increased from Stage 0/1 (4.3%) to Stage 2 (6.6%), Stage 3 (18.6%) and Stage 4 (21.6%) (p = 0.008) (Fig. 3). Death for cardiovascular causes occurred in 1 (4.3%) patient in Stage 0/1, 5 (4.7%) patients in Stage 2, 7 (11.9%) patients in Stage 3 and 11 (14.9%) patients in Stage 4 (p = 0.012).
Table 3
Clinical outcomes at 1-year after TAVI stratified by stage of cardiac damage

<table>
<thead>
<tr>
<th></th>
<th>Stage 0/1 (n = 23)</th>
<th>Stage 2 (n = 106)</th>
<th>Stage 3 (n = 59)</th>
<th>Stage 4 (n = 74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>1 (4.3%)</td>
<td>7 (6.6%)</td>
<td>10 (16.7%)</td>
<td>15 (20.3%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1 (4.3%)</td>
<td>5 (4.7%)</td>
<td>7 (11.9%)</td>
<td>11 (14.9%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0%)</td>
<td>2 (1.9%)</td>
<td>2 (3.4%)</td>
<td>3 (4.1%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0%)</td>
<td>2 (1.9%)</td>
<td>2 (3.4%)</td>
<td>5 (6.8%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>6 (26.1%)</td>
<td>15 (14.2%)</td>
<td>7 (11.9%)</td>
<td>16 (21.6%)</td>
<td>0.24</td>
</tr>
<tr>
<td>implantation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (4.3%)</td>
<td>1 (0.9%)</td>
<td>0 (0%)</td>
<td>2 (2.7%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Re-hospitalization</td>
<td>0 (0%)</td>
<td>10 (9.4%)</td>
<td>4 (6.8%)</td>
<td>9 (12.2%)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

No differences were found for secondary endpoints including cerebrovascular accident, myocardial infarction, permanent pacemaker implantation, endocarditis and re-hospitalization for all causes at 1-year after the procedure.

**Discussion**

The main findings of the present analysis can be summarized as follows:

1. The staging classification of AS-related cardiac changes, derived from randomized trial, maintains its prognostic performance in real-world TAVI patients;
2. TAVI triggers an early reversal of cardiac dysfunction, mainly driven by the amelioration of LV diastolic and RV function;
3. Nevertheless, the extent of extra- aortic valve cardiac damage at baseline significantly affects survival at 1-year after the procedure.

The identification of clinical and anatomic factors that affect clinical outcomes of patients with severe AS represents an important unmet need. Several scoring systems that account for baseline features and measures of frailty have been proposed for counselling AS patients.\(^{(17, 18)}\) However, their use in clinical practice is challenged by the lack or limited availability of all the required variables. In this context, the staging classification of cardiac damage by Généreaux et al features the unique advantage to be widely applicable as it is based on echocardiographic parameters that are routinely evaluated in patients with severe AS. This system was formulated by leveraging on data of 1,661 patients from the PARTNER 2 trial and proved a powerful predictor of mortality at 1-year after aortic valve intervention (either surgical or transcatheter).\(^{(7)}\) In our study, including real-world patients, the system retains its prognostic ability as a
greater extent of cardiac damage was associated with increased risk of all-cause mortality after TAVI. These findings are in line with prior studies that applied the staging classification system in larger populations. In a retrospective analysis of 1,189 symptomatic severe AS patients, stage of cardiac injury was independently associated with all-cause mortality and combined endpoint of all-cause mortality, stroke, and cardiac-related hospitalization.(19) Among asymptomatic patients with moderate to severe AS, 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 proved incremental value over other traditional risk markers.(20) Another study applied the staging system to TAVI patients and found a graded association between cardiac damage and all-cause mortality.(21)

However, our analysis is the first to assess the impact of TAVI on the extent of extra-aortic valve cardiac damage. We found that the procedure triggers an early (within 30-day) re-classification of the stages owing to significant changes in measures of LV diastolic and RV function. LV hypertrophy and collagen abnormalities develop in patients with severe AS and impair diastolic function. Objective evidence of variable degree of LV diastolic dysfunction, indeed, has been reported in up to two-thirds of patients undergoing TAVI.(22) Similarly, RV dysfunction has been documented in up to 1 in 4 patients with severe AS as consequence of transmission of elevated left-sided pressures back through the pulmonary vascular system. The suppression of pressure overload by TAVI ameliorates LV filling pressures (E/e' ratio), as suggested by the concomitant reduction of left atrial volume. Along the same line, a trend towards normalization of TAPSE may occur after TAVI (23, 24) as well as a reduction of pulmonary hypertension.(25) Nevertheless, these changes do not improve survival after TAVI as baseline conditions predominate in determining prognosis at 1-year. Consistently, we observed an overall improvement of myocardial function suggested by changes in LV-GLS after TAVI with no relevant impact on mortality at 1-year.

The main clinical implication of the results of our study is the need for rethinking the optimal timing of intervention in patients with AS. Multiple lines of evidence indicate that the greater is the extent of cardiac damage before TAVI, the higher is the probability of worse outcomes after the procedure. Moreover, irreversible structural cardiac changes induced by longstanding AS neutralize the beneficial impact of TAVI on some functional parameters. In this perspective, anticipating the intervention might have the potential advantage to obtain the full reversibility of cardiac function and improve survival at a greater extent.

Our study has several limitations. It is a retrospective analysis of data collected at a single center, thus subject to inherent flaws related to that design. A comprehensive assessment of echocardiographic parameters after TAVI was not performed in the overall population affecting the completeness of our observations. Parameters used for staging the extent of cardiac damage are those obtained in the context of the routine echocardiogram of TAVI patients and potentially subject to measurement errors and variability. We did not assess the potential modifying effect of paravalvular aortic regurgitation on echocardiographic and clinical outcomes after TAVI.
In conclusion, the staging classification confirms its utility as additive clinical tool to enhance risk stratification and therapeutic decision making in patients with AS. TAVI might reverse functional cardiac changes associated with AS; however, survival at medium-term is mainly related to the baseline grade of extent of cardiac damage. Further and larger studies are needed to assess the value of the staging classification in the post-procedural setting.

**Declarations**

**Acknowledgements**

This paper is dedicated to the memory of our friend and colleague Maurizio Galderisi who died on March 2020 because of COVID-19.

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**Disclosures**

FI, CI and CS receive research grant support from Cardiopath PhD program. Other authors have nothing to disclose.

**References**


Figures
Figure 1

Distribution of stages of cardiac damage in the study population. The figure shows the prevalence of cardiac damage stages in the study group.
Figure 2

Re-assessment of cardiac damage at discharge and at 30-day after TAVI.
Figure 3

All-cause mortality according to the stage of cardiac damage. Kaplan-Meier curves of all-cause mortality according to the staging classification.